THE ROLE OF CT-GUIDED PERCUTANEOUS TRANSTHORACIC NEEDLE BIOPSY WITH VIETNAM BIOPSY CALIBRATOR FOR THE DIAGNOSIS OF PULMONARY NODULES

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ABSTRACT

Outline: CT guided percutaneous transthoracic needle biopsy is a relatively non-invasive way to obtain tissue for the diagnosis of pulmonary nodules. One barrier to its use is the difficulty of positioning the needle at the right angle and depth. We have developed a three-dimensional positioning angle meter to assist biopsy needle during lung biopsy. **Purpose**: To determine the role of the "Vietnam Biopsy Callibrator" (VBC) and CT-guided percutaneous transthoracic needle biopsy in the diagnosis of lung nodules. **Methods**: 85 patients with lung nodules had a CT-guided percutaneous transthoracic needle biopsy done with the assistance of the VBC, three-dimensional positioning angle. We report the results of this prospective series **Results**: 45.3% had a nodule size < 3cm. 98.8% of patients were performed in supine and prone position. The average depth of penetration was: 53 mm ± 18 mm. The percentage of adequate specimens for cytological diagnosis was 97.6%, and adequate specimens for histopathology was 100%. Histopathological diagnosis: 45 patients (52.9%) had cancer, tuberculosis inflammation: 17 (20.0%) patients, and other benign pulmonary lesions. Overall incidence of complications: 22.4%, mostly mild with only 1 patient (1.2%) developed a clinically significant pneumothorax requring intervention. **Conclusion**: Pulmonary CT-guided percutaneous transthoracic biopsy with the assistance of the VBC is an efficient technique in diagnosis lung nodules that has a low incidence of complications.

Key words: *Transthoracic needle biopsy, Vietnam biopsy calibrator, CT-guided transthoracic needle biopsy*

I. BACKGROUND

Methods for diagnosing lung nodules include bronchoscopy, transthoracic fine needle aspiration under ultrasound or CT scan guidance. In Vietnam, transthoracic needle biopsy under CT guidance is currently performed in central and provincial hospitals. One difficulty in implementing the technique is the need to correctly align the biopsy needle with the angle and depth defined on the computerized tomography.

The research team at Haiphong International Hospital has developed a 3D calibrator to assist in guiding biopsy needle at a predefined angle and depth by CT scanner. This is something easy to manufacture and can easily be used in low resource settings. The study aims to assess the role of CT-guided percutaneous transthoracic needle biopsy for the diagnosis of pulmonary nodules with the assistance of Vietnam biopsy calibrator (VBC).

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II. SUBJECTS AND METHODS OF RESEARCH

2.1. Study population

85 patients with lung nodules were biopsied by CT-guided percutaneous transthoracic needle biopsy technique using the VBC. We report on the success of this method.

2.2. Methodology

Prospective, descriptive, cross-sectional study.

2.3. The Vietnam biopsy calibrator (VBC) (figure 1) is a unique method of assuring the proper depth and angle of needle placement in CT guided biopsy.

It is composed of hard plastic, cut with 3D CNC machine, model: SUDA SD3025S, with deviation of cutting: ± 0.04mm / m. Rear cutter has curve edge, vertical and horizontal axis parameters. Curve edge is a scale of 90 degrees, vertical and horizontal axis is a scale in cm;

Three-dimensional positioning is accomplished using a circular "bubble level" attached to the body of the VBC.

Figure 1: Vietnam biopsy calibrator

2.4. Biopsy procedures:

Patients with pulmonary nodules had diagnostic testing including blood count, prothombine time, AFB testing and bronchoscopy. In cases of unclear diagnosis, CT-guided percutaneous transthoracic needle biopsy was performed. Patients had a chest CT scan done with determination of the location of the nodules in relationship to thoracic wall. The depth and angle of needle insertion was determined by using the software of CT Scan. Using sterile technique and local anesthesia with lidocaine 1%, a biopsy sheath was inserted to the target lesion in the chest with the assistance of the VBC. CT Scan was then repeated to determine the location of the tip of the biopsy sheath in relationship to the pulmonary nodule. Once correct sheath placement was confirmed, 3-5 biopsy samples were taken from the nodule. The specimens were placed into a preservative solution. After biopsy, the syringe was used to create negative pressure aspiration in order to obtain sample for cytology. A post-biopsy chest x-ray was done to assess for post-procedure pneumothorax, parenchymal bleeding or hemothorax.

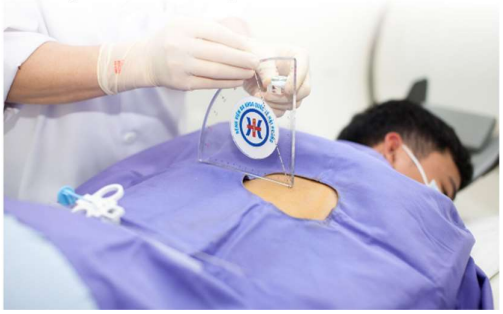

Figure 2: CT-guided needle biopsy with Vietnam biopsy calibrator

2.5. Statistical analysis

85 consecutive patients with lung nodules underwent biopsy. Data on patient positions, depth of needle insertion, adequate specimen for cytological, histopathological diagnosis and incidence of complications are reported and summarized in tables 1 to 3.

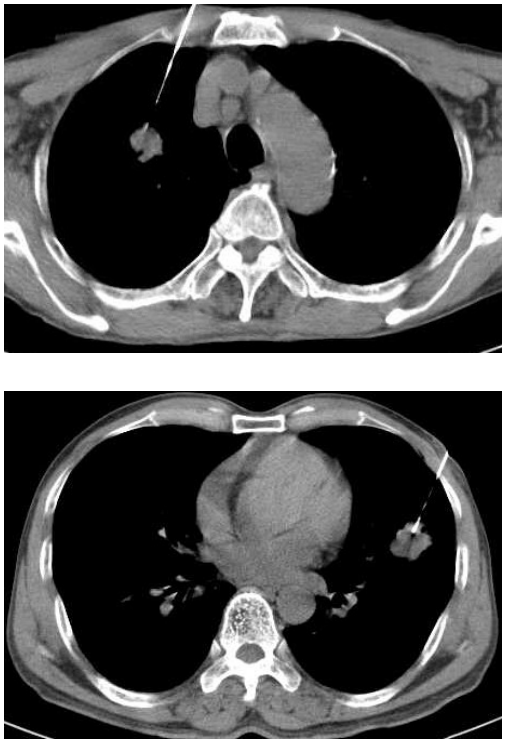

Figure 3: *CT-guided percutaneous transthoracic biopsy of two different patients.*

III. RESULTS

Size of nodules

In the study, 85 patients underwent lung nodule biopsy. The results of pre-biopsy CT Scan show that 3 cases had a nodule| size ≤ 1 cm - these are difficult cases for biopsy; 43.5% of cases were <3 cm in size.

Position and depth of biopsy sheath

Patient positioning depended on the location of the nodule. In 85 patients, 40 patients (47.1%) were biopsied in supine position, 44 patients (51.8%) were biopsied in the prone position and only one patient (1.1%) was biopsied in the lateral position.

The biopsy sheath was inserted to the target lesion under the assistance of VBC and CT Scan. After seeing the tip of biopsy sheath in the border of tumor: the biopsy was done to take samples.

Table 1. Depth of biopsy sheath insertion (n=85)

Characteristics		*Number (n=85)*	*Percentage (%)*
Depth of biopsy sheath insertion	≤ 30 mm	10	11.8
	30-50 mm	26	30.6
	>50 mm	49	57.6
	Total	85	100

The shortest depth of the biopsy sheath was 16 mm, the deepest was 96 mm, the average depth was 53 mm ± 18 mm.

The success of taking specimens

The most important goal of this technique is to obtain enough specimen for histopathological diagnosis. In the study, all 85 patients (100%) were obtained adequate specimen for histopathological diagnosis, and adequate specimen for cytological diagnosis in 83 patients (97.6%). We could not perform aspiration for cytology in two patients because of hemoptysis, which happened immediately after taking histopathology samples, it interrupted the procedure.

Results of cytology and histopathology

Cytological results from 83 patients revealed that: 34 patients (41.0%) were diagnosed as malignant diseases; 7 patients (8.4%) were diagnosed as tuberculosis; 17 cases (20.5%) were confirmed as chronic inflammation, and 25 cases (30.1%) still did not have a clear diagnosis.

Histopathological samples have gotten further diagnosis for 28 patients: 11 lung cancer, 10 tuberculosis, 1 sclerosant

hemangioma, 2 ganglioma, 1 thyroid tumor, 1 solitary fibrous tumor, 2 thymoma (all of these patients did not have clear diagnosis with cytology). The results are summarized in table 2

Table 2. Histopathological results (n=85)

Types of diseases	Histopathology	n	%
Carcinoma	Adenocarcinoma	31	36.5
	Squamous cell carcinoma	5	5.9
	Adenosquamous carcinoma	1	1.2
	Small cell lung cancer	7	8.2
	Undifferentiated lung carcinoma	1	1.2
Benign nodules	Tuberculosis	17	20.0
	Thymoma	2	2.3
	Ganglioma	2	2.3
	Sclerosant hemangioma	1	1.2
	Solitary fibrous tumor	1	1.2
	Thyroid tumor	1	1.2
	Chronic Inflammatory	17	20.0
Total		**85**	**100**

100% patients had histopathological results. Lung cancer: 45/85 patients (52.9%); benign diseases: 40/85 patients (47.1%).

Incidents of the technique

In the biopsy procedures, the team members always chose (1) the shortest distance to the lesion; (2) the least number of pleural penetrations; and (3) avoided areas with bullae and areas with emphysema.

Among complications: pneumothorax was the most common complication (11.8%) with most patients requiring only oxygen therapy. Only one patient with a pneumothorax needed a chest tube dranage. Five patients with post-procedure hemoptysis, but all were mild. The results are summarized in table 3

Table 3. Incidence of complications (n=85)

Complications	n	%
No complications	66	77.6
Pneumothorax	10	11.8
Parenchymal bleeding	4	4.7
Hemoptysis	5	5.9
Total	**85**	**100**

The data indicated that 77.6% of cases had no evidence of pneumothorax, lung parenchymal bleeding, or hemoptysis.

IV. DISCUSSION

Transthoracic biopsy technique is performed commonly in Vietnam

There are several invasive techniques for diagnosing lung nodules: bronchoscopy, transthoracic fine needle aspiration, CT-guided percutaneous transthoracic needle biopsy. However, CT-guided percutaneous transthoracic needle biopsy is the the most available and the most frequently used

technique in Vietnam. [1,2,3,4]. It can be technically difficult to insert the biopsy needle to the right angle and depth when measured on a computerized screen. Many tools have been used to assist biopsy needle insertion, such as the hand-held guidance device in Palestran AM's study (1990) [5], or an angle gauge fitted with two-dimensional positioning in Ngo Quy Chau's study [1,2], Nguyen Thanh Hoi [4]. However, the hand-held guidance device in Palestran AM's study is hard to find, and the price is expensive, while the two-dimensional angle gauge of Ngo Quy Chau, Nguyen Thanh Hoi when applied may lead to deviation from biopsy lesions. The team then developed a three-dimensional calibrator and applied it in biopsies of lung nodules for patients in Haiphong International Hospital - Vietnam.

Position and depth of biopsy sheath

The depth of the biopsy sheath is closely related to the accuracy of the procedure. In this study, we determined the depth of biopsy sheath approach from the skin to the surface of the lesion, thus recording a minimum depth of 16 mm, and the maximum depth of 96 mm, the depth in others study of many authors is the depth of the parietal pleural to the surface of the lesion. According to Choi et al (2012), the depth of the guide needle to the lesion surface is 0-102 mm [6]. The Yamagami et al. (2002) biopsy in 134 cases of transthoracic biopsy revealed a depth of 0-79 mm, an average of 20.4 ± 17.4 mm [7]. The position of the patient depends on the location of the nodule. The most commonly used position for biopsy are supine and prone position, the reason is: patients are more likely to maintain position when insert biopsy sheath, thus minimizing the risk of deviation. The study recorded supine and prone position accounted for 84/85 patients (98.8%). This finding is similar to that of Choi et al., Who performed the biopsy in 173 patients with lung nodule (<2 cm). All 173 patients (100%) were placed in a supine or prone position [6].

Effectiveness of technique

With the assistance of computerized tomography and the VBC, it is possible to accurately position the needle in 100% of patients. We were able to get adequate specimens for cytological diagnosis in 83/85 patients (97.6%), and adequate specimens for histopathological diagnosis in 85/85 patients (100%).

When looking at the cytological and histopathological findings, 42 patients (49.4%) had negative cytological results but most of them had positive histopathology, resulting in the histopathological diagnosis for 11 cases of cancer. 10 cases of tuberculosis, 1 sclerosant hemangioma, 2 ganglioma, 1 thyroid tumor, 1 solitary fibrosis tumor, 2 thymoma. In addition, in cancer cases: histopathology allows for the type of cancer to be identified, which is important in the choice of treatment options for patients. This further confirms the superiority of histopathology to cytology in the diagnosis of lung nodules. The results were similar to those of Larscheid et al. (1998), who studied over 130 patients with transthoracic biopsy. There were 95 cases of malignant nodule, in which adenocarcinoma was 36%; squamous cell carcinoma: 32%; small cell carcinoma: 8% [9]. According to a study by Ngo Quy Chau and colleagues (2006), 265 cases with lung lesion have been diagnosed with CT were suffered from CT-guided transthoracic biopsy technique. Histopathological findings showed 63% of cancer, 0.4% of fungus, 24.5% of chronic inflammation [1]. In addition, with the

efficacy of specimen taking for histopathology was 100% and 97.6% for cytological diagnosis, the technique continues to be a preferred choice among specimen collection techniques for diagnosis of lung nodules, and a higher value when compared with biopsy under the guidance of endobronchial ultrasound [10].

Complications

CT-guided percutaneous transthoracic needle biopsy is a safe proceduce. A total of 85 patients undergoing percutaneous transthoracic needle biopsy had 66/85 patients (77.6%) without any complications. Of the 19 patients suffering from the complications, only one patient (1.2%) had to have a chest tube dranage; the rest only needed oxygen therapy. In patients who had hemoptysis or parenchymal bleeding, they all were administered a subcutaneous injection 5mg morphine and infusion 1g tranexamic acid. The incidence of complications was generally similar to many studies. According to Lee HN et al (2018), percutaneous transthoracic needle biopsy in 1,735 patients with lung nodules, the overall incidence of complications was 22.5%, of which 338 / 1,735 patients (19.5%) developed pneumothorax, and 52 / 1,735 patients (3.0%) had hemoptysis as complications [11]. The Wiener et al (2011) studied of 22,176 procedures of CT-guided percutaneous transthoracic needle biopsy in four states found a bleeding rate of 1.0% (95% CI 0.9-1.2%), the rate of pneumothorax was 15.0% (95% CI 14.0-16.2%), and the rate of pneumothorax with chest tube drainage was 6.6% (95% CI 6.0 - 7.2%) [12].

V. CONCLUSIONS

85 patients with lung nodules diagnosed by CT-guided percutaneous transthoracic needle biopsy were prospectively evaluated. CT-guided percutaneous transthoracic with the assistance of the Vietnam biopsy calibrator is safe, highly effective and has an acceptably low complication rate for histopathological and cytological diagnosis.

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RÉSUMÉ:

LE RÔLE DU CALIBRATEUR POUR LA BIOPSIE TRANSTHORACIQUE AVEC L'AIGUILLE GUIDÉE PAR LE CT DANS LE DIAGNOSTIC DES NODULES PULMONAIRES

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Généralités: La biopsie transthoracique avec l'aiguille guidée par le CT pour l'abtention de tissus pulmonaires nodulaires est une technique non-iunvasive relativement simple. L'obstacle réside dans la difficulté de positionner correctement l'aiguille dans la direction et la profondeur. Nous avons developpé un appareil visant à faciliter cette technique dans ses trois dimensions. **Buts:** Définir le rôle du "calibrateur Vietnamien pour biopsie" (VBC) et la biopsie transthoracique par l'aiguille guidée par le CT dans le diagnostic des nodulles pulmonaires. **Méthodes:** 85 pastients avec nodules pulmonaires ont été biopsies avec une aiguille CT guidée, avec l'assistance du VBC, et par voie transthoracique. Voici le rapport de cette étude prospective. **Résultats:** 45.3% de nodules ont pour dimension <3cm, 98.8% de patients avaient subi la biopsie en position couchée, face contre la couverture. La profondeur moyenne de penetration était de 53mm±18mm. Les échantillons adéquats pour l'étude cytologique étaient 97.6% et pour l'histopathologique: 45 patients (52.9%) avaient un cancer, l'inflammation tuberculeuse 17 (20%), d'autres avaient des lésions pulmonaires bénignes. Les complications totalisèrent 22.4%, la plupart bénignes, seul un patient (1.2%) avait un pneumothorax nécessitant l'intervention. **Conclusion:** La biopsie transthoracique guidée par CT avec l'assistance du VBC est une technique diagnostique efficace pour les nodules avec faible incidence de complications.

Mots clés: *Transthoracic needle biopsy, Vietnam biopsy calibrator, CT-guided transthoracic needle biopsy.*

TREATMENT EFFECTS OF BOTULINUM TOXIN A TO INTRACTABLE POST-STROKE HEMIPLEGIC SHOULDER PAIN IN PATIENTS TREATED AT MILITARY HOSPITAL 103

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ABSTRACT

Objective: To evaluate the beneficial effect of botulinum toxin A in patients with intractable post-stroke hemiplegic shoulder pain. **Methods:** 27 stroke patients with intractablepost-stroke hemiplegic shoulder painwere treatedat the Stroke department of the Military Hospital 103 from November 2017 to May 2018. **Results:** After botulinum toxin injectionat 1 and 3 months, VAS score (3.31 ± 0.98; 0.47 ± 0.15) respectively was significantly reduced compared to before injecting (5.27 ± 0.88), MAS core was significantly declined ($p<0.05$), range of motion (ROM) was also improved ($p<0.05$). **Conclusion:** Botulinum toxin A injection hadan effect on in reducing intractable hemiplegic shoulder pain.

Keywords: *Hemiplegia, Shoulder pain, Intractable pain, Type A botulinum toxins, Intramuscular injections*

I. INTRODUCTION

Hemiplegic shoulder pain (HSP) is a common complication after stroke with a reported prevalence of 29%-65% [3]. HSP inhibits recovery and rehabilitation and impairs the quality of life of stroke survivors. Although the etiology of HSP is not well known, it has been suggested that multiple factors contribute to HSP, such as adhesive capsulitis, rotator cuff disorder, myofascial pain, complex regional pain syndrome, and shoulder-hand syndrome [4].

Physiatrists have applied a wide variety of approaches against HSP, including correct positioning, physical therapy, neuromuscular electrical stimulation, modalities (hot pack, infrared, and interferential current therapy), oral medication, and local injection [4]. However, a large number of patients suffer from intractable hemiplegic shoulder pain (iHSP). In addition, individuals with iHSP have limited treatment options.

Botulinum toxin type A (BTX) has been widely used to treat many conditions including spasticity, dystonia, myoclonus, muscle spasm, myofascial pain syndrome, and autonomic overactivity syndromes. BTX was recently introduced as a novel treatment option for a variety of pain syndromes including shoulder pain [6]. A recent systematic review concluded that BTX injections had a better effect on shoulder pain than conventional therapies (steroid or placebo injection) [10]. Most studies applied BTX injections at the glenohumeral joint, subacromial bursa, pectoralis major, subscapularis, and other muscles. Interestingly, BTX injections into the subscapularis have shown therapeutic effects in the case of HSP. Nevertheless, studies on the therapeutic effect of BTX injection into the subscapularis muscle for iHSP are lacking. Therefore, the aim of this study was to:*assesstreatment effects of BTX injections inpatients with iHSP*

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II. SUBJECTS AND RESEARCH METHODS

2. 1. Subjects

27 patients suffering from iHSP after stroketreated at the Stroke Department, Military Hospital103 from November 2017 to 2018.

2.2. Method and content of research.

* *Researchdesign:* A prospective, randomized, placebo-controlled study of patients receiving botulinum injections type A at the time 1 month and 3 months.

* *Research content*

- Injecting the BTX group A into the Subscapularis muscle, Pectoralis major muscle, Teres major muscle, Latissimus dorsi muscle by the dose of Huber M and Heck G (2002), approved by Vietnam Ministry of Health.

- iHSP was defined according to Singh's standard [8].

- Muscle spasticity was defined as a modified Ashworth scale (MAS) from 0 (normal) to 4 (severe).

- The pain was evaluated on a VAS scale (1- <4 points: light, 4- <7 points: medium;> 7 points: heavy).

- A range of shoulder joints: measured by the two-point angle scale by the zero method.

2.3. Data analysis

Data was analyzed by SPSS 20.0. A significant difference was defined at p <0,05.

III. RESULTS AND DISCUSSION

The study group consisted of 27 patients with shoulder pain due to hemiplegia after stroke: 14 men (accounting for 51.85%), 13 women (accounting for 48.15%); The median age was 56.5, the lowest was 42, the highest was 89.

1. Clinical characteristics

Table 1: HSP distribution according to the type of stroke

Type of stroke		n (ratio %)	p
Cause	Ischemic stroke	55.56 (15)	>0.05
	Hemorrhagestroke	44.44 (12)	
	Both	0 (0)	
Time of treatment after stroke (months)		Mean 32	Limition 1-59

The results showed that iHSP was 55.56%, cerebral hemorrhage (44.44%) was not significantly different, the lowest of a duration of stroke was 1 month, the highest was59 months, the average was 32 months. According to Nguyen Minh Hien (2012) [1], ischemic stroke 80%, hemorrhage stroke 20%. Thus, the incidence of shoulder pain after hemorrhage stroke was higher than that of ischemic stroke. According to Adey Walkeling et al. [3], shoulder pain after a stroke appears to begin at the third week and peak at the fourth month, in our study patients with iHSP appeared at least one month after the stroke. Because of the pain, patients should be given medication and physical therapy before the botulinum injection. Important risk factors for shoulder pain after stroke are ageing, severe stroke, low Barthel score, upper limb paralysis, combined myoclonus, and accompanying arthritis.

2. The results of treatment of shoulder pain with type A botulinum injection.

Table 2: Asworth's modified score

MAS Muscle groups	Admission (aa)	One month p(aa-1)	3 months p(aa-3)
Subscapularis muscle	2.58 ± 0.51 (p < 0.05)	1.23 ± 0.14 (p < 0.05)	1,46 ± 0.43 (p < 0.05)
Pectoralis major muscle	2.45 ± 0.13 (p < 0.05)	1.08 ± 0.26 (p < 0.05)	1.13 ± 0.24 (p < 0.05)
Teres major muscle	1.93 ± 0.37 (p < 0,05)	0.95 ± 0.22 (p < 0.05)	0.14 ± 0.34 (p < 0.05)
Latissimus dorsi muscle	1.87 ± 0.44 (p < 0.05)	0.9 ± 0.08 (p < 0.05)	0.25 ± 0.21 (p < 0.05)

At 1 month, 3 months, MAS scores were significantly lower (p <0.05) than before hospitalization (p <0.05) in all muscle groups. MAS scores were lower in studies of 1 point at 1 month and 3 months as compared to those of Luong Tuan Khanh [2]. At the sixth week, MAS scores in wrist and knee joints were statistically significant (p <0.05). Jeong-Gue Choi and Cs [10] reported a decrease in MAS scores after first, second, third, fourth weeks following the administration of botulinum toxin in group A with statistically significant (p <0, 05).

The purpose of the study was to inject BTX into the Subscapularis muscle, Pectoralis major muscle, Teres major muscle, Latissimus dorsi muscle that improved shoulder pain, movement area and muscle contraction in iHSP patients. The condition of shoulder pain improvement is related to the free movement of the shoulder and shoulder twitch. The Subscapularis muscle is one of the primary muscles of the shoulder, which plays a crucial role in the autonomic system; Pectoralis major muscle is closed and rotated in the shoulder joint; Latissimus dorsi muscle work in rotation, closing and stretching the shoulder joint, lowering the shoulder belt and helping to tilt the body to the side; Teres major muscle motions rotate in, close and extend the shoulder joint [2].

Table 3: Pain levelfollowed VAS scale

Pain level	Before injection n(%) (1)	After one month n (%) (2)	After three month n(%) (3)	P
Low	3 (11.11)	6 (22.22)	10 (37.04)	(2-1) < 0.05 (3-1)<0.01
Medium	9 (33.33)	14 (51.85)	17 (62.96)	(2-1)<0.05 (3-1)<0.01
Serious	15 (55.56)	7 (25.93)	0 (0.00)	(2-1)<0.05 (3-1)<0.01
Medium score	5.27 ± 0.88 (4-7)	3.31 ± 0.98 (1-4)	0.47 ± 0.15 (0-1)	(2-1)<0.05 (3-1)<0.01

The results showed that pain level after 1 month of botulinum injection was significantly (p <0.05) lower than before treatment. After 3 months, the pain was significantly decreased (p <0.01). The research results were similar to those of Luong Tuan Khanh [2], John W Dunne [4]. Yelnik and Cs, a randomized, double-blind, placebo-controlled study of patients with shoulder pain after strokes, were injected with group A botulinum into the spasmodic muscles, reduction pain was statistically significant with p <0.05 compared to control group [7]. Jeong-Gue Choi et al. [10] reported the results of iHSPafter stroke improved (p = 0.004) after botox injection into Subscapularis muscle.

The results showed that pain level after 1 month of botulinum injection was significantly (p <0.05) lower than before treatment. The cause of pain in muscle contraction was not fully understood. There are now many theories that explain spasticity and pain. One of the theories is the long-term and abnormal contraction of the muscle that acts on the artery wall, excessive consumption oxygen gradually becoming forced. Muscle in hypoxia, which creates inflammatory and painful mediators such as bradykinin, prostaglandins (PGE2), potassium in the blood and tendon sites; Pain can be a long-term muscle spasticity that causes deforming of joints, arthritis pain. Pain is also a contribution to increasing the degree of contraction of the muscles, which is a pathological twist that promotethe disease. Injection of Botulinum toxin A cuts neuromuscular transmission to soften the muscles, cuts off the adverse cycle and alleviates pain. The results have been documented and proven in the treatment of postmenopausal stroke and brain injury [9]. Another theory about the mechanism of the study results is the BTX's anti-inflammatory effect. BTX is effectively anesthetized by nerve peptides released from the nerve endothelial nerve endings, although the mechanism of musculoskeletal involvement is painful and its mechanism of mitigating is unclear. Anesthetic effectshave also been reported in muscular contraction associated with pain [10].

Table 4: Range of shoulder joint

Characteristics	Before injection ($\overline{X}$ ±SD) degree (1)	After one month ($\overline{X}$ ±SD) degree (1)	After three months($\overline{X}$ ±SD) degree (1)	p
Put your arm forward, up (normal 180 degrees) **Active** **Passive**	91.3 ± 13.9 96.2 ± 11.7	161.1 ± 8.6 179.2 ± 1.3	185.6 ± 1.2 180.0 ± 1.5	(2-1)<0.05 (3-1)<0.01
Put your arm backward (normal 50 degrees) **Active** **Passive**	21.3 ± 3.3 22.2 ± 1.3	41.3 ± 2.4 49.2 ± 1.4	41.3 ± 1.3 48.2 ± 1.2	(2-1)<0.05 (3-1)<0.01
Shoulder joint and arm upward (normal 100 degrees) **Active** **Passive**	81.6±5.8 82.2 ± 2.5	159.1±7.5 178.0 ± 1.2	175.2 ± 1.9 181.0 ± 1.3	(2-1)<0.05 (3-1)<0.01

The results showed that after 1 month and 3 months of botulinum injection, the active range shoulder joint was nearly normal, the passive the range was normal. Patients also hadmoderate pain at the end of range. The results were similar to those of Jeong-Gue Choi et al. [10] with shoulder movements (p = 0.003), rotating outside p = 0.005 and inside p = 0.005. Interestingly, shoulder restriction was considered to be a circulating factor that length HSP (> 6 months) [10].

In conclusion, the main cause of iHSP is the contractionof the internal-rotation shoulder muscles. Injections of BTX into the Subscapularis muscle, Pectoralis major muscle, Teres major muscle, Latissimus dorsi muscle reduce the contraction of the internal-rotation muscles, leading to restoration of the outer shoulder restriction region and reduction of iHSP status by disruptionpathological twist. The results of Jeong-Gue Choi et al. [10] studies also showed a high correlation between the movement area (ROM) and muscle contraction and pain.

* Unwanted effects: Fake flu syndrome: 2 patients (7.4%); Dry mouth: 1 patient (3.7%), these symptoms disappear after 10 days; Irritation of the skin to be injected and swallowing disorders not seen. According to Geoffrey Sheean [11], with a total dose of 1.500 UI, undesirable effectswere very rare, unlike the placebo group that was not statistically significant.

IV. CONCLUSION

Treating 27 patients with shoulder pain due to hemiplegia after stroke with botulinum type A in the Department of Stroke, Military Hospital 103, we obtained the following results:

- After botulinum injections 1 month and 3 months pain level (VAS) were 3.31 ± 0.98, 0.47 ± 0.15 respectively, significantly different from the pre-treatment (5.27 ± 0.88), patients almost had no pain in the shoulder joint.

- Active shoulder joint flexion became nearly normal and passive shoulder joint became normal after 1 and 3 months with botulinum injection.

- In the first month, the third month, MAS score was one-point lower than at admission in all muscle groups, which was statistically significant (p <0.05).

- Unwanted effects: 7.4% fake flu syndrome, 3.7% dry mouth. Unwanted effects disappeared after 3 days of injection.

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RÉSUMÉ:

LES EFFETS DU TRAITEMENT PAR LA TOXINE A DU BOTULUS CHEZ LES PATIENTS HÉMIPLÉGIQUES SE PLAIGNANT DE DOULEUR POST-ICTUS DE L'ÉPAULE À L'HÔPITAL 103

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Objectif: Évaluer l'effet bénéfique de la toxine A du botulus chez les patients hémiplégiques se plaignant de douleur post-ictus de l'épaule. **Méthodes:** 27 patients avec ictus et douleur irréductible de l'épaule post hémiplégique on été traités au Département d'ictus de l'Hôpital Militaire 103 du mois de Novembre 2017 à Mai 2018. **Résultats:** Après l'injection de la toxine du botulus de 1 à 3 mois, le score VAS (3.31±0.98; 0.47±0.15) respectivement, est reduit de facon significative compare à celui d'avant (5.27±0.88), le score MAS est reduit de facon significative ($p<0.05$), le mouvement a été amélioré (ROM) ($p<0.05$).

Mots clés: *Hemiplegia, shoulder pain, intractable pain, type A botulinum toxins, intramuscular injections.*

CORRELATIONS BETWEEN ATTENTION DEFICITS AND CLINICAL CHARACTERISTICS IN PATIENTS WITH CHRONIC ALCOHOLISM

Nguyen Tat Dinh*, Pham Hong Van, Le Van Quan*****

ABSTRACT

Objects: To investigate correlations between clinical characteristics of chronic alcoholism and attention deficits. ***Methods:*** Analyzing corrlations between clinical characteristics and levels of attention deficits in 56 patients with chronic alcoholism treated at Psychiatric Department, Military Hospital 103. ***Results:*** ***D***aily drinking durations, and levels of alcoholism were significantly negatively correlated to levels of attentional deficits while daily volume of alcohol was not significantly negatively related to not to attention disorders. ***Conclusion:*** In the present study, results indicated that alcohol might induce attention deficits in patients with chronic alcoholism.

Keywords: *chronic alcoholism, correlations, attention deficits*

I. INTRODUCTION

In the recent decades, there are increases in proportions of people with chronic alcoholism in many countries in the wold, including Vietnam [1]. According to Vietnam Pychiatric Society, number of people with chronic alcoholism accounts for about 4-5% population. This might induce economic burdens to families and societies. In patients, chronic acoholisminduces not only social acitivities such as their neglect of work or low quality of work but also serious dysfunctions of many organs, such as liver, muscles and so on.

Recently, many studies were conducted to investigate effects of alcohol to brain functions. According to Prof. Cao Tien Duc (2016), attentional and memory deficits are main symptoms in patients with chronic alcoholism [2]. Nguyen Tat Dinh et al (2017) also found that in groups of patients who have higher daily alcohol volume, longer drinking periods and more serious levels of alcolism, levels of attentional and memory dificits were more serious [3]. Hower, all these studies have not prodided direct evidences of correlations between chronic alcoholism and attentional and memory deficits. Thus, the present study was conducted to investigate: *Relations between some clinical characteristics and attentional deficits in patients with chronic alcoholism.*

II. MATERIALS AND METHODS

2.1. Subjects

56 patients with chronic alcoholism (35-60 year olds, mean age: 44,77 ± 6,83) were diagnosed using DSM-V criteria and empoyed in the present study. All patients were inhospital patients treated at Department of Psychiatry, Military Hospital 103 in a period from October, 2016 to June, 2017.

Exclusion criteria included patients with heroin adiction and other substance abuse; patients with serious deseases such as Cirrhosis or liver cancer; patients with traumatic brain injury, stroke or brain tumor;

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patients with other mental disorders such as schizophrenia, depression and patients were more than 60 year olds

2.2. Methods

2.2.1. Study of clinical characteristics of chronic alcoholism

Clinical records were designed to get information to diagnose levels of chronic alcoholism according to DSM-Vcriteria as well as to record information about daily drinking durations, daily alcohol volumes. Patients and their families were required to fill these information into clinical records

2.2.3. Attentional measurements by number sorting tests

Patients were required to rearrage random numbers to gradually increasing numbers. Total attentional scores were total numbers rearraged correctly (Fig 1) [4].

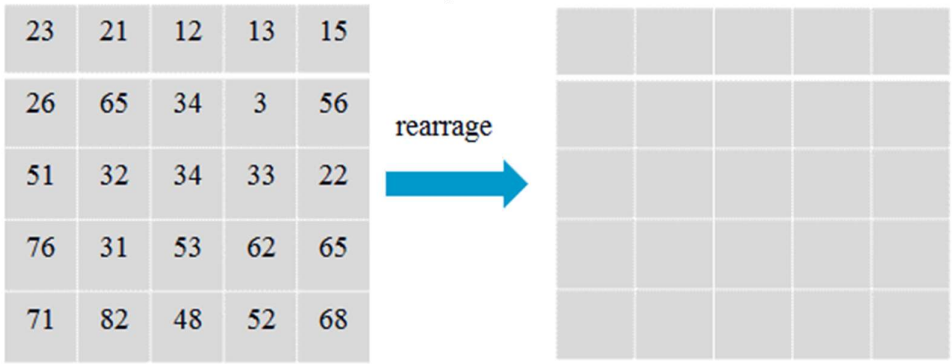

Fig 1. Number sorting test

2.3. Data analysis

Correlations between clinical characteristics and attentinal deficits were analyzed by linear regressionusing SPSS 19.0. Significant corrrelations were defined at p <0,05.

III. RESULTS

3.1. Correlations between drinking durations and attentional deficits

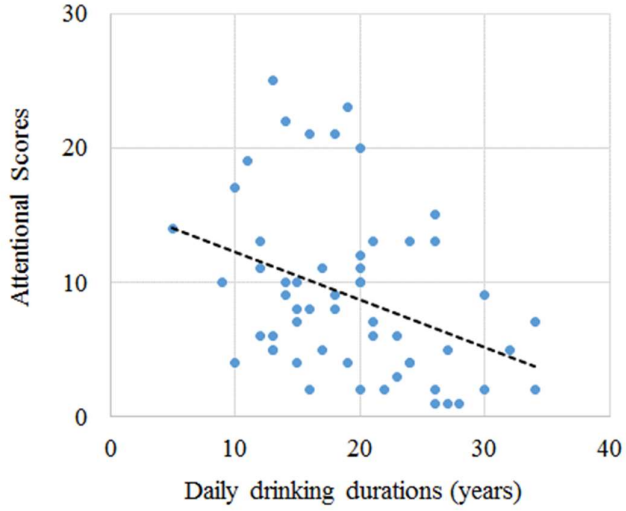

Fig 2. Correlation between drinking durations and attention scores

Result in fig. 2 showed correlations between daily drinking durations and attentional deficits in patients with chronic alcoholism. Result indicated that there was significantly negative correlations between daily drinking durations and attentional deficits (R= -0,375, p<0,01). This result suggested that higher drinking durations, moreserious attentional deficits.

3.2. Correlations between daily volumes of alcohol and attentional dedicits

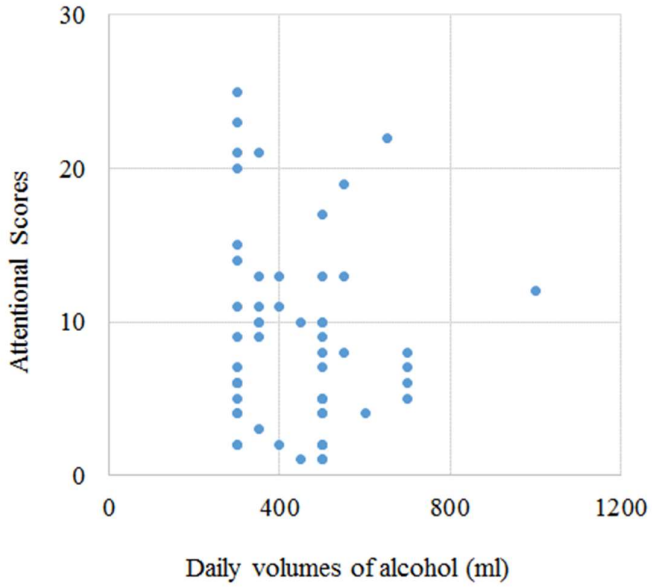

Fig 3. Correlation between daily volumes of alcohol and attentional scores

Fig 3 showed result of correlation between daily volumes of alcohol and attentional dedicits. This result indicated that there were no significant correlations between daily volumes of alcohol and attentional dedicits (R= -0,112, p>0,05). This result suggested that daily volumes of alcohol have less effects to attention in patients with chronic alcoholism.

3.3. Correlations between levels of alcoholism and attentional deficits

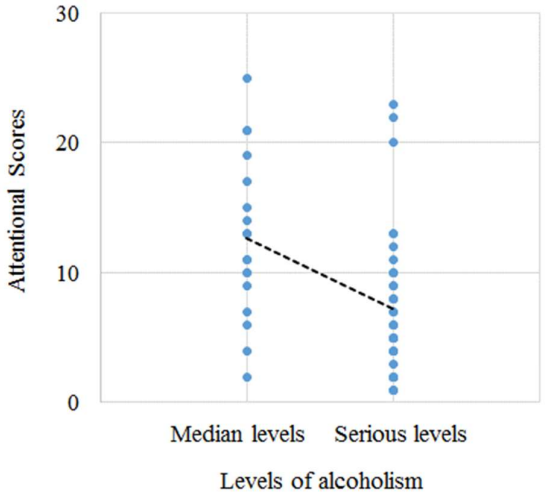

Fig 4. Correlations between levels of alcoholism and attentional scores

Result of fig 4 showed correlations between levels of alcoholism and attentional scores. Results indicated that there was a significantly negative correlation between levels of alcoholism and attentional scores (R= -0,412, p<0,01). This result suggested that more serious levels of alcoholism, more serious attentional deficits.

IV. DISCUSSION

Attentional deficit is one of main disorders in patients with chronic alcoholism. In the present study, we investigated correlations between some clinical characteristics and levels of attentional deficits in patients with chronic alcoholims who were treated in Department of Psychiatry, Military Hospital 103 from October, 2016 to June, 2017. Of clinical charateristics, we chose 3 main ones including daily drinking durations, daily volumes of alcohol and levels of alcoholims. To measure attentional deficits, we used number sorting test. This test has been used in recent studies in the world and Vietnam as well [5]. Our results indicated there were strong correlations between clinical charateristics and attentional deficits. Those are: Daily drinking durations and levels of alcoholims were significantly negatively correlated to attentional scores while there was no correlations between daily volumes of alcohol and attentional deficits. Thus, longer drinking duration and more serious alcoholim, more serious attentional deficits. These results are consistent with previous studies. Prof. Cao Tien Duc indicated that attentional deficit is one of main disorders in patients with chronic alcoholism [2]. Similarly, Nguyen Tat Dinh et al showed that in groups of patients have longer drinking durations and higher daily volumes of alcohol, levels of attentional deficits are more serious [4]. Many authors indicated that attentional deficits might relate to brain damages in patients with alcoholism [6]. Furthermore, in the present study, we did not find a significant correlation between daily volumes of alcohol and attentional deficits. This might relate to patients` abilities of alcohol tolerance.

V. CONCLUSION

In the present study, we analyzed correlations between clinical charateristics and attentional deficits in 56 patients with chronic alcoholism. Our results showed that: there were significantly negative correlations between daily drinking durations, levels of alcoholism (but not daily volumes of alcohol) and levels of attention deficits. This results suggested that alcohol might cause directly attentional deficits in patients with chronic alcoholism.

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RÉSUMÉ:

CORRÉLATIONS ENTRE LES DÉFICITS DE L'ATTENTION ET LES CARACTÉRISTIQUES CLINIQUES DES PATIENTS ATTEINTS D'ALCOOLISME CHRONIQUE

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Objectif: Retrouver les corrélations entre les caractéristiques cliniques des patients atteints d'alcoolisme chronique et les déficits d'attention. **Méthodes:** 56 patients atteints d'alcoolisme chronique traités au Departement de Psychiatrie de l'Hôpital Militaire 103 ont été suivis pour analyse. **Résultats:** La durée consacrée à la boisson, et le degré de l'alcoolisme sont corrélés négativement au déficit de l'attention de façon significative, tandis que le volume journalier d'alcool ingéré ne l'est pas.

Mots clés: *Chronic alcoholism, correlations, attention deficits.*

THE RELATIONSHIP BETWEEN THE PHENOTYPES OF HUMAN LEUCOCYTE CLASS I, II AND THE END-STAGE RENAL DISEASE

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ABSTRACT

Aims: To assess the relationship between HLA class I, II and end-stage renal disease (ESRD). ***Method:*** Retrospective combines a cross-sectional with a comparativestudy from secondary data analysis, in 197 ERSD patients and 194 controls from 2009 to 2017. The phenotype of HLA-A, -B, and DRB1 are detected by multiplex Polymerase Chain Reaction (PCR) - Sequence Specific Primers (SSP). ***Results:*** HLA-B*07, DRB1*10 are the protective factors from ERSD; HLA-B*07 and B*13 are protective factors from ERSD caused by nephritis; HLA-A*11, -B*15, -DRB*12, and -DRB*14 are risk factors with ERSD caused by nephritis. ***Conclusion:*** The phenotype of HLA is related to ERSD.

Keywords: *HLA, end-stage renal disease (ESRD)*

I. INTRODUCTION

The prevalence of chronic kidney failure is significantly increasing in Viet Nam, raising the public health care concern and cost[4,9]. In Viet Nam, there is lacking a national study of chronic kidney failure, most of the reportsare limited in the epidemicregion[4]. According to published research 2017, the prevalence is around 12,7%[8].

Human Leucocyte Antigen (HLA) belongs to Major Histocompatibility Complex (MHC) and located on chromosome 6 (6p21)[3]. The mission of HLA is present the antigen which is peptide fragments in the surface de Lympho T[3,6]. The HLA is classified into two class: class I and class II. HLA class I includes 3 main loci: HLA-A, HLA-B, and HLA-C. HLA class II includes HLA-DP, HLA-DQ, or HLA-DR which is glycopeptide[3]. After the success of the first kidney transplant, the role of HLA was confirmed and applied according to the type of organ transplanted. In the indication of kidney transplantation, the locus HLA-A, -B, and -DR are mainly concerned[3]. Many studies show the relation between HLA phenotypes and pathophysiology of ankylo spondylosis, rheumatoid arthritis, chronic hepatitis, lupus erythematous, hepatic cancer, lung cancer[1,6] and statistical description of ERSD [5-7,9,10]. However, the HLA relating to ESRD is not properly recorded. In this study, we would like to assess the relationship between the alleles of phenotypes HLA-A, -B, and -DRB1 and ESRD.

II. OBJECTS AND METHODOLOGY

2.1. Objects:

There were 197 patients with kidney transplantation indication due to kidney failure and 194 donors who were healthy volunteering and brain death from 1/2009 to 1/2018 in the Military Hospital 103 and The Military Center Hospital 108. The general information of patients is described in Table 1.

2.2.Study design:

Retrospective and prospective, cross-sectional and controlled study.

Secondary data analysis based on collecting non-continuously from 103

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hospital and Military center hospital 108. The patient and donor profiles were copied: age, sex, the causes of renal failure, and phenotypes of HLA. All data were collected by one doctor who does not involve data analysis. The general information of objects is described in Table 1.

2.3. Method to identify of HLA:

HLA typing is detected by multiplex Polymerase Chain Reaction (PCR) - Sequence Specific Primers (SSP). Morgan TM HLA SSP kit (TBG Biotechnology Corp, America) and TBG software were applied to identify locus HLA-A, -B, -DRB1 according to the producer.

2.4. Data analysis:

The allele HLA is indicated whether at least one of two-locus is positive. The patients information is presented with frequency (n), and percentage (%). Age is presented with an average value and deviation standard. The relationship of HLA and chronic kidney disease is indicated by relative risk (RR) and confidence interval (CI 95%). The p-value is evaluated by Chi and Fisher test, and statistical significance if $p < 0.05$.

III. RESULT

Table1: General informationabout objects

General characteristic	ERSD (n=197)	Controls (n=194)
Sex (male/female, %)	147/50 (75.0)	112/82 (57.7)
Average age (years)	37.8 ±11.8	39.0 ± 11.8

The prevalence of male in ERSD is higher than in control (75.0% and 57.7%). There was no significant difference in age between two groups.

Table 2: The distribution of allele HLA-A, -B, and -DRB1 of the objects (n=391)

Allele	Percentage (%)	Allele	Percentage (%)	Allele	Percentage (%)
Phenotypes HLA-A (13 alleles)					
A*01	5.9	A*24	27.6	A*33	20.7
A*02	41.4	A*26	4.3	A*34	2.6
A*03	3.8	A*29	15.9	A*68	1.3
A*11	50.4	A*30	3.8	A*74	1.0
A*21	0.3				
Phenotypes HLA-B (24 alleles)					
B*07	18.4	B*38	13.6	B*52	2.3
B*08	0.8	B*39	4.3	B*55	3.6
B*13	11.0	B*40	12.0	B*56	0.8
B*15	49.6	B*41	0.5	B*57	4.1
B*18	2.3	B*44	4.9	B*58	14.1
B*27	4.6	B*46	20.2	B*61	0.3
B*35	10.2	B*48	2.0	B*73	0.5
B*37	1.0	B*51	4.9	B*95	0.3
Phenotypes HLA-DRB1 (24 alleles)					
DRB1*01	1.5	DRB1*09	18.7	DRB1*13	8.2
DRB1*03	12.3	DRB1*10	16.1	DRB1*14	10.2
DRB1*04	17.9	DRB1*11	3.8	DRB1*15	17.9
DRB1*07	10.2	DRB1*12	50.4	DRB1*16	4.1
DRB1*08	8.2				

There are 13 alleles HLA-A, and 24 alleles HLA-B, and 13 HLA-DRB1. In these alleles: A*11 and A*02 (50.4% and 41.4%); B*15 and B*46 (49.6% and 20.2%); and DRB1*12 and DRB1*09 (50.4% and 18.7%) are the most frequent alleles.

Table 3: The relationship between phenotypes HLA class I, II and ERSD patients (only p<0.05 presented here)

HLA	ERSD patients (n=197)		Controls (n=194)		p	RR	CI 95%
	n	%	n	%			
B*07	26	13.2	46	23.7	0.007	0.67	0.49 to 0.93
DRB1*10	24	12.2	39	20.1	0.033	0.72	0.52 to 0.99

People who have alleles HLA-B*07 and HLA-DRB1*10, have a lower risk of ESRD than the others (RR=0.67; CI 95%: 0.49 to 0.93, p<0.05 and RR=0.72; CI 95%: 0.52 to 0.99, p<0.05 respectively).

Table 4: The relationship between phenotypes of HLA and ESRD caused by nephritis (only p<0.05 presented here)

HLA	ERSD caused by nephritis (n=149)		Control (n=187)		p	RR	95%CI
	n	%	n	%			
A*11	84	56.4	83	44.4	0.029	1.31	1.03 to 1.67
B*07	21	14.1	45	24.1	0.022	0.67	0.46 to 0.97
B*13	10	6.7	27	14.4	0.025	0.58	0.34 to 0.999
B*15	83	55.7	83	44.4	0.039	1.288	1.011 to 1.641
DRB1*12	86	57.7	87	46.5	0.041	1.286	1.007 to 1.643
DRB1*14	23	15.4	15	8.0	0.033	1.43	1.07 to 1.91

People who have alleles B*07 and B*13 have a higher prevalence of ESRD caused by nephritis than the others 33% and 43% respectively. People who have HLA-A*11, HLA-B*15, DRB1*12, DRB1*14, have a higher risk of ESRD than those without these alleles 31%, 28.8%,and 43% respectively.

Table 5: The relationship between phenotypes of HLA and ESRD caused by hypertension (only p<0.05 presented here)

HLA	ESRD caused by hypertension(n=19)		Controls (n=187)		p	RR	95%CI
	n	%	n	%			
B*52	2	10.5	3	1.6	0.016	4.73	1.74 to 15.18
B*57	5	26.3	5	2.7	0.0001	7.00	3.15 to 15.57

People with HLA-B*52 or-B*57 has a higher prevalence of ESRD caused by hypertension RR = 4.73 and 7.00 respectively.

IV. DISCUSSION

The frequencies of alleles class I (HLA-A and HLA-B) and class II (HLA-DRB1) are similar with the results of Le Xuan Hai et al in 761 Kinh ethnicity[2].

In this study, there is no significant difference between the proportion of ESRD patients with alleles HLA and the control. Some studies showed that HLA-A*26 and A*28 are protective factors with ERSD[7,10]. A cohort study in Taiwan and Turkey also proved no relation between HLA-A and ESRD[6,9]

In the alleles located in locus HLA-B, the patients with HLA-B*07 and HLA-DRB1*10 have higher risks of ERSD than those without these alleles 33.0% and 22.8% respectively. Many studies show that the prevalence of some alleles is lower significantly than the others such as: B*39, B*50[7], B52, B*58[9]. However, the population with allele B*08 in Kuwaiti [10], and B*15, B*18, B*49 in Arab Saudi[7] have higher risks of ESRD than the control. The result from Kuwaiti shows the protective effect of DR*11 with ESRD[10].

This study also evaluates the relationship of phenotypes of HLA and the causes of ESRD such as nephritis, hypertension, and diabetes. The present study shows that alleles B*07 and B*13 are protective factors for ESRD caused by nephritis, the rates are lower 33% and 43%. A study in Taiwan proved gene DR*08 is a protective factor with ESRD[6]. It also showed the other alleles which are risk factors for ESRD caused by nephritis: HLA-A*11, HLA-B*15, DRB1*12, DRB1*14. Population with these genes has a higher risk of ESRD caused by nephritis than the one without HLA-A*11 31%, HLA-B*15 28.8%, HLA-DRB1*12 28.6% and HLA-DRB*14 43%. A study in China proved that the prevalence of ESRD caused by nephritis patients, HLA-A*11 positive is significantly higher than the ones without[5].A study in Arab Saudi has the same result with this study: HLA-B*15 is the risk factor with nephritis RR=2.59 (95%CI: 1.26 to 5.29)[7]. A study in Turkey also proved that population with HLA-DRB1*12 also have a higher prevalence of ESRD than the control (8.3% and 3.2% respectively, p=0.028)[9]. Other phenotypes of HLA are confirmed as the risk factor for ESRD in many studies such as: Arab Saudi B*18, B*49[7]; Turkey B*40; DRB*12; CW*04, DQB1*03[9]; Kuwaiti B*8[10]; Taiwan DR*3 and DR*11[6]; and China B*55, B*54, B*40, DRB1*04[5].

In the relationship between the phenotypes of HLA and ESRD caused by hypertension, the population with HLA-B*52 and -B*57 of ESRD is significantly higher than the control $p<0.05$. However, the conclusion from Turkey study shows the contrast[9]. Nevertheless, the amount of hypertensive patients in this study is not enough to conclude.

The relationship between the phenotypes of HLA and ESRD caused by diabetes mellitus was also investigated. However, there was no relationship found. The reason could be the number of patients not enough.

V. CONCLUSION

The phenotypes of HLA class I and II and ESRD have a significant relationship. This analysis used small population case and control data set and the results of our study should be confirmed in further investigations.

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RÉSUMÉ:

RELATIONS ENTRE LES PHÉNOTYPES DE LEUCOCYTES HUMAINS CLASSE I, II ET LE STADE TERMINAL DE LA MALADIE RÉNALE

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Objectifs: Évaluer les relations entre le HLA de classe I, II et l'insuffisance rénale chronique terminale (IRT). **Méthode:** Une étude rétrospective transversale et comparative de l'analyse des données secondaires a été réalisée, chez 197 patients IRCT et 194 contrôlés de 2009 à 2017. Le phénotype de HLA-A, -B et DRB1 ont été détectés par multiplex Polymerase Chain Reaction (PCR)-Les amorces spécifiques de séquence (SSP). **Résultats:** HLA-B*07, DRB1*10 avaient les facteurs de protection de l'IRCT; HLAB*07 et B813 avaient des facteurs protecteurs de l'IRCT causés par une néphrite; HLA-A*11, -B*15, -DRB*12 et DRB* 14 avaient des facteurs de risque d'IRCT causés par une néphrite. **Conclusion:** Le phénotype de HLA est lié à IRCT.

Mots clés: *HLA (Human leucocyte antigen ou antigène leucocytaire humain), insuffisance rénale chronique terminale (IRCT).*

ABSENT LEFT MAIN CORONARY ARTERY: A CASE REPORT AND MEDICAL LITERATURE REVIEW

Le Duc Nam*, Nguyen Quoc Dung*

ABSTRACT

Absent left main coronary artery (Absent LMCA) is a rare congenital cardiacvascular with very less described. Diagnostic still depend on digital substration angiography (DSA) and operated. Nowadays, multi detector computerized tomography (MDCT) has made this abnormal diagnosis easier without intrusion. We would like to introduce a case of a 80-year-old male patient, who had been hospitalized for unstable chest pain, computerized tomography 256 rows of coronary arteries that detected left anterior descending artery (LAD) and left circumflex (LCX) comes directly from the left Valsalva sinus and did not seen LMCA.

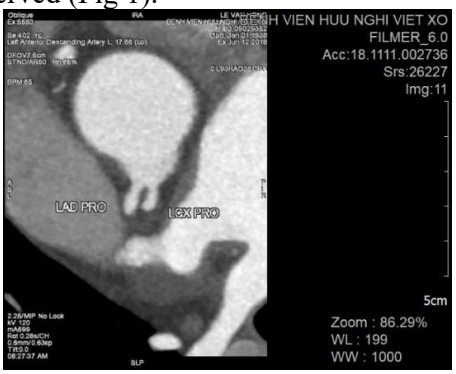
Keywords: *Absent left main coronary artery, anomalus congenital cardiacvascular, multi detector computer tomography (MDCT).*

I. INTRODUCTION:

LMCA comes from left coronary sinus, 5mm and 10mm long, runs to the left side of heart and posterior to the main pulmonary artery, it branches into left anterior descending (LAD) and the left circumflex artery (LCx) [**1**]. Absent LMCA is origins coronary artery anomalous, in which LAD and LCx are separated from the left coronary sinus. Previously, the diagnosis of absent LMCA was based on DSA and operation. However, nowadays the MDCT can be used for detecting this anomalous more easily because it is non - invasive and gives clinician has an overview before the treatment.

II. CASE REPORT:

A 80-year-old male patient, with a healthy history, went to our hospital with atypical chest pain, which had started in about 1 year. Biochemical tests, blood and urine test values were within normal limits. An 256 slices - MDCT coronary angiography was indicated. Axial, MIP, VR images on MDCT 256 slices show the LAD and LCx arteries are separated from the left sinus of Valsalva, absent LMCA. The coronary artery system was not observed (Fig 1).



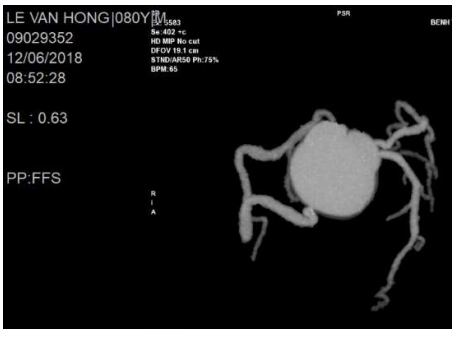


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Fig 1: 256 Slices - MDCTA with 3D volume rendering show the LAD and LCx arteries is separated from the left sinus of Valsalva, absent LMCA

III. DISCUSSION:

Coronary artery anomalies include abnormalities of the origin, course, structure and terminal of the epicardial coronary arteries. According to the statistics, an anomalous of coronary artery is in about 0,6-1,3 of population, anomalous of LMCA origins is about 0,02 to 0,07%. [1]. Absent LMCA is rare, which incidence is account for about 0,41% of origin LMCA anomalous, the LAD and LCx coronary artery arising separated from left coronary sinus [2-3-4].

According to our research, there has been no large amount of statistics for absent LMCA in medical literature, in which most of them are reported cases or group of cases. Age is not yet generalized; these abnormal reports are all over the age of 50. However, the incidence of anomalous LMCA in infancy is higher than the incidence in adults because patients with LMCA arising from the pulmonary trunk may have died in infancy [2-6-7]. The gender statistics was not reported.

Patients with this abnormality are usually asymptomatic, some patients experience chest pain but may not be related to this anomalous [**3].** Detecting for LMCA anomalous and absent LMCA are important because these can cause myocardial infarction, but only in case reports [**6**].

Gold standard diagnostics for absent LMCA based on DSA or cardiac surgery. However, DSA is an invasive procedure, needed some experience, and only applied when the patient needs indicating for coronary artery intervention. The limitations of DSA in assessing the pathway and anatomical correlation with major blood vessels have been addressed by multiband antiretroviral or magnetic resonance especially MDCT 64 slices and 256 slices are recommended as the methods for the detection of coronary congenital abnormalities [**2-3-5**].

Yamanaka reported 1.3% incidence of coronary artery abnormalities in 126,595 patients with DSA. Graidis study and Dragana study detected with the incidence from 2,3 to 2,8%[**2-5**]. With the rise in the use of coronary CT angiography (CTA), the number of incidentally found this anomalous has been increasing.

The advantage of MDCTA has non - invasive and having a short time for acquisition, wide availability, and relatively high spatial resolution. Images of MDCTA with multiplanar reconstruction and 3D volume rendering detect cardiac and coronary anatomy and the surrounding structures. MDCTA are findings the anomalous of the coronary artery origin, course, communications, and termination

from any projection angle and thus are considers for planning intervention. The coronary artery course and the surrounding structures relation are difficult to determined base on coronary artery DSA [4-5].

Common weak point MDCTA is the high - dose of radiation, however it can be decrease from 50 to 80%, based on new technique of 256 slices - MDCTA.

IV. CONCLUSION:

MDCTA with multiple reconstructions and 3D volume rendering is non - invasive, have high value for diagnosis an abnormal LMCA origins and absent LMCA. Understanding surrounding structures relation can be beneficial for planning treatments.

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RÉSUMÉ:

ABSENCE D'ARTÈRE CORONAIRE GAUCHE : UN RAPPORT ET REVUE DE LA LITTÉRATURE MÉDICALE

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L'absence de l'artère coronaire gauche principale (ACG) est une cardiopathie congénitale plutôt rare et dont la description est moins bien détaillée que pour les autres cardiopathies. Le diagnostic en était fait par l'angiographie de soustraction digitale, actuellement, il est nettement amélioré par un simple procédé: La tomographie par ordinateur à détecteurs multiples (TODM). Nous présentons ici un patient de 80 ans, admis à l'hôpital pour douleurs thoraciques atypiques, la TODM à 256 coupes retrouve l'IVA, la Cx gauche, mais la CG est absente.

Mots clés: *L'absence d'artère coronaire gauche, anomalie congénitale cardiovasculaire, tomographie par ordinateur à détecteurs multiples.*

EFFECTS OF SITAGLIPTIN AS ADD ON BLOOD GLUCAGON LEVEL IN PATIENTS WITH TYPE 2 DIABETES

Le Thi Viet Ha*, Doan Van De**

ABSTRACT

Objectives: To evaluate effects of Dipeptidyl Peptidase (DPP)-4 Inbibitors Sitagliptin as add-on blood glucagon in patients with type 2 diabetes inadequately controlled with oral antidiabetic drug (OAD) monotherapy or combination. ***Subjects and methods:*** An intervention study was conducted in 101 patients with adult type 2 diabetes inadequately controlled with OAD monotherapy or combination other than DPP-4 inhibitors with HbA1c from 7 to 10%. The outcome measures were fasting plasma glucose (FPG), 2 hour postprandial glucose (2hPPG) and HbA1c that were assessed at the baseline, after 12 were fasting plasma glucagon that were assessed at the baseline, after 12 weeks. A DDP-4 inhibitor was started with a half or full dose for the first 12 weeks and could increased to full dose for the last 12 weeks if started as half dose. The other OAD and their doses were kept unchainged during the whole study. ***Results:*** The mean age and diabetes duration was 54.1 ± 10.1 and 2.4 ± 3.4 years, respectively. Before the study start, metformin monotherapy was used by 60.4% of patients, and the most used combination was metformin plus sulfonylurea (39.6% all the patients). Sitagliptin was the only used DPP-4 inhibitor with mean dose of 88.1mg/day and 86.6mg/day for the first and second 12 weeks. After 12 weeks, compared the baseline, the mean fasting plasma glucagon that decreased by 13.63 pg/ml, respectively (p < 0,001), and the proportions of patients achieving ADA 2015 FPG, 2hPPG and HbA1c targets significantly increased from 18.8%, 11.9% and 0% to 69.3%, 78.2% và 69.3%, respectively (p<0.001) the duration of the intervention was 12 weeks. ***Conclusions:*** The add-on of the DPP-4 inhibitor Sitagliptin in patients with type 2 diabetes inadequately controlled with metformin alone or OAD combinations resulted in improvements of glycemic control for a period of 12 weeks.

Key words: *Type 2 diabetes, Dipeptidyl Peptidase Inhibitor, blood glucagon plasma.*

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I. INTRODUCTION

Number of type 2 diabetes is increasing all over the world, especially in developing countries. It causes numerous severe complications in almost all body organs and systems, in particular eyes, kidneys, nerves, heart and blood vessels. Type 2 diabetes has multiple pathophysiologic defects. Beside the long well known defects such as insulin resistance, beta cell failure and increased hepatic glucose production, relatively new defects have been discovered some of which are incretin defects and inappropriately increased glucagon secretion. Multiple pathophysiologic defects and progressive beta cell failure results in failure of even multiple old OAD combinations in long run. It is necessary to develop new antidiabetic drug classes that aim at these new defects and complement the old OADs effects. One of the new OAD classes is Dipeptidyl peptidase (DPP-4) inhibitors that prolong endogenous incretins that are rapidly inactivated by that enzyme. Incretins are gut hormones secreted in response to nutrients (maily carohydrate). There are two incretins:

glucagon like peptide (GLP) - 1 and glucose-dependent insulinotropic peptide (GIP). They simulate insulin release and supress glucagon release in response to a meal in a glucose-dependent manner, slow gastric emptying and enhance satiety. Add-on of DPP-4 inhibitors to ongoing different OAD monotherapy or combinations have been shown to improve blood glucose control in numerous studies abroad, but has not been studied in Vietnam. The present study aims at evaluating effects of DPP-4 inhibitors sitagliptin as add-on therapy on but glucose level in patients with type 2 diabetes inadequately controlled with oral antidiabetic drug (OAD) monotherapy or combination in National Hospital of Endocrinology.

II. SUBJECTS AND METHODS

2.1. Subjects are patients with type 2 diabetes diagnosed by the ADA 2015 criteria and inadequately controlled with OAD(s).

2.1.1. Inclusion criteria

+Patients Type 2 diabetic patients who were treated for diabetes mellitus by oral hypoglycaemic or combination non-DPP-4 combination therapy were given stable doses over 3 months and failed to achieve glycemic control.

+ The standard has not met the target based on GM from 7 mmol /l to ≤ 16 mmol / l and has HbA1C from 7.0% to ≤ 10%.

+ No anemia; age of 30 years or above; Agree to participate in research

2.1.2. Exclusion criteria

+ Over 30 years old.

+ Currently identified as healthy people based on histry, physical examination and basic biochemical tess

+ No risk factors; FPG, HbA1C normal

+ Agree to participate in research.

2.2. Methods

2.2.1. Study design: This was an uncontrolled trial evaluating effects on blood glucose of DDP4 inhibitors added to other oral antidiabetic drug monotherapy or combination in patients with type 2 diabetes who had not reach HbA1c target of below 7,0%.

Oral antidiabetic drugs and their dosage remained unchanged throughout the follow-up period. Sitagliptin, a DPP-4 inhibitor, is supplemented with a starting dose of 50 or 100 mg once a day. In cases where the dose is increased to 100 mg per day at week 12 if HbA1c remains above 7.0%, if hba1c is less than 7.0%, the dose should be reduced to 50 mg. Intervention time is 12 weeks.

2.2.2. Sample collection: All the patients who met the inclusion and exclusion criteria were recruited into the study.

2.2.3. Outcomes measures

The patients' baseline characteristics that were assessed included age, sex, BMI, diabetes duration, use of oral diabetic drugs, and blood glucose control indices (FPG, 2hPPG and HbA1c). The three last measurements were reassessed at weeks 12 and 24.

- The American Diabetes Assosiation (ADA) 2015 targets of blood glucose control were as follow: FPG: 4.4 - 7.2 mmol/L; 2hPPG: < 10 mmol/L; HbA1c < 7.0%.

2.4. Statistical analysis: SPSS version 20.0 was used for data analyzing. The effects of adding DPP-4 inhibitors on blood glucagon were evaluated by comparing the blood glucagon control indices in weeks 12 at baseline by using fraired T-test, and the rates of achieving blood glucose control targets at those points of time.

III. RESULTS

3.1. Patients baseline characteristics

A total of 101 eligible patients with type 2 diabetes participated in the study, including 48 men (47.5%) and 53 women (52.5%).The mean age was 54.1 ± 10.1 years. Most patients were in age range from above 30 to 79 years, Age group 50-59 years old accounts for 40.6%.The mean diabetes duration (defined as time period elapsed since diabetes was diagnosed) was 2.4 ± 3.4 years. Most patients had diabetes for less than 5 years (84.1%). Before the intervention at baseline, all the patients were on oral antidiabetic drug(s) only (no patient was on insulin). Metformin monotherapy was used by 60.4% and metformin and sulfonylurea combination by 39.6% of the patient. The mean FPG, 2hPPG and HbA1c was 8.62 ± 1.67 mmol/L, 12.36 ± 2.36 mmol/L and 7.93 ± 0.83%, respectively.

3.2.Baseline blood glucagon indices

Table 3.1. Mean of blood glucagon indices control and Diabetic

Blood glucagon indices (n = 30)		Control (n=30)	Diabetis (n=30)	p
Glucagon (Pg/ml)	($\overline{X}$ ± SD)	34.29 ± 4.41	70.86 ± 12.73	< 0.001
	Upper limit ($\overline{X}$ - SD	29.88		
	Decread (<29.88)	4 (13.3%)	0 (0.0%)	< 0.001
	Nomal (29.88-38.70)	22 (73.3%)	0 (0.0%)	
	Incread (>38.70)	4 (13.3%)	30 (10.0%)	

The mean glucagon was 70.86 ± 12.73 pmol/ml, increased to 100.0%

3.3.Correlation between FPG, PPG, HbA1C with blood glucagon

Table 3.2. Correlation between FPG, PPG, HbA1C with blood glucagon indices baseline

Indices (Y)	Correlate	r	P
FPG (mmol/l)	Y = 4.982X + 26.818	0.682	< 0.001
2hPPG (mmol/l)	Y = 2.564X + 36.969	0.498	< 0.01
HbA1C (%)	Y = 10.1X - 6.316	0.568	< 0.01

Fasting plasma glucagon atry initialization priority, the level, respectively with FPG, 2hPPG, HbA1C at the beginning.

3.4. Effects of adding DPP-4 inhibitors on blood glucose

Table 3.3. Changes of blood glucose indices and fasting plasma glucagon at week 12 compared with baseline

All bn use blood glucose blood before the last gen saved and not changed in the research of the time, All the patients use sitagliptin with 50 mg or 100mg per day

Blood glucose indices	Baseline	Week 12	Changes	p
FPG (mmol/l)(n=101)	8.62 ± 1.67	6.92 ± 1.69	-1.70 ± 2,06	< 0.001
2hPPG (mmol/l)(n=101)	12.36 ± 2.36	9,56 ± 1.19	-2.80 ± 2.26	< 0.001
HbA1C (%)(n=101)	7.93 ± 0.83	6.72 ± 0.86	-1.21 ± 0.86	< 0.001
Glucagon (pg/ml)(n=30)	70.86 ± 12.73	57.23 ± 14.76	-13.63 ± 9.60	< 0.001

Note: Values are mean ± SD

Compared with the baseline values, the mean FPG, 2hPPG and HbA1c at week 12 decreased by 1.70 ± 2.06 mmol/L, 2.80 ± 2.26mmol/L and 1.21

Compared with the baseline values, the mean glucagon at week 12 decreased by -13.63 ± 9.60 pg/ml, significant with p < 0.001.

3.5. ***Correlation between FPG, PPG, HbA1C with blood glucagon at the 12 week***

Table 3.4. Correlation between FPG, PPG, HbA1C with blood glucagon indices at the 12 week

Indices (Y)	Correlate	r	P
FPG (mmol/l)	Y = 5.513X + 19.062	0.763	< 0.001
2hPPG (mmol/l)	Y = 4.577X + 12.573	0.496	< 0.01
HbA1C (%)	Y = 8.708X + 1.181	0.454	< 0.05

Fasting plasma glucagon atry initialization priority, the level**,** respectively with FPG, 2hPPG, HbA1C at the 12 week**,** respectively, all reductions were statistically significant.

Table 3.5. Intercontated between blood glucagon at the changed with FPG, PPG, HbA1C after 12 weeks

Indices (Y)	Correlate	r	p*
FPG (mmol/l)	Y = 3.47X + 7.681	0.729	< 0.001
2hPPG (mmol/l)	Y = 0.766X + 11.681	0.215	> 0.05
HbA1C (%)	Y = 3.555X + 10.078	0.345	> 0.05

Intercontated between blood glucagon at the changed with FPG, 2hPPG, HbA1C after 12 weeks that lower glucagon huyết thanh level changed in the following after 12 week compatibility level, that the following the FPG change the following the following 12 weeks after the following but that are no match that that that that that that the 2hPPG and HbA1C is changed to match.

IV. DISCUSSIONS

1. Baseline patients' characteristics

That increased overweight or obese prevalence in patients with type 2 diabetes may reflect the tendency in our general population over time. Most patients had short duration of diabetes with 84.1% having diabetes less than 5 years. Only small proportion of patients had diabetes for more than 10% (5%). The baseline mean FPG, 2hPPG, HbA1c was 8.62 mmol/L, 12.36 mmol/L, 7.93%, respectively. Most patients did not achieved ADA 2015 PFG and 2hPPG targets that were 81.2% and 88.1%, respectively. All the patients had baseline HbA1c > 7%.

Most patients in our study were outpatients so their blood glucose control was better than in the hospitalized patients participating in other studies in Vietnam. In a study by Nguyen Thi Ho Lan in the hospitalized type 2 diabetes patients at National Hospital of Endocrinology (NHoE) the baseline mean FPG and HbA1c was 12.1 mmol/L and 9.8%; in a study by Nguyen Thi Duyen in hospitalized patients with type diabetes the mean FPG and HbA1c was 10.32 mmol/L and 9.29%, respectively [1],[2].

2. Use of OAD during the study

Before the intervention at baseline, all the patients were on oral antidiabetic drug(s) only (no patient was on insulin). Metformin monotherapy was used 60.4% and metformin and sulfonylurea combination 39.6% of the patient.

3. Correlation between FPG, PPG, HbA1C with fasting plasma glucagon baseline

We found that the correlation between fasting plasma glucagon and fasting plasma glucose and HbA1C in the initial group of patients, the initial fasting plasma glucagon correlated well with the severity, which was statistically significant with blood glucose at hunger. This result suggests that fasting blood glucagon may be one of the factors that contribute to hyperglycaemia.

This study is not similar to the authors:

In the control group Nguyen Thi Duyen, serum glucagon concentration was moderately correlated with glucose concentration, r = 0.336, p <0.05. In the diabetic group, there was no statistically significant correlation between fasting serum glucose concentrations and glucose concentrations (p> 0.05).

Taborsky GJ et al. (2010) study on the physiologic effect of glucagon: when increasing endogenous glucagon levels increases glucose production from the liver, primarily by the glucose-degrading pathway, eg (10pg/ml) endogenous glucagon will increase glucose production from the liver by about 25%. Thus, glucagon excretion within the physiological limits is responsible for controlling glucose production within the physiological limits of the body

Because the blood glucose group higher than the control group, High blood glucose levels may indicate elevated glucagon secretion, not only when hungry but also after meals. This may explain the association between fasting glucagon and postprandial glucose as well as HbA1C.

4. Effects of add-on of DPP-4 inhibitors on blood glucose

All bn use blood glucose blood before the last gen saved and not changed in the research of the time. In our study the add-on of sitagliptin to the patients who were already on other OAD monotherapy or combinations their blood glucose control substantially improved with significant reductions of the mean FPG, 2hPPG and HbA1c, and high proportion of the patients achieved blood glucose indices targets. After 12 weeks, compared with the baseline, FPG, 2hPPG and HbA1c significantly decreased by 1.7 ± 2.06 mmol/L, 2.8 ± 2.26 mmol/L and 1.21 ± 0.86%, respectively, compared with the baseline values. Compared with the baseline values, the mean glucagon at week 12 decreased by -13.63 ± 9.60 pg/ml, significant with p < 0.001.

Concerning the blood glucose targets achievement, at week 12, about two thirds of the patients achieved ADA 2015 targets of FPG, 2hPPG and HbA1C. At week 12, 69.3%, 70.3% and 61.4% of the patients achieved the targets of FPG, 2hPPG and HbA1c, respectively. Those were substantial increases compared with the baseline when the proportions of the patients achieving the targets were only 18.8%, 11.9% and 0%, respectively.

Numerous randomized control trials have proved that sitagliptin add-on to other OAD

monotherapy (mainly metformin) or combinations improved glycemic control compared with placebo in type 2 diabetes patients not achieving blood glucose targets.

Charbonnel et al studied effects of sitagliptin add-on (100 mg/day) to ongoing metformin monotherapy (≥ 1500mg/day) in type 2 diabetes patients with mean HbA1c of 8% compared with continued metformin monotherapy alone [3]. After 24 weeks FPG and HbA1c in the sitagliptin add on group significantly decreased by 1.4 mmol/L and 0.65% (both p values < 0.001), respectively, compared with those indices in the metformin monotherapy group. A significantly greater proportion of patients achieved an A1C<7% with sitagliptin (47.0%) than with placebo (18.3%).

In a study by Chien et al [7], Taiwanese type 2 diabetes patients (n = 97) were randomized to receive the existing OAD combinations or add-on with sitagliptin (100 mg daily) for 24 weeks. Compared with the change of 0.0% (95% confidence interval: -0.6% to 0.5%) from a baseline of 10.0% in the controlled arm, HbA1c change from a mean baseline of 9.5% was -1.14% ± 1.18 after add-on sitagliptin (p< 0.0001).

In randomized controlled trials that compared combination of sitagliptin and metformin with metformin or sitagliptin monotherapy as initial OAD therapy, the former resulted in clearly better glycemic control than the latter.

Williams-Herman et al [8] compared different sitagliptin and metformin combinations with sitagliptin or metformin monotherapy in type 2 diabetes drug-naïve patients in a 54 week multinational study. At week 54, the HbA1C reduction was highest in the combination with high metformin dose (S100/M2000mg/day), -1.8%, followed by the combination with low metformin dose (S100mg/M1000mg/day),-1.4%, monotherapy with higher metformin dose (M2000mg/day),-1.3%, monotherapy with low metformin dose (M1000mg/day), - 1.0% and monotherapy with sitagliptin (100mg/day), - 0,8%. Similarly, the proportions of patients with an HbA1c < 7% at week 54 were 67%, 48% (S100/M1000), 44%, 25% and 23%, respectively. The extents of effects of adding sitagliptin to existing OAD(s) therapy or those of combinations of sitagliptin and metformin compared to metformin or sitaglitin monotherapy are different from study to study because patients' characteristics varied from study to study. However, the improvement of glycemic control after adding sitagliptin to existing OAD(s) or better glycemic control of sitagliptin combinations compared with metformin or sitagliptin monotherapy have been proved. The mechanisms of action of DPP-4 inhibitors are different from those of other OAD classes such as biguanide, sulfonylureas and alpha-glucosidase inhibitors. This explains additional effects of adding DPP-4 inhibitors to the other OADs on glycemic control.

5. Correlation between FPG, PPG, HbA1C with fasting plasma glucagon at the 12 week

In our study, fasting plasma glucagon concentrations were strongly correlated with fasting plasma glucose, postprandial and HbA1C levels prior to treatment with DPP-4 inhibitor. After 12 weeks of supplementation with DPP-4 inhibitors, these correlations

were also noted: fasting serum glucagon concentrations were statistically significantly correlated with fasting plasma glucose, Postprandial blood glucose and HbA1C. Increased levels of fasting blood glucagon also reflect elevated glucagon secretion, both at the time of hunger and after meals in patients with type 2 diabetes. This suggests that glucagon secretion contributes to hyperglycemia, both after fasting and mean blood glucose levels through HbA1C. Moreover, after 12 weeks of treatment with DPP-4 inhibitor, there was a positive correlation between fasting plasma glucagon changes and fasting plasma glucose change. This adds to the evidence that a decrease in glucagon concentration by inhibiting DPP-4 enzymes may be a contributing factor to fasting plasma glucose. However, after 12 weeks there was no statistically significant correlation between fasting plasma glucagon changes with postprandial glucose change and HbA1C change. This may be due to increased insulin secretion due to the effects of DPP-4 inhibitor play a key role in postprandial and postprandial hypoglycemia.

V. CONCLUSIONS

The add-on of the DPP-4 inhibitor Sitagliptin in patients with type 2 diabetes inadequately control with metformin alone or OAD combinations resulted in substantial improvements of glycemic control for a period of 12 weeks. After 12 weeks, compared the baseline, the mean FPG, 2hPPG and HbA1c significantly decreased by 1.70 mmol/L, 2.80 mmol/L and 1.21%, Compared with the baseline values, the mean glucagon at week 12 decreased by -13.63 ± 9.60 pg/ml, respectively ($p < 0.001$ for all), and the proportions of patients achieving ADA 2015 FPG, 2hPPG and HbA1c targets significantly increased from 18.8%, 11.9% and 0% to 69.3%, 70.3% and 61.4%, respectively, with $p < 0.001$.

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RÉSUMÉ:

LES EFFETS DU SITAGLIPTINE JOUANT LE RÔLE DE GLUCAGON SURAJOUTÉ CHEZ LES PATIENTS AVEC DIABÈTE TYPE 2

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Objectifs: Évaluer les effets de l'inhibiteur du Dipeptidyl Peptidase (DPP)-4 Sitagliptin jouant le rôle de Glucagon surajouté chez les patients avec diabète type 2 mal contrôlé avec un antidiabétique oral utilisé seul ou en combinaison avec un autre produit.

Sujets et méthodes: L'étude est conduit chez 101 patients avec diabète type 2 adulte mal contrôlé avec un antidiabétique oral en monothérapie ou en combinaison avec un autre produit autre que les inhibiteurs et dont l'HbA1c est de 7 à 10%. Les mesures prises étant le Glucose du plasma à jeun (FPG), le Glucose 2 heures après repas (2hPPG) et l'HbA1c (déjà prise dès le commencement). Un inhibiteur du DDP-4 est commencé à moitié la dose ou en pleine dose pour les 12 premières semaines. Si la dose de l'inhibiteur du DDP-4 était la moitié, elle peut être augmentée à pleine dose pour les 12 semaines suivantes. L'autre produit antidiabétique ainsi que l'antidiabétique oral déjà donné sont inchangés.

Résultats: L'âge moyen ainsi que la durée du diabète ont été 54.1 ± 10.1 et 2.4 ± 3.4 années, respectivement. Avant l'étude, la monothérapie à la Metformine a été utilisée par 60.4% de patients, et la combinaison la plus utilisée étant Metformine + Sulfonylurée (39.6% de patients). La Sitagliptine a été le seul inhibiteur de DPP-4 à la dose moyenne de 88.1mg/jour et 86.6mg/jour pour les 12 premières et secondes semaines. Après 12 semaines, comparés au début du traitement, le Glucagon du plasma qui avait été diminué à 13.63 pg/ml, augmentait, et les proportions de patients ayant atteint les normes définies par l'ADA 2015: le FPG, 2hPPG et l'HbA1c sont augmentées de 18.8%, 11.9%,et 0 à 69.3%. 78.2%, et 69.3% respectivement ($p<0.001$). L'intervention avait duré 12 semaines.

Conclusions: En 12 semaines, l'inhibiteur Sitagliptin de DPP-4 donne aux patients avec diabète type 2 mal contrôlés avec la Metformine utilisée seule ou en combinaison avec un autre produit antidiabétique, améliore le contrôle du Glucose, ce qui permet de conclure à son effet de "surajouter au Glucagon"

Mots clés: *Type 2 diabetes, Dipeptidyl Peptidase Inhibitor, blood Glucagon plasma.*

NATTOKINASE FOR BRAIN INFARCTION IN ACUTE VIRAL ENCEPHALITIS

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ABSTRACT

Infarction in the central nervous system, especially in the brainstem plays a crucial role in the pathology of many acute viral encephalitis, such as Japanese encephalitis.Nattokinase an oral fibrinolytic product, shows as an add-on effective treatment in these conditions.We would like to present one clinical case report related to this pharmaceutical speciality.

I. JAPANESE ENCEPHALITIS (JE)

JE is caused by Japanese encephalitis virus (JEV). JEV is a single RNA genome of 11kb. This RNA genome encodes a single polypeptide, that is cleaved into 3 structural proteins (C - capsule, M- membrane, E - envelop), and 7 non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5). JEV is transmitted in a zoonotic cycle among mosquitoes and vertebrate-amplyfing hosts, chiefly pigs and wading birds. Culex tritaeniorhynchus is the major mosquito vector of JE in the South-East Asia.

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Clinically, the patients present high fever, seizures and high grade coma associated with motor deficits, muscular rigidity, decorticated or decerebrated postures, cachexy… Death may occur in the first week in a respiratory failure state. In the last stage, the patients may recover from the disease or may remain with severe neurological sequelae like movement disorders, epilepsy, aphasia,... For diagnosis, beside haematological, biochemical and imaging investigations, JE is confirmed by Mac-Elisa test with IgM anti - JEV positive in the patient's serum or cerebro-spinal fluid.

Pathological studies performed by international and Vietnamese authors from 1933 to 2010 (1, 2, 3, 4, 5,6, 7) have revealed in JE death cases thrombus formation in the cerebral vessels of the brainstem, cerebral cortex, cerebellum, leptomeninges of the spinal cord associated with widespread embolism in the lungs, spleen, liver, kidneys, adrenal glands, myocardium, gastro-intestinal mucosa. These authors emphasized "… Microscopically the blood vessels of the brain, medulla oblongata, and spinal cord are dilated and congested. Stasis, diapedetic haemorrhages, accumulation of liquid exudate, obstruction of lumen are common. More fat was demonstrated within phagocytes".

Based on signs of respiratory failure before death, accompanied by thrombus formation in the brainstem, embolism in the lungs and other visceral organs in fatal cases, we believe that JE patients die of these

severe lesions, not by virus directly.From this point of view,we would like to propose the following physiopathology in JE and some other viral encephalitis.

II. PROPOSED PHYSIOPATHOLOGY OF JE AND SOME OTHER ACUTE VIRAL ENCEPHALITIS

After primary infection with JEV, protein NS5 of JEV interacts with mitochondrial trifunctional protein (MTP), impairing fatty acid beta-oxidation. Accumulation of long-chain-3 -hydroxy fatty acids, trapped inside the mitochondrial matrix, induces reactive oxygen species (ROS) production and proinflammatory cytokine expression. A cytokine storm results in increasing the permeability of the blood-brain -barrier(8). Disrupted blood-brain-barrier leads:

- To increase the plasminogen-activator inhibitor (PAI-1) in the cerebrospinal fluid, a risk factor for infarction (9);
- To liberate endothelial - I (ET-I), a very potent vasoconstriction, which involved in the vasospasm(10);
- To increase interleukin-6 (IL- 6), an important marker that predicts stroke (11,12);
- To activate complement with the liberation of complement C3, C5a. C5a, a potent anaphylactoxic peptid, induces a range of pro-inflammatory and pro-thrombotic effects (13, 14,15,16).
- To activate mast cells degranulated in the brain during lethal JEV encephalitis.Once activated, mast cells release preformed granules containing inflammatory mediators proteases (including chymase, tryptase), vasoactivate molecules, like histamine, noradrenalin,adrenalin,serotonin,vasopressin, angiotensin(17).Thus, the vascular system is compressed severely leading to ischemia. Ischemic neurons recruit natural killer cells, that accelerate brain infarctions (18). The vascular compression leads to decrease the effective perfusion, and the brain again is hypoperfused with more ischemia.

The sequelae of compressed vessels is a congestive state, leading to extravascular serum escape. The blood in the brain vessels becomes visceous, hyperosmole - a risk factor for brain infarction. Disturbance of thermoregulatory centre due to thalamus lesion causes high fever and a dehydrated state easily leading to infarction.Brainstem infarction leads to increase pulmonary permeability then to pulmonary edema.(31)

To resolve this problem, we would like to propose the use of fibrinolyitc products.

III. CLINICAL USE OF NATTOKINASE (NK)

Nattokinase -F, 5000Fu, a product of A.N.Z pharma C0,L.T.D, is a serine protease, that has 275 amin acid residues with a nuclear weight of approximately 28kDa.

Bioavaiability

NK is effectively absorbed across the rat intestinal tract inducing fibrinolysis after intraduodenal administration (19).Ero and collegues presented the first bioavailability data of NK in human by enzyme -linked immunosorbent assay.Following 2000 FU NK administration, they demonstrated NK serum activity between 2 through to 24 hours in healthy subjects (20).Yuko Kurusawa and colleagues, by a double- blind, placebo-controlled cross -over study, determined the fibrinolysis /coagulation parameters before and after administration of 2000FU of NK (21). These two studies confirmed an increase in activity of fibrinolysis and anticoagulant parameters between 2 and 8 hours after NK intake (21).

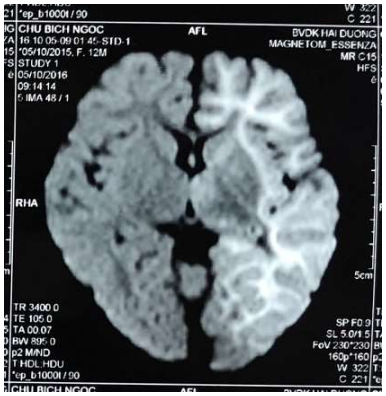
Nattokinase can breakdown blood clots by inhibiting platelet aggregation, decreasing plasma levels of fibrinogen, factor VII, factor VIII, increasing t-PA formation, converting endogenous prourokinases to urokinase (u-PA), inactivation of PAI-1. Thus, Nattokinase is useful for cerebral infarction treatment (22).Unlike other fibrinolytic proteases such as t-PA, and u-PA, which can produce various side effects as bleeding, Nattokinase exhibits little to no side effects. In human clinical studies, no adverse effect level was found when human volunteers consumed Nattokinase 10mg/kg/day for 28 days (23).

In our study, Nattokinase was used from 20mg/kg/day to 100mg/kg/day.

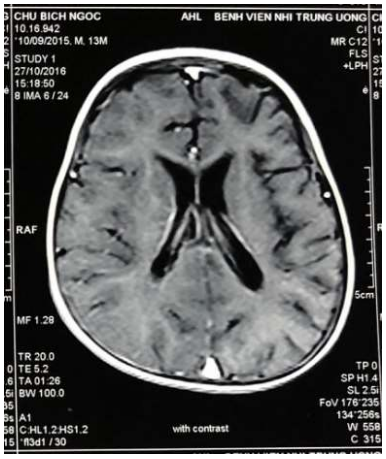
IV. CASE REPORT

A 13 month -old girl was admitted to the National Children Hospital (N.H.P) with a right -sided hemiplegia on October 5th 2016.She was the first child of a non-consaguineous couple, delivered via Cesarean method, without asphyxia. She had a head trauma when she was 3 months old. A brain CT scan wasn't done at that moment.She could roll over at 7 months and could sit at 13 months. She couldn't speak. Two days before her admission, she presented a fever of 38°C. With antipyretic drugs, the fever still persisted. She developed a generalized seizure predominantly on the right side, lasting for 20 minutes. At local hospital, her brain MRI showed a large infarction on the left hemisphere. She was sent to the N.H.P. Upon examination, she was lethargic, Glasgow coma scale of 10/15. She presented a right -sided hemiplegia and a right facial paralysis.Pulses 150 beats/min, sP02 98%, temperature 39° C, body weight of 10kgs.At N.H.P, a status of partial epilepsy occurred with seizures on the right side. The investigations showed a full blood count with white blood cells of 25870/mm3 (79% neutrophiles), hemoglobin 8.3g/l, platelet 448000/mm3,CRP 21.7mmol/l,GOT 46,4 u/l, GPT 18.7u/l, Uremia 2.19mmol/l, Creatininemia 29microммol/l, glucose 4.24mmol/l, Na 127mmol/l, Kalemia 3.8mmol/l,Chlor 94.3mmol/l. Calcemia 2.19mmol/l. Cholesterolemia 5.52 mmol/l (normal < 4.42 mmol/l).Triglyceridemia 2.03mmol/l (normal < 1.65mmol/l), anti-thrombin III 99%, PT 63%, Fibrinogen 4.5mg/dl, APPT 28 seconds, Protein C 68%. Protein S 79%. The evaluation of genetic coagulation disorders, plasma levels of homocysteine and factor VIII couldn't be performed.The echocardiography and echo doppler carotid artery were normal.The antibody HIV, PCR for haemophilus influnzae,the blood culture were negative.The cerebro-spinal fluid was clear with 15 cells/mm3, proteinorachia 0.67g/l, glucorachia 3.8mmol/l,chlor 120mmol/l, Pandy reaction was positive.ELISA for JE showed IgM positive. The child was diagnosed as Japanese encephalitis.A brain MRI for her was performed again at N.H.P, showing a large infarction on the left hemisphere. We decided to give her acyclovir, antibiotic, antiepileptic and Nattokinase 5000Fu x 2 capsules/day for her body weight of 10kgs (20mg/kg/day).On the second day of acyclovir treatment, the child become seizure-free. As the PCR for HSV was negative, we stopped acyclovir after 5 days of treatment.However, antibiotic intravenously was continued for 7 days. On October 13th 2016,the child was discharged, her right hemiplegia ameliorated. We continued to give her Nattokinase 5000Fu x2

capsules/day for 2 weeks.On October 27th 2016,upon her reexamination, she could sit on the bed,she had no more seizure.Her control brain MRI showed signs of brain atrophy on the right side.We continued to give her antiepileptic drug for 1 month and Nattokinase with the same dose for 2 months. Now she is 3 years old, she can run normally without sequelae.



Before treatment



Twenty two days after treatment

- From 2016 to 2019, at N.H.P,Nattokinase was used as an important add-on product for other viral encephalitis, such as Varicellar virus, Epstein Barr virus, Enterovirus, influenzae virus, Herpes - simplex virus, measles virus encephalitis with good improvement.

V. DISCUSSION

In many acute viral encephalitis,disruption of the blood- brain - barrier is the main reason of brain infarction.Cerebral deep venous thrombosis, brainstem infarction, brain infarction, visceral embolism are present inJapanese encephalitis contributing to the main symptom of the disease, that is intracranial hypertension.Brain infarction is also found in other acute viral encephalitis such as influenzae virus (24),varicellar virus (25), Herpes simplex virus(26),HIV (27)….Therefore, antifibrinolyitc drugs may play an important role in the treatment of these severe conditions.

1. Alteplase catalyzes the conversion of blot bound plasminogen to plasmin which then activates the fibrinolytic cascade.According to the literature, Alteplase (t-PA) in 1987, was the first product approved by the FDA for treating acute myocardial infarctions. From 1996, Alteplase was used for stroke patients.In fact, in 1970, Pham Ngoc Trong used Fibrase, another name of Alteplase, successfully for 2 Japanese encephalitis patients in severe coma, needing mechanical ventilation.These two patients were out of coma and discharged home without sequelae after 10 days of treatment (private conversation).

2. Heparin augements the function of antithrombin III,by inhibition of thrombin and factor Xa.In 2012, Jia M et al, in their article "Japanese encephalitis accompanied by cerebral venous thrombosis " reported the use of heparin with success in their patient (28)In 2015, Mokkapan S et al used heparin with success in a patient suffering from "

Bilateral thalamic bleed and cerebral venous sinus thrombosis "(29).

3. Salicylates within a range of 1 to 5mM not only restrict flavivirus replications but also abrogated flavivirus - triggered apoptosis (30).

However, because of hemorrhasgic side effect of t-PA, heparin, salycilates, Nattokinase a safely medical product, with fibrinolytic activity, could be used as an effective add - on therapy in viral encephalitis.

In the future, we hope to have recombinant thrombolytic product such as nanoparticulate encapsulation or complexation for viral encephalitis treatment safely.

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RÉSUMÉ:

LE NATTOKINASE DANS L'INFARCTUS DU CERVEAU DANS LA PHASE AIGUEE DE L'ENCEPHALITE VIRALE

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L'Infarctus du systeme nerveux central, en particulier dans le tronc cérébral, joue un rôle crucial dans la pathologie de plusieurs cas d'encéphalite virale aigue. Telle que l'encéphalite japonaise. Le Nattokinase, un produit fibrinolytique oral, a montré un effet bénéfique surajoutant. Nous voudrions presenter un cas clinique lie à cette specialité pharmaceutique.

REPORTING THE PERFORMANCE EFFICIENCY OF PET/CT AFTER ONE YEAR INTO OPERATING IN THE NUCLEAR MEDICINE DEPARTMENT AT VIETNAM NATIONAL CANCER HOSPITAL

Nguyen Duc Loi*

ABSTRACT

Objective: Preliminary report of PET / CT operation after one year of implementation at national cancer hospital. Research subjects: All patients received PET / CT scans at national cancer hospital from 6/2017 to 7/2018. ***Research method:*** The descriptive study. ***Results:*** in 2641 patients assigned to PET / CT scan, lung cancer accounted for the highest proportion (19,9%), lymphoma (18,7%), breast cancer (14,6%), carcinoma of unknown primary tumors is 4,1% and other types of cancer accounted for (42,7%). Indicators for pre-treatment evaluation (38,2%), recurrent and metastases (37,2%), evaluation of treatment response (20,5%). PET/CT detected 60% of primary malignant lesions in patients with primary metastases. ***Conclusion:*** PET / CT contributes to improved diagnostic efficacy, provides appropriate treatment regimens in cancer patients, helps track disease progression accurately.

I. INTRODUCTION

Every year, in Vietnam there are about 150,000 new cases and 75,000 people die from cancer. The reason is that in Vietnam, the system of early diagnosis of cancer is weak and lacking; Most cancer patients are detected in the late stages, so the therapeutic effect is not high. If they were detected early, cancer can be cured and treated promptly, but that depends very much on the diagnostic equipment, especially devices that can diagnose early and screening for tumors.

National cancer hospital is the leading hospital for cancer diagnosis and treatment. On average, about 3,500 patients come to the hospital every day and a total of 1800 hospital beds in 3 establishments (Base I, II and III). With a large number of patients examined and treated, national cancer hospital has equipped the PET / CT system in the Nuclear Medicine Department to contribute to the diagnosis and improve the treatment effectiveness for cancer patients. PET / CT is a combination of a PET (Positron Emission Tomography) and CT (Computed Tomography). PET / CT is a combination of images between early diagnosis of PET and anatomical structure of CT. Therefore, PET / CT has the ability to detect abnormalities and changes in the body in very early stages - molecular level - especially the formation, development and metastasis of tumors. PET / CT results contribute to improving the quality of cancer diagnosis and treatment, changes in previous treatment regimens and perspectives have helped doctors choose the optimal regimen to ensure the highest therapeutic efficacy for patients.

For pre-treatment evaluation: the patient has been diagnosed with cancer and untreated, with the whole body advantage of PET / CT, the patient will be re-evaluated in size tumors and distant metastatic lesions,

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thereby accurately assessing the stage of the disease before embarking on treatment.

Evaluate the effectiveness of treatments: with PET / CT images, it is possible to detect cancer early and metastasis before other methods such as CT, MRI. PET / CT is particularly effective in evaluation of treatment results, after a course of treatment, PET / CT helps check tumor status, distinguish scar tissue or recurrent tissue after surgery. Based on this result, your doctor can predict and adjust or change treatment to achieve the best results.

In all cancer patients, primary cancer of unknown rate accounts for about 2%. By traditional tests: CT, MRI, ultrasound... only detecting and assessing lesions had changes in anatomical structure at a sufficiently large level and only detected primary tumors with the rate of 40% - 50%. While PET / CT can detect metabolic abnormalities, record pathological images early, small even when there is no change in structure. Therefore, PET / CT has the advantage of finding the primary tumor higher than conventional imaging diagnostic methods.

With the above advantages, since the introduction of PET / CT in the Nuclear Medicine Department, it has contributed to improving the diagnosis and treatment effectiveness for cancer patients in national cancer hospital. After 1 year of operation, more than 2000 patients have been assigned to PET / CT scans, which have great benefits for patients and treating physicians.

II. RESULT:

Table 1: Number of patients who have taken PET / CT scans at Nuclear Medicine Department, National Cancer Hospital from 6/2017 - 7/2018

Serial	Cancer	Number	Ratio
1	Lung cancer	526	19,9%
2	Lymphoma	490	18,7%
3	Breast cancer	385	14,6%
4	Esophageal cancer	318	12%
5	Arch and throat - larynx cancer	307	11,7%
6	Cervical cancer	204	7,7%
7	Colorectal cancer	180	6,8%
8	The cancer metastasis is unknown	107	4%
9	Gastric adenocarcinoma	19	0,7%
10	Ovarian Cancer	46	1,7%
11	Thyroid cancer	51	1,9%
12	Prostate cancer	8	0,3%
	Total	**2641**	**100%**

According to statistic data, the leading lung cancer in all cancers designated for PET / CT: 526 patients (19.9%), second is malignant lymphoma: 490 patients (18.7%), followed by breast cancer: 385 patients (14.6%). Through research for lung cancer, PET / CT can detect recurrent and metastatic lesions with very high sensitivity and specificity (this ratio is 100% and 83%, respectively), while the ratio with lymphoma is 95% and 67%.

Some types such as thyroid cancer, prostate cancer, gastric adenocarcinoma and ovarian cancer, only PET / CT indications are limited.

Table 2: Total number of PET / CT scans

Serial	Assgin	Number	Ratio
1	Evaluate the pre-treatment stage	1010	38,2%
2	Evaluate the effectiveness of treatment	542	20,5%
3	Evaluate relapse and metastasis	982	37,2%
4	Metastasis is unknown	107	4,1%
Total		**2641**	**100%**

In 2641 patients, 1010 patients were assigned a PET / CT scan before treatment (accounting for 38.2%) and 982 patients were taken for evaluation of relapse, metastasis (37.2%), PET / CT has an important role in making the right treatments, can change the increase or decrease of the disease stage. On PET / CT images can identify the area of malignant lesions and inflammation in the same block u, thereby avoiding extensive surgery or unnecessary irradiation. According to the study, it is found that up to 89-96% of patients will get the right treatment decision and up to 45-60% of patients have changed treatment after doing PET / CT. So PET / CT scan is recommended to be used routinely for cancer patients before treatment.

Table 3: Specify PET / CT scan before treatment

Serial	Evaluate the pre-treatment stage	Number	Ratio
1	Arch, throat - larynx cancer	128	12,7%
2	Lung cancer	312	30,9%
3	Esophageal cacncer	198	19,6%
4	Lymphoma	183	18,1%
5	Colorectal cacncer	57	5,6%
6	Breast cancer	73	7,2%
7	Cervical cancer	40	4%
8	Gastric adenocarcinoma	19	1,9%
	Total	**1010**	**100%**

In 1010 patients with PET / CT scans assessed before treatment, there were 312 patients with lung cancer (accounting for 30.9%), 198 patients with esophageal cancer (accounting for 19.8%), 128 patients with regional cancer. arch, throat, larynx (12.7%) and 183 lymphoma patients (18.1%). For patients in this group, PET / CT will help to re-evaluate and correct the stage, and help treat radiation in the right position of malignant lesions.

Table 4: Designation of PET / CT scan for assessment of treatment efficacy

Serial	Evaluate the effectiveness of treatment	Number	Ratio
1	Arch, throat - larynx cancer	54	9,9%
2	Lung cancer	72	13,3%
3	Esophageal cancer	40	7,5%
4	Breast cancer	106	19,6%
5	Cervical cancer	60	11%
6	Lymphoma	210	38,7%
	Total	**542**	100%

There were 542/2641 patients assigned to assess the treatment effect (accounting for 20.5%), PET / CT helps predict early treatment results and treatment response of one or more treatments, special scar tissue due to healing or residual lesions or tissue recurring due to cancer. The lymphoma has a specific indication to evaluate the highest treatment effect: 210 patients (38.7%), due to lymphoma sensitive to chemotherapy, early response time, PET / CT helps assess the effectiveness of the regimen used in these patients, and can change the regimen early if the disease does not respond to the treatment. In addition, breast cancer has 106 patients (19.6%) and lung cancer 72 patients (13.3%). For lung tumors designated chemicals, radiation or target therapy, after a period of treatment if the disease responds, the tumor image seen on CT usually does not change in size, it is difficult to be sure. is the remaining malignant tumor or fibrous organism, however, on PET / CT images, it is possible to clearly distinguish that as fibrosis, not increase FDG metabolism, meaning that the disease responds well to treatment.

Table 5: Indications for PET/CT scan to determine whether the cancer has recurred or metastasized

Serial	Evaluate relapse and metastasis	Number	Ratio
1	Arch, throat - larynx cancer	125	12,7%
2	Lung cancer	142	14,5%
3	Esophageal cancer	80	8,1%
4	Colorectal cancer	123	12,5%
5	Breast cancer	206	21%
6	Cervical cancer	104	10,6%
7	Ovarian cancer (CA125> 35u / ml)	46	4,7%
8	Lymphoma	97	9,9%
9	Thyroid cancer (when I-131 radiation is negative, Tg is high)	51	5,2%
10	Prostate cancer (PSA> 4ng / ml)	8	0,8%
	Total	**982**	**100%**

982/2641 patients (37.2%) were assigned to PET / CT scans to assess relapse and metastasis. Among these 982 patients, the incidence did not differ significantly between different cancers. Some were: lung cancer 142 patients (14.5%), 206 patients with breast cancer (21%), cancer of the throat, throat cancer - laryngeal 125 patients (12.7%), colorectal cancer 123 patients (12.5%)...

Cancer is systemic, systematic, important characteristics of the disease are relapse and metastasis. After a period of treatment, all cancer patients will have that condition. When suspicion of relapse and metastasis (via maker, ultrasound, radiography, CT, MRI...), patients will be assigned PET / CT for systemic evaluation, PET / CT may help find vulnerabilities other than suspected locations.

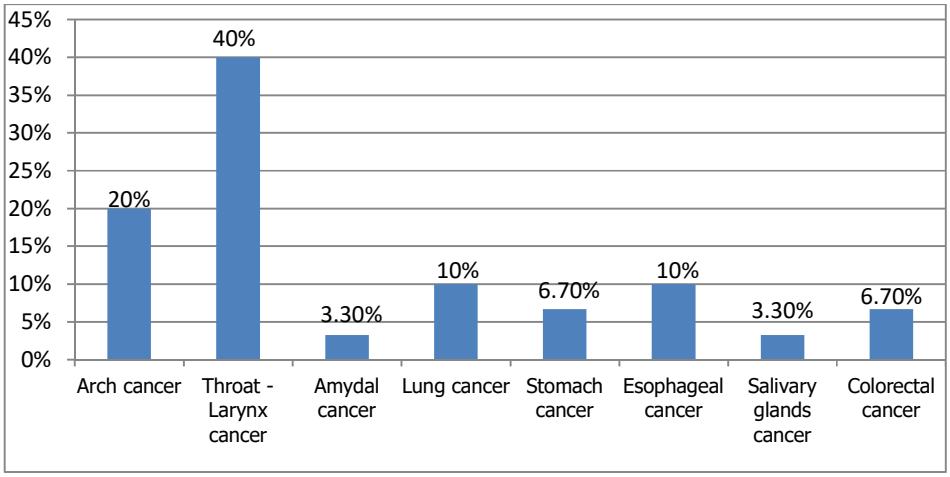

Chart 1: Primary unknown metastatic lymphoma

There were 107 primary unidentified metastatic cancer patients who applied PET / CT to find primary lesions. Preliminary assessment of 30/107 patients, there are 18/30 patients (60%) detected primary tumors with PET / CT (compared with pathology), the rest are false positive 12/30 patients (40%). The most common types of pathology are squamous carcinoma (56.7%), adenocarcinoma (16.7%) and cancers of differentiation (26.7%). Proportion of suspected primary cancer sites on PET / CT: throat - larynx cancer: 12/30 patients (40%), throat cancer 6/30 patients (20%), lung cancer 3 / 30 patients (10%). The remaining are amydal cancer, esophageal cancer, stomach cancer, colon cancer and salivary glands.

Table 6: Pathology of metastatic lymph nodes

Pathology	**Number**	**Ratio**
Non-differentiated carcinoma	8	26,7 %
Adenocarcinoma	5	16,7 %
Squamous carcinoma	17	56,7 %
Total	**30**	**100**

The anatomy of metastatic lymph nodes: squamous carcinoma accounts for 56.7%, adenocarcinoma accounts for 16.7%, and non - differentiated carcinoma 26.7%.

Table 7. Comparison of pathology in tumors and lymph nodes

Pathology	**Tumors (n=30)**	**Lymph nodes (n=30)**
Adenocarcinoma	6.7%	16,7 %
Squamous carcinoma	33.3%	56,7 %
Non-differentiated carcinoma	23.3%	26,7 %
	P=0.793	

We see a certain similarity between pathology of metastatic lymph nodes and primary tumors found by PET / CT. However this study should still be expanded and intensive to continue reporting.

III. OPERATION SITUATION OF PET / CT IN SOME HOSPITALS OF VIETNAM IN 2017:

Serial	Hospital	Number
1	Viet Duc Hospital	1288
2	Bach Mai Hospital	1033
3	Military Central Hospital 108	837
4	National Cancer Hospital	**2641**
5	Military 103 Hospital	476
6	Ha Noi Cancer Hospial	449
7	Hospital 175	178
8	Da Nang Hospital	671
9	Cho Ray Hospital	744

In Vietnam today, there are 9 hospitals that have put the PET / CT system into service of diagnosis and treatment, most of them are concentrated in large hospitals. In 2017, there were 8317 patients assigned to take PET / CT, in which National cancer hospital had 2641 patients, Viet Duc hospital had 1288 patients, Bach Mai hospital had 1033 patients and Central Military Hospital 108 had 837 patients multiply, others were other hospitals. The number of patients assigned to PET / CT scan is increasing in number, showing the effectiveness of this method in diagnosis and treatment. Especially at national cancer hospital, the number of patients designated as the highest indicates the significance of PET / CT in the specialty of cancer.

IV. CONCLUTION:

PET / CT is a new and modern technique that can support other common diagnostic methods in the diagnosis and treatment of cancer diseases, help assess the pre-treatment phase, evaluate the effectiveness of treatment and relapse and metastasis status of the disease. In more than 2000 patients assigned to PET / CT scan at the Nuclear Medicine Department, National Cancer Hospital, there were 1010 patients (accounting for 38.2%) to assess the pre-treatment period, 542 patients (accounting for 20, 5%) assessed treatment efficacy and 982 patients (37.2%) assessed relapse and metastasis.

There were 107/2641 metastatic cancer patients who were originally diagnosed with PET / CT for primary malignant lesions. Preliminary assessment on about 30 patients who had pathological surgery based on the orientation of PET / CT, there were 18/30 patients diagnosed with primary cancer (accounting for 60%), 12/30 patients were not diagnosed get primary cancer (40%). The remaining patients are being collected and studied.

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RÉSUMÉ:

RAPPORT SUR LA PERFORMANCE DU PET/CT APRÈS UN AN D'ACTIVITÉ AU DÉPARTEMENT DE MÉDECINE NUCLÉAIRE A L'HÔPITAL NATIONAL DU VIETNAM DU CANCER

Nguyen Duc Loi*

** L'Hôpital National du Vietnam du Cancer*

Objectif: Premier rapport sur les activités de PET/CT après un an d'opération à l'Hôpital National du Cancer.

Materiel: Tous les patients nécessitant des scans de PET/CT à l'Hôpital National du Vietnam du Cancer.

Methode: Etude descriptive.

Résultats: Chez 2641 patients avec indication du PET/CT, la plupart avaient un cancer du poumon (19.9%), le lymphome (18.7%), le cancer du sein (14.6%), carcinome d'origine inconnue (4.1%), et les autres types de cancer (42.7%). Les buts étant: Évaluation pour pré-traitement: 38.7%, recurrences ou métastases: 37.2%, évaluation de la reponse au traitement: 20.5%. Le PET/CT a contribué à détecter 60% de lésions malignes primaires pour les métastases primaires.

Conclusion: Le PET/CT a contribué à améliorer le diagnostic, apporter un traitement adéquat, et aider à suivre la progression de la maladie avec précision.

OPERATIVE TREATMENT OF CARPOMETACARPAL FRACTURE DISLOCATIONS OF LONG FINGERS IN ADULT

Bui Lan Huong*, Nguyen Van Thai**,
Nguyen Thuc Boi Chau*, Mai Trong Tuong*, Tran Cong Toai**

ABSTRACT

Introduction: The carpometacarpal (CMC) fracture dislocation is very uncommon and still is a challenge for hand surgeons. Sometimes, this injury is missed for the first diagnosis. Correct diagnosis and treatment will help to obtain the best hand functional recovery. **Purpose**: to study the properties of this injury and to evaluate the hand functional results after operative treatment. **Material and Method**: Material: The carpometacarpal fracture dislocations of long fingers in 43 cases were treated by opened reduction and K - wires fixation from Jan 2011 to Mars 2015 at the Hospital for Traumatology and Orthopaedics, Ho Chi Minh city. Method: retrospective and prospective case series study. **Results:** Young men have highest incidence of CMC joint injury. The main cause is the motocycle accident. The first diagnosis is missed in 61.29% of the cases. All 4 CMC joints injury is the most frequent, then the injury of the 4th and 5th CMC. The 2nd, 3rd or single CMC injuries are less common. Good bone healing in all cases, no recurrent dislocation. Grip strength is recovered of 78.22% on average. All patients come back to their old work. The hand functional result is Exellent in 48.84%, Good in 18.60%, Satisfactory in 25.58%. Poor in 6.98%. **Conclusion:** The carpometacarpal fracture dislocations of long fingers are uncommon, due to high energy injury. The incidence of missed diagnosis is high. The grip strength of injured hand is about 78% of the normal hand. Early diagnosis and treatment are necessary for better hand functional recovery.

Key words: *Carpometacarpal joint, fracture, dislocation, long finger, operative treatment*

I. INTRODUCTION

The CMC fracture dislocations of long fingers are uncommon, account fof less than 1% of hand injuries [1, 2, 3, 8, 14]. In cases of closed injuries, the diagnosis are frequently overlooked or missed because of the complexity of tiny bones in this area, or in polytrauma when treating physician may be overwhelmed by othes injuties. Open injuries due to high energy trauma content of complex lesions of bones, joints and ligaments [2,6,8,11,16]. Early diagnosis and treatment help to obtain better recovery of hand functions. This study purpose is to evaluate the characteristics of this injury and the functional results after operating treatment at the Hospital for Traumatology and Orthopaedics, Ho Chi Minh city.

II. MATERIAL AND METHOD

2.1. Material: Patients who had dislocation or fracture - dislocations of long fingers treated surgically in the Hospital for Traumatology and Orthopaedics, Ho Chi Minh city (HTO) from 01/2011 to 03/2015, with at least 3 months follow up. The cases of isolated fracture - dislocation of the thumb, or severe crushing hand, or amputated fingers were excluded.

2.2. Method:

- Review of the case records of the HTO.

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Date of scientific judgment: 22/4/2019
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- Invite the patients come back to evaluate the hand functions as well as X ray images.

- The functional results were evaluated maily on the bases of the Mayo Clinic score.

III. RESULTS

3.1. Materials

There were 43 patients, 34 males (79.07%); 9 females (20.93%). Average age was 32.72 (range, 16 - 68 y.o). 21 cases of right hand injured, 22 cases of left hand injured (21 cases of dominant hand).

3.2. Causes:

-Road traffic accident (motocycle accident): 32 cases (74.42%).

- Domestic accident: 02 cases (4.65%).

- Work accident (crushing machine): 08 cases (18.60%).

- Sport accident (football): 01 case (2.33%).

3.3. First behaviour

31 cases (72.10%) went to the hospitals; 4 cases treated themselves with traditional medicine (9.30%); 8 cases (18.60%) didn't have any treatment immediately after injury.

In 31 cases treated in hospitals, there were only 12 cases (38.71%) which were correctly diagnosed at first presentation; 19 cases (61.29%) overlooked.

There were 13 cases (30.23%) of opened injury and 30 cases (69.77%) of closed fracture - dislocation.

Average time from injury to operation was 25 days.

3.4. Distribution of injuries

Table 1: Number of injured fingers distribution

Number Of Injured Fingers		Cases	%
1 finger	2nd metacarpal: 4 cases 4th metacarpal: 1 case 5th metacarpal: 2 cases	7	16.28
2 fingers	2nd - 3rd Metacarpal: 2 cases 4th - 5th metacarpal: 10 cases	12	27.91
3 fingers		5	11.63
4 fingers		17	39.53
5 fingers		2	4.65
Total		**43**	**100**

3.5. Associated injuries:

16 cases (37.2%) having cartilage injury and dorsal side fracture of carpal bones due to dorsal CMC dislocation.

11 cases (25.58%) having other hand injuries (thenar and hypothenar lessions, phalangeal fractures, extensor tendon lacerations).

4 cases (9.30%) suspected of compartment syndrom.

2 cases (4.65%) having deep branch of ulnar nerve.

1 case (2.33%) having both ulnar and median nerve.

→ The more associated injuries, the more complicated treatment and the more limited functional recovery.

3.6. Treatment method:

All the 43 cases were open reduced in which 36 cases (83.72%) undergone K-wires fixation and ligament repair, 7 cases (16.28%) primary arthrodesis.

A postop splint was used for all patients during 2 to 4 weeks. Early gentle movement of fingers was recommended for patients in order

to prevent the stiffness. Active execises were indicated 1 month after operation to obtain the best range of motion and strength recovery.

3.7. Postop complications

Infection: 1 case (2.33%)

Wound border necrosis due to "lóc da": 1 case (2.33%)

Revision due to bad reduction: 2 cases (4.65%).

3.8. Treatment evaluation

Follow up time: 3 - 53 months (average: 20 months).

Long term results:

Functional recovery

- All the patients have returned to previous occupation: 32 cases (74.42%) have worked without difficulty; 11 cases (25.58%) have worked with some difficulty. The average time returning to work was 2.4 months (from 1 to 4 months).

- There is the statistically significant correlation between delay time before operation and time returning to work ($p = 0.02$).

Range of motion of the wrist:

Average ROM of the wrist was 144.77^0 (min 45^0, max 170^0).

Pain:

No pain: 29 cases (67.44%)

Mild pain: 12 cases (27.91%)

Moderate pain: 2 cases (4.65%)

Grip strength

Average recovery of grip strength of operated hand obtained 78.22% of intact side (36.36% - 100%). The difference was statistically significant ($p<0.0001$).

Average recovery of grip strength was 83.16% in closed group and was 66.81% in opened group. The difference was statistically significant ($p < 0.01$).

X ray

All cases obtaining bone healing; 9 cases (20.93%) having fused joint image; 2 cases (4.65%) having arthosis; No cases having redislocation or subluxation.

Patient's satisfaction: 8.34 / 10 on average.

Final grading

According to Mayo Clinic Score, the final result was classified into 4 levels: Excellent (≥90 pts), Good (≥80 pts), Satisfactory (≥ 65 pts), Poor (<65 pts).

Average Mayo Clinic score was 84 points (from 50 to 100 points).

Table 2: Final result

Result	Cases	%
Excellent	21	48.84
Good	8	18.60
Satisfactory	11	25.58
Poor	3	6.98
Total	**43**	**100**

Table 3: Comperison the Final result with Closed/Opened group

Result	Closed	Opened	Total
Excellent	18 (60 %)	3 (23.08 %)	21 (48.84 %)
Good	5 (16.67 %)	3 (23.08 %)	8 (18.60 %)
Satisfactory	7 (23.33 %)	4 (30.76 %)	11 (25.58 %)
Poor	0	3 (23.08 %)	3 (6.98 %)
Total	**30 (100 %)**	**13 (100 %)**	**43 (100 %)**

There was a significant diference between closed and opened group results ($p < 0.05$).

Table 4: Comperison the Final results of literature

Authors	Exc. + Good	Satis.	Poor	Total
Guimaraes	13 (65%)	3 (15%)	4 (20%)	20 (100%)
Lawlis	15 (75%)	1 (5%)	4 (20%)	20 (100%)
Kural	8 (88.89%)	1 (11.11%)	0	9 (100%)
Garcia-Elias	9 (69.23%)	3 (23.08%)	1 (7.69%)	13 (100%)
We	**29 (67.44%)**	**11 (25.58%)**	**3 (6.98%)**	**43 (100%)**

There was no significant diferent results among these studies ($p > 0.05$).

IV. DISCUSSION

4.1. Characteristics

- The characteristics (young men, high energy trauma such as motocle accident, crushing machine) were similar to others literatures [4, 5, 7, 8, 11, 15, 16].

- 12 patients (27.91%) didn't go to the hospitals and treated themselves with traditional treatment or ignored the injury. After certain time, they presented to hospitals with pain and disfunction of their hand. The treatment, therefore, became more difficult. Stiffness of the joints and algodystrophy of patient's hands caused prolongation of the functional recovery time.

- In literature, the percentage of missed diagnosis varied from 19% to 71% [2, 4, 5, 6, 8, 11, 12]. It means that the careful examination and analyzing Xray images are very important in order to have exact diagnosis. The P-A X ray and true lateral are the best positions to find the CMC dislocation [6,9,10].

- Because of the intermetacarpal ligament, the dislocation of all four CMC joints is frequent. In others cases, only ulnar side joints were damage because both 4th and 5th metacarpal bases join to the hamate so that they are looser than 2nd and 3rd metacarpal bases.

- According to the literature, when the patient came to hospital early in first wek after injury, they can be treated by closed reduction and transcutaneous pinning [4,5,11,14]. However, in our serie, most of the patients were admitted to hospital lately, that why open reduction was used for the best anatomical restoration. In cases of comminuted fracture and dislocations, or very long delay of operation, the arthrodesis of the joints were used in order to prevent the pain.

4.2. Treatment Results and Functional recovery

All cases have got good anatomical restoration (good bone healing, no redislocation). However, functional recovery was not obtained totally in all cases. In our opinion, these were the factors which influented to the functional results:

- Carpometacarpal joints have little motion, then they don't have big influence to carpometacarpal function. The disfunction of the wrist and hand could be consequent of

the injuries of arrounding structures such as MP joints or IP joints.

-The forces causing a CMC fracture - dislocation were usually very strong and direct, that damaged not only the injuries of bones and joints, but also the ligaments and soft tissues in this area. After reducting of the joints, the injured soft tissues could become fibrosis that reduce range of motion of the wrist and fingers [1,2,11]. Besides that, high energy trauma could damage the nerves of the hand (usually the ulnar nerve) that caused the intrinsic muscles paralysis [3,8,14,15]. This was the reason why the results in open group were worse than those of closed group, especially for the grip strength recovery.

-Missed diagnosis at first examination could prolong the bad conditions of injured soft tissues and the functional results after treatment were limited [4,6,8,13].

-Grip strength of injured hand recovered less than 20% than intact hand. This remark was reported in many different studies worldwide [4,5,7,8,13]. This is an important factor influencing the function of the hand as well as the satisfactory of the patient.

V. CONCLUSION

Fracture - dislocation of carpometacarpal joints of long fingers are rare, usually dued to the direct and violent forces. The diagnosis are easily missed, especially when the soft tissues were also damaged. Careful examination and X ray analysis are very important to have ecxact diagnosis. Open reduction and pinning is a good method to treat this injury.

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CLINICAL CASES

CASE 1:

Male, 30 yo, mechanician

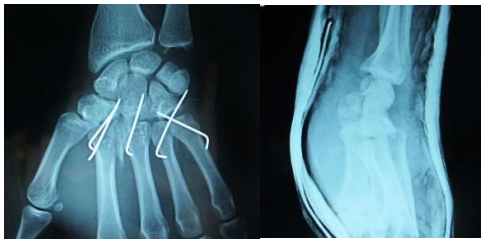
History:

- 1/2011 he fell off from motobike, left hand was traumatized → Admitted to Traumatology and Orthopeadic Hospital with the diagnosis: fracture of base II-V metacarpal bones of the left hand. He had got a conservative treatment with forearm-hand cast. One week later, on reexamination, dislocation of II-V CMC joints were detected on X ray → admission and planning for operation.

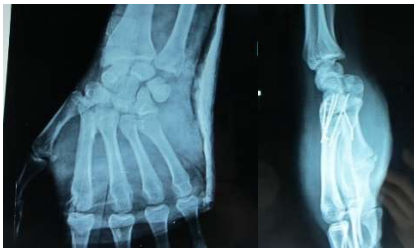
Diagnosis: Fracture and dislocation of II-V CMC joints of left hand

Treatment: Reduction and Pinning II-V CMC joints, postop splint.

Operative timming: 14th day after accident.



A



B

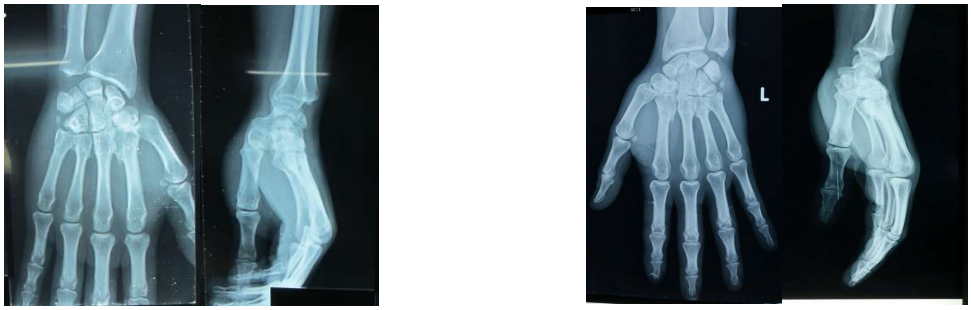
Fig 1: X ray 1 week after conservative treatment (A); X ray after operation (B)

Follow up:

- 3 weeks: splint removal and physiotheraphy.
- 4 weeks: Moderate pain.
- 3 months: normal working.
- 20 months: Remove the K wire. Bone healing on X ray.

Final examination: after 53 months

- Mild pain on operative area while longtime hard working.
- ROM of wrist + hand: good
- Gtrip strength: 40 kg (intact dominant Hand: 46kg) → 86.96% recovery.
- X ray: arthritis of CMC II, III
- Satisfaction of patient: 9/10
- Mayo clinic score: 85
- Final result: Good



A B

Fig 2: Xray after 20 months (A);after 53 months (B)

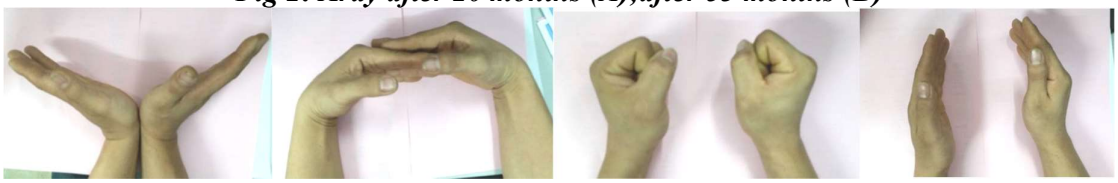


Fig 3:ROM of wrist and fingers after 53 months

CASE 2

Female patient, 17 y.o, clothes saler

History

6/2014 accident of motocycle, the moto crushed over the left hand → went to the HTO.

Examination + X ray

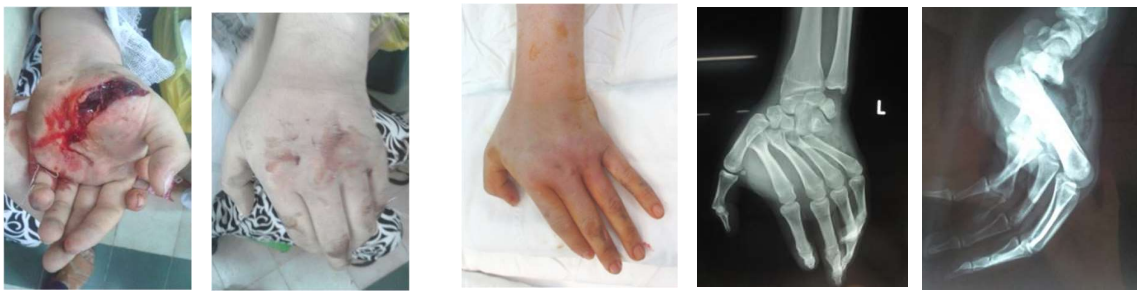


Fig 1: preop images Fig 2: Preop X ray

Diagnosis: Thenar wound (T), open dislocation of CMC II, III, IV, V (volar).

Treatment: Debridment, suture the wound, reduce CMC joints, pinning, restore ligaments, splint post op.

Operation timming: 5 h after injury

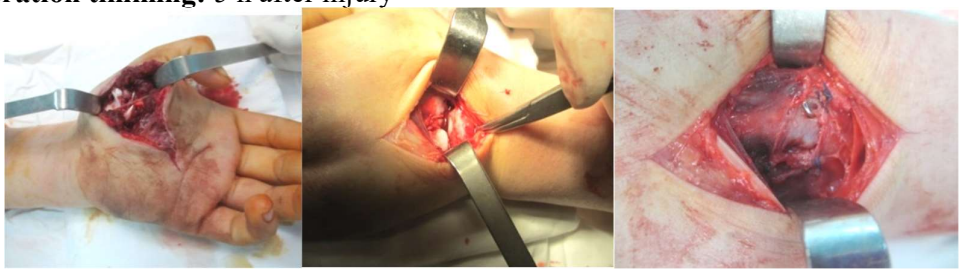


Fig 3: thenar wound - dorsal reduction - pinning and ligament suture

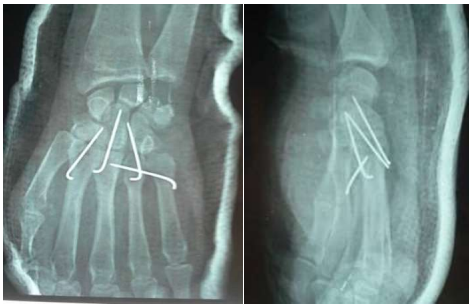


Fig 4: X ray post op

Posrop:

- Carrying the splint for 3 weeks, then physiotherapy
- 1 month: No more pain, ROM of wrist and fingers limited
- 2 months:Good wound healing, ROM of wrist 30^0 - 0^0 - 30^0

Good ROM of fingers

- 3 months: Return to prior work.

Last examination: 12 months follow up:

- No pain.
- ROM of wrist: 90^0 - 0^0 - 80^0
- Good ROM of fingers.
- Grip strength:left hand 16 kg (right hand: 24kg) → 66.67% recovered.
- X ray: good.
- satisfaction of the patient: 10/10
- Mayo Clinic score: 85
- Final result: Good

Fig 5: ROM of wrist and fingers

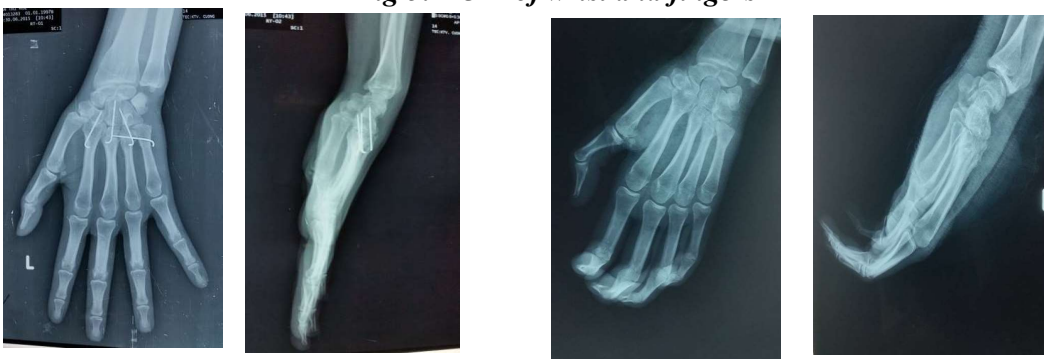


Fig 6: X ray after 1 year (Before and after removal K wire)

RÉSUMÉ:

TRAITEMENT CHIRURGICAL DE LA FRACTURE CARPOMÉTACARPALE ET DE LA DISLOCATION DES DOIGTS CHEZ L'ADULTE

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Objectif: La fracture et dislocation carpométacarpale (CMC) est très peu commune, et reste un défi pour le chirurgien de la main. Parfois, on ne fait pas de bon diagnostic du premier abord. Un bon diagnostic et traitement adéquat aidera l'obtention de la meilleure récuperation fonctionnelle.

But du travail: Etudier les caractéristiques de la lésion et évaluer les résultats du traitement chirurgical sur les fonctions de la main.

Matériel: Les fractures carpometacarpales et dislocations des doigts chez 43 cas ont été traités par réduction ouverte et fixation par fils K, de Janvier 2011 à Mars 2015 à l'Hôpital de Traumatologie et d'Orthopédie, Ho Chi Minh ville.

Méthode: Rétrospective et prospective.

Résultats: L'incidence de la CMC est élevée chez les jeunes gens. La cause majeure étant les accidents de motos. Le diagnostic de premier abord est erroné dans 61.29% de cas. Le plus frequemment rencontré est la blessure de tous les CMC, puis la blessure des 4ème et 5ème CMC. La 2ème, 3ème ou une CMC seule est moins fréquente. Une bonne guérison osseuse se retrouve dans tous les cas, il n'y a pas eu de dislocation récurrente. La force de serrer la main est retrouvée chez 78.22% en moyenne. Tous les patients retournent à leur ancienne occupation. Les résultats fonctionnels de la main sont excellents chez 48.84%, bons chez 18.6%, satisfaisants chez 25.58%, et mauvais chez 6.98%.

Conclusion: Les fractures carpométacarpales et dislocations des doigts ne sont pas fréquentes, car c'est une blessure violente. L'incidence de faux diagnostic est élevée. Le pouvoir de serrer la main de la main blessée est passée à 78% par rapport au normal. Un bon diagnostic et un traitement précoce sont indispensables pour une bonne guérison.

Mots clés: *Carpometacarpal joint, fracture, dislocation, long finger, operarative treatment,*

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SOME DENTAL MORPHOLOGICAL TRAITS OF THE CHAM ETHNIC GROUP IN NINH THUAN

Nguyen Thi My Linh*, Nguyen The Dung*

ABSTRACT

Objective*:** To study some dental morphological characteristics of the Cham people in Ninh Thuan. ***Method: The shovel-shaped morphology of maxillary central incisors, cusp of Carabelli of maxillary first molar and central groove patterns of mandibular first molars were studied from 80 pairs of studying casts of the Cham ethnic group in Ninh Thuan. ***Results:*** Non-shovel-shaped trait of maxillary incisors is more prevalent. There is no significant difference in the prevalence of shovel-shaped morphology of maxillary central incisors between contralateral arches. The cusp of Carabelli trait is also not predominant between contralateral arches. Y-pattern of central groove is predominant. ***Conclusion***: Cham people have similar dental morphological traits to those of Ragai and Ede people.

I. INTRODUCTION

Tooth morphologies are source of study not only for dentists but also for anthropologists because teeth contain valuable traits helpful for researches in anthropology, genetics and evolution.

Historically, many studies about tooth anthropology have been carried out for a long time: De-Terra (1905), Hrdlicka (1911,1920), Flower (1985) and etc. In Vietnam, the scientists have researched on morphological traits of Vietnamese teeth such as Ede, Coho (Hoang Tu Hung), Katu (Phan Anh Chi), Raglai (Nguyen Thi My Linh). Among tooth morphologies, shovel-shaped of maxillary incisors, cusps of Carabelli and groove patterns are the characteristics providing the valuable metric to distinguish different ethnic groups. Within the scope of this study, with the desire to contribute to the dental anthropological source of the Vietnamese ethnic groups, we conducted the collection of studying samples, data analyzation on the described characteristics of Cham ethnic group and compared these dental morphologies to other ethnic groups in the country with the aim of: Within the scope of this research, with the desire to contribute to the dental anthropological material source of the Vietnamese ethnic community, we conduct the collection of function samples and data extraction on the characteristics described above Cham people 's teeth in Ninh Thuan and comparing the morphology of the Cham people's teeth with other ethnic groups in the country with the aim of:

* Studying the prevalence of shovel-shaped traits of maxillary central incisors.

* Studying the prevalence of cusp of Carabelli of maxillary first molar.

* Studying the prevalence of Y-shaped pattern of central groove of mandibular first molar

* Comparing the anthropological characteristics of Cham people in Ninh Thuan with other ethnic groups in the country.

II. MATERIALS AND METHODS

1.1. Materials: 80 pairs of studying casts were collected from 80 Cham people aged

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18-25 years old, whose parents are Cham living in Ninh Thuan.

Exclusion criteria: Poor quality cast, chipped or broken teeth; worn teeth; large cavities and restorative teeth.

The studying casts were taken using Alginate and poured with hard plaster within 3 minutes after removing the impressions from the mouth.

Age of study from 18-25 years old, when permanent teeth erupted almost complete and teeth have not been worn much.

Sample size: size of sample was calculated based on the formula:

$$n = \frac{Z^2_{1-a/2}\, P\,(1-P)}{d^2} = \frac{1{,}96^2 \times 0{,}298 \times (1-0{,}298)}{0{,}1^2} = 80$$

Z21-α / 2 = 1.96, with α being a type 1 error (α = 0.05) 95% confidence level

p = 29.8% (based on the study of the same author group (2014) about shovel-shaped incisors on Raglai ethnic people belonging to the Malyo-Ponesian language family with the Cham people d: allowable error, taken as 0.1 (10%). Hence, the minimum of sample size is 80 people.

2.2. Method: Descriptive cross-sectional study, analyzed whole dentitions.

2.2.1. Shovel-shaped characteristics (SSC): Observed visually by eyes and 4X magnification loupes the lingual surfaces of maxillary central and lateral incisors, evaluating and classifying based on Hrdlicka study in 1920 [6]:

* No shovel-shaped incisors: There is no trait of fossa: degree 0.

* Light shovel-shaped morphology: There is a light trait of fossa but not deep enough to consider to be classified as half shovel: degree 1.

* Mediocre shovel-shaped morphology: Prominence marginal ridge but shallow fossa: degree 2.

* Shovel-shaped morphology:Prominence marginal ridge and prominence fossa: degree 3

2.2.2. Cusp of Carabelli: evaluation and classification according to Dahlberg (1963) [12]:

- Level 0: no ridges, pits or any features of cusp of Carabelli.
- Level1: a slight ridge and groove.
- Level 2: a small pit with minor grooves diverging from depression.
- Level 3: double vertical ridges or slight and incomplete cusp outline.
- Level 4: Y form: moderate grooves curving in opposite directions.
- Level 5: small tubercle.
- Level 6: broad cusp outlines moderate tubercle.
- Level 7: large tubercle with free apex.

The subjects of the cusp of Carabelli are divided into three groups: no Carabelli expression (grade 0); Carabelli pits and grooves (Grade 1,2,3,4) and Carabelli tubercle (grade 5,6,7).

2.2.3 Central groove patterns of mandibular 1st molar: evaluation and classification according to Jorgensen study in 1955 [7]:

* Y-pattern: mesiolingual cusp and distobuccal cusp meet at central fossa.

* + pattern: mesiobuccal cusp and distolingual cusp meet at central fossa.

* X-pattern: mesiobuccal cusp, mesiolingual cusp, distobuccal cusp and distolingual cusp meet at central fossa.

III. RESULTS AND DISCUSSION

***3.1. Shovel-shaped morphology of incisors*:** The results show that the percentage of shovel-shaped morphology of central incisors is more prevalent and the percentage of non-shovel-shaped morphology is low (table 1). Additionally, there is no significant difference in the characteristics of shovel-shaped morphology of maxillary central incisors between contralateral arches. These results are similar to the study of Hrdlicka [6], Ling [10] and Phan Anh Chi [1]. This demonstrates that the shoved-shaped morphology is symmetrical even though their levels of expressions are not similar in contralateral arches.

Table 1: ***The percentages of levels of shovel-shaped expressions of maxillary central incisors***

	0 (%)	**1** (%)	**2** (%)	**3** (%)	**p**
Right	0,4	41,7	21,4	36,5	0,94
Left	0,5	43,5	23,6	32,4	
Both	0,5	42,6	22,5	34,4	

The results of figure 1 and table 2 show statistically significant differences in the level of expression of shovel-shaped morphology of maxillary central incisors, between the Cham and the other ethnic Vietnamese, Ede, Coho and Katu but there are not statistically significant differences with Raglai people.

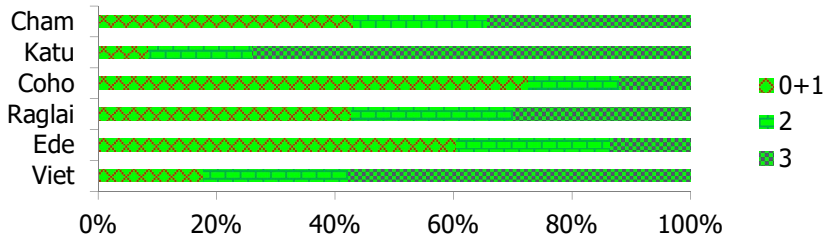

Figure 1: Distribution of shovel-shaped incisors of some ethnic groups in the country

Table 2: Comparison of levels of shovel-shaped morphology expressions between the Cham and some other ethnic groups in the country.

Pairs in comparision	**0+1** (%)	**2** (%)	**3** (%)	**P**
Chăm	43,2	22,5	34,4	0,0003
Việt	17,86	24,4	57,74	
Chăm	43,2	22,5	34,4	0,0021
Êđê	60,45	26,12	13,43	
Chăm	43,2	22,5	34,4	< 0,0001
Cơho	72,67	15,33	12	
Chăm	43,2	22,5	34,4	0,67
Raglai	42,8	27,4	29,8	
Chăm	43,2	22,5	34,4	< 0,0001

3.2. Cusp of Carabelli: the study's results indicate that cusp of Carabelli characteristics manifest the most prevalence as "no expression" trait, followed by pits and grooves. There is no difference in the level of expression of cusp of Carabelli characteristics between the two contralateral arches (Table 3).

Table 3: Cusp of Carabelli trait of maxillary first molar

	0 (%)	**1** (%)	**2** (%)	**3** (%)	**4** (%)	**5** (%)	**6** (%)	**7** (%)	**p**
Right	27,5	19,5	16,1	12,6	16,8	4,3	2,8	0,4	0,995
Left	28,9	17,1	18,9	12,6	12,6	4,7	3,4	0,8	
Both	28,2	18,3	17,5	12,6	15,2	4,,5	3,1	0,6	

Table 4: Comparison of cusp of Carabelli levels between Cham ethnicity and some other ethnic groups in the country

Pairs in comparision	**Không có biểu hiện Carabelli** (%)	**Carabelli dạng hố và rãnh** (%)	**Carabelli dạng núm** (%)	**P**
Chăm	28,2	63,6	8,2	0,1695
Việt	40,74	53,34	5,92	
Chăm	28,2	63,6	8,2	0,0913
Êđê	31,58	51,13	17,29	
Chăm	28,2	63,6	8,2	0,5741
Cơ ho	35,09	57,89	7,01	
Chăm	28,2	63,6	8,2	0,005
Raglai	19,3	55,8	24,9	
Chăm	28,2	63,6	8,2	0,516
Katu	35,5	56	8,5	

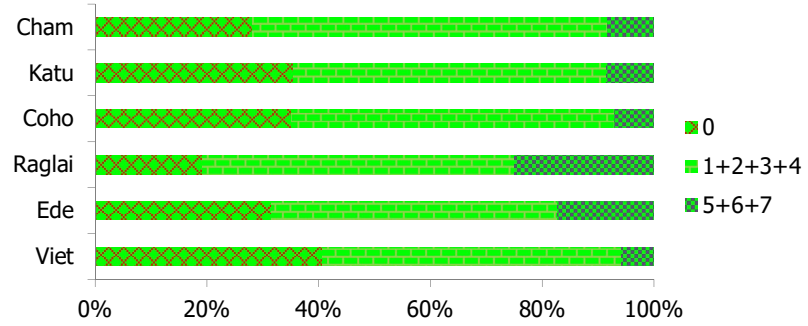

Figure 2: Distribution of Cusp of Carabelli of some ethnic groups in the country

The results in Table 4 and figure 2 exhibited that the distribution of cusp of Carabelli characteristics in Cham people is different from that of Raglai people, but there is no difference between the ethnic Vietnamese, Ede, Co ho and Katu.

3.3. Central groove pattern of mandibular first molars: the "Y" groove pattern dominates in Cham people's dentitions. (Table 5). In comparison to other ethnic groups in the country, the percentage of central groove pattern in Cham people is different from that of Viet, Ede, Raglai and Coho ethnic groups (p <0.001) (graph 3).

Table 5: Comparison of the ratio of the central groove patterns of mandibular first molar between the Cham and other ethnic groups in the country

Pairs in comparision	**"+"pattern** (%)	**"X" pattern** (%)	**"Y" pattern** (%)	**P**
Cham	36,5	9,5	54	< 0,001
Viet	12,5	0,88	86,62	
Cham	36,5	9,5	54	< 0,001
Ede	15,27	0	84,73	
Cham	36,5	9,5	54	< 0,001
Raglai	9,5	8,1	82,3	
Cham	36,5	9,5	54	< 0,001
Coho	11,11	0	88,89	

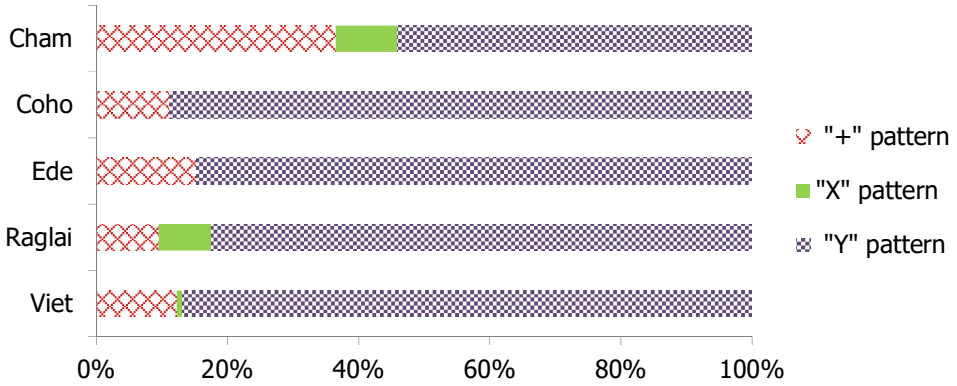

Figure 3: Comparison of central groove patterns among ethnic groups in the country.

In summary, the anthropology characteristics of Cham people in Ninh Thuan compared to other ethnic groups in the country:

- Shovel-shaped morphology of central incisors: Cham people are similarto Raglai people.

- Cusp of Carabelli trait: Cham people are similar to Ede, Viet, Coho, Katu people.

- Central groove pattern of mandibular first molar: the Cham people are different from Raglai, Ede and Coho ethnic groups.

In terms of human anthropology, Cham people belong to the Nam Dao linguistic system (Malayo-Ponesian), which is closely related to Ede, Raglai, Churu and Giarai ethnic groups. The dentitions of Cham people in Ninh Thuan also have similar characteristics with Raglai and Ede people.

IV. CONCLUSION

- Shovel-shaped morphology of maxillary central incisors

Central incisors: the percentage of non-shovel-shaped morphology (degree 0 + 1) is: 43.2%; mediocre shovel-shaped (level 2) is: 22.5% and shovel-shaped morphology (level 3): 34.4%. There is no significant difference in the level of expression of shovel-shaped morphology between two contralateral arches.

- Cusp of Carabelli characteristic of maxillary first molars

No Carabelli expression: 28.2%; Carabelli with pits and grooves: 63.6%; Carabelli with tubercle shape: 8.2%. There is no significant difference in the level of expression of Carabelli characteristics between the two contralateral arches.

- Central groove patterns of mandibular first molars

Y- pattern: 54%; X- pattern: 9.5% and + form: 36.5%.

In comparison to other ethnic groups in the country, dental characteristic anthropology of Cham people in Ninh Thuan have following traits:

. Shovel-shaped incisors: Cham people are close to Raglai people.

. Cusp of Carabelli: Cham people are close to Ede, Viet, Coho, Katu people.

. Central groove pattern of first mandibular molar: Cham people are different from Raglai, Ede and Coho ethnic groups.

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RÉSUMÉ:

QUELQUES TRAITS MORPHOLOGIQUES RELATIFS AU SYSTÈME DENTAIRE CHEZ L'ETHNICITÉ CHAM À NINH THUAN

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Objectifs*:* Etudier quelques caractéristiques de la morphologie dentaire chez l'ethnicité Cham de Ninh Thuan.

Méthode: La morphologie qui rappelle les pelles des incisives à la partie centrale du maxillaire, la partie saillante de Carabelli, de la première molaire, et la rainure des molaires du mandibule, ont été étudiées chez 80 pairs de l'ethnicité Cham de Ninh Thuan.

Résultats: Les incisives n'ayant pas la forme de pelles se retrouvent pour la plupart. Il n'y a pas de différence notable. Le modèle Y de la rainure centrale est prédominant.

Conclusion: Les Cham ont la même morphologie dentaire que les Ragai et les Ede.

SURVEYING THE SITUATION OF USING ANTIBIOTIC IN CAN THO CITY GENERAL HOSPITAL

Bui Tung Hiep*

ABSTRACT

Objectives: Survey characteristics of the research sample at Can Tho City General Hospital. Surveying the effectiveness of antibiotic use at Can Tho City General Hospital. ***Subjects and research methods:***Retrospective study of over 100 medical records at Can Tho City General Hospital 1 from January, 2018 – March, 2018 for inpatient treatment with a hospital stay of 2 days or more and prescribing treatment with at least 1 type of antibiotic during hospitalization. ***Results:***Of the 100 patients studied, 53% were female and 47% were male. Proportion of female patients higher than in male patients 18-60 (27%; 25%) and over 60 (25%; 22%). Most patients with normal renal function (63.04%) and no patients suffer together (35%). Patients with respiratory infections accounted for the highest proportion in the hospital (45.33%), *Streptococcus pneumoniae* accounted for the highest proportion (36.36%) in the bacteria isolated in the research sample. The most used group of Beta - lactam accounted for 56.63%, specifically Cefoxitin (accounting for 21.69%). Injectable antibiotics used the most (90.07%), antibiotics used for prophylactic purposes accounted for 67.79%. Adverse events account for 5% of research records. The average antibiotic duration for each patient is 4 days and the average hospital stay / patient is 8 days. Percentage of patients treated with support, decreased by 78%. ***Conclusion:***Research shows that the use of antibiotics at the hospital is reasonable and safe.

Keywords: *Antibiotics, antimicrobial use, infection.*

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Reviewed date: 28/5/2019

I. INTRODUCTION

Antibiotics are an important group of drugs and are widely used in treatment. The birth of antibiotics saved millions of lives, marking a new era of medicine for treating infectious diseases. However, due to the widespread and prolonged use, it is not reasonable, so the antibiotic resistance of microorganisms is increasing. The level of drug resistance is increasingly severe, affecting treatment effectiveness, high risk of death, prolonged treatment period, high treatment costs, affecting the health of patients and the community. Therefore, the survey of the use of antibiotics at health care facilities is one of the solutions that contribute to making recommendations to make the use of antibiotics safer, more reasonable and improve the effectiveness. fruit and shorten the duration of treatment.

But, most of the studies examined the use of antibiotics that was conducted recently in large-scale hospitals. Meanwhile, research investigates the use of antibiotics at Can Tho City General Hospital less done in recent years. Therefore research: "Surveying the situation of using environment in Can Tho City General Hospital" conducted with two objectives:

- Survey characteristics of the research sample at Can Tho City General Hospital.

- Surveying the effectiveness of antibiotic use at Can Tho City General Hospital.

II. SUBJECTS AND RESEARCH METHODS:

1. Subjects

The medical records of inpatient patients at Can Tho City General Hospital meet the following selection criteria and exclusion criteria:

Selection criteria:

- Having a hospital stay of 2 days or more.
- Prescribed for treatment with at least one type of antibiotic during hospitalization.
- *Exclusion criteria:*
- Cases of patients treated as outpatients or discharged on the same day.
- Prescribed treatment with topical antibiotics (eyedrops, out of skin).
- Patients positive for HIV / AIDS.

2. Methods

Research design:

Methods Retrospective descriptive research.

Sampling method:

Randomly selected 100 patients treated at the hospital during the period from 1/2018 - 3/2018 based on selection criteria and exclusion criteria.

According to the data provided by the storage information department of Can Tho City General Hospital, a random arrangement based on Excel software randomly took samples and took the first 100 medical records to conduct research.

Methods of information collection:

The medical records meet the selection criteria and the exclusion criteria are filled out in a patient information form (Appendix 1).

Data processing methods:

Analysis and statistical processing software Microsoft Excel 2010. The analysis used in the study: frequencies and percentage rate.

Sample size:

Number of samples: 100 medical records

The provisions in the research:

Age: calculated according to the calendar year by taking the year of admission except for the year of birth.

Gender: consists of two values (Male; Female).

Serum creatinine concentration: recorded by medical staff in the medical record.

Liquidation coefficient: calculated according to the formula in Appendix 2.

Infectious diseases: Target organ damage is diagnosed by a doctor and recorded in the medical record.

Characteristics of infectious diseases of the research sample: the disease uses antibiotics to treat by doctors diagnosed and recorded in medical records.

Number of antibiotics used: based on medical records.

Sugar using antibiotics: based on medical records

Purpose of use: based on the length of the treatment and the surgical card written in the medical record.

Duration of treatment: From the first day of using antibiotics to the last day of using antibiotics.

Characteristics of isolated bacteria: based on microbiological test in the medical record.

Duration of treatment: From when the patient is hospitalized to the day the patient is discharged.

III. RESULTS AND DISCUSSION

1. Characteristics of the research sample

The research was conducted at Can Tho City General Hospital in the period from 1/2018 - 3/2018 per 100 patients we obtained the following results:

1.1. Characteristics of age and gender

The survey of 100 medical records of patients, shows the percentage of patients according to age and gender statistics in table 3.1.

Table 1. Distribution of patients by age and gender

Age groups	Gender					
	Male		Female		Total	
	Patients	Rate (%)	Patients	Rate (%)	Patients	Rate (%)
< 1	0	0	0	0	0	0
1 – 18	0	0	1	1	1	1
18 – 60	25	25	27	27	52	52
>60	22	22	25	25	47	47
Total	47	47	53	53	100	100

In terms of gender of inpatient patients in the hospital, the survey showed that in the study sample, mainly female patients (53%) accounted for a higher rate than men (47%). The rate of antibiotic use in both sexes is highest at the ages of 18-60 years old (men account for 25%, women account for 27%).

The age group from 18-60 accounts for the highest rate of antibiotic use (52%), the age group <1 accounts for the lowest rate (0%). In men, the rate of antibiotic use is highest in the age group of 18-60 years (25%), the lowest rate in 2 age groups <1 (0%) and from 1 to 18 years (0%). In women, the rate of antibiotic use is highest in the age group of 18-60 years (27%), the lowest in the age group <1 (0%).

1.2. Characteristics of kidney function

Evaluate the patient's kidney function to help physicians choose the drug as well as the dose of the drug more appropriately. Renal function of patients is assessed by creatinine clearance coefficient (Clcr). Of the total 100 medical records with 92 medical records (accounting for 92%) have sufficient information to calculate creatinine clearance coefficients, and 7 medical records (accounting for 8%) lack of weight information or creatinine index of patients. Therefore, 92 medical records calculated creatin clearance are presented in the following table:

Table 2. The patient's renal function according to creatinine clearance coefficient

The degree of kidney failure	Clcr (ml/ minute)	Patients	Rate (%)
0	Clcr > 60	58	63,04
I	40 < Clcr ≤ 60	24	26,09
II	20 < Clcr ≤ 40	8	8,70
IIIa	10 < Clcr ≤ 20	2	2,17
IIIb	5 < Clcr ≤ 10	0	0,00
IV	Clcr ≤ 5	0	0,00
Total		**92**	**100**

Renal function according to creatinine clearance (Cockroft & Gault formula) is one of the most important indicators to monitor when using highly toxic antibiotics on the kidneys such as Aminoglycoside, Cephalosporin. In addition, this index is also needed to calculate the dose or dilate the dosing interval when the patient has impaired renal function (Pham Thi Thuy Van, 2013).

Most patients in the study sample had normal renal function, accounting for 63.04%. And patients with impaired renal function only accounted for 36.96%. This group of subjects should be considered when using the dose for the use of antidepressant in patients with impaired renal function, especially Cephalosporin and Minoglycosid antibiotics.

1.3. Characteristics of attached diseases of the research sample

In the 100 study patients, there were recorded diseases such as tuberculosis, gastritis, type II diabetes, senility, pneumonia, fever, dyspnea, unexplained allergies, acute diarrhea, kidney failure. The results are presented in table 3.3.

Table 3. Characteristics of co-morbidities of the research sample

Order number	Attached diseases	Patients	Rate (%)
1	No attached disease	35	35
2	An accompanying disease	20	20
3	Two attached diseases	15	15
4	Three attached diseases	18	18
5	More than three attached diseases	12	12
Total		**100**	**100**

According to the research results, the majority of patients without comorbidities (35%) and the number of co-morbidities with more than three diseases accounted for the lowest rate (12%).

1.4. Characteristics of bacterial infections of the research sample

The study investigated 100 patients, 78 patients indicated that they were infected. The results of infectious diseases of the research sample and accompanying diseases are shown in Table 3.4.

Table 4. Characteristics of the sample contamination diagnosis research

Order number	Infection form	Patients	Rate (%)
1	Injury	1	1,33
2	respiratory infections	34	45,33
3	Kidney-urinary infections	15	20
4	Gastrointestinal infections	10	13,33
5	Other infections	15	20
Total		**75**	**100**

The results showed that patients with respiratory infections were the most common (accounting for 45.33%), while the injured patients had the lowest rate of antibiotic treatment of antibiotics (accounting for 1, 33%).

1.5. Characteristics of bacteria isolated in the study sample

Bacteria test is a clinical evidence to confirm the presence or absence of infection in patients. Results of isolated bacteria will help doctors choose antibiotics for more reasonable treatment. By studying 100 patients surveyed, obtained 11 patients with isolated bacteria. Results of isolated bacteria are presented in Table 3.5.

Table 5. List of bacteria isolated in the study sample

Type Of Bacteria	Bacteria	Patients	Rate (%)	Total (%)
Bacteria Gr (+)	Streptococcus pneumoniae	4	36,36	36,36
Bacteria Gr (-)	Enterobacter aerogenes	1	9,09	63,64
	Escherichia coli	3	27,27	
	Acinetobacter baumannii	3	27,27	
Total		**11**	**100**	**100**

Microbial testing is a laboratory test to confirm whether or not there is infection in the patient. Results of isolated bacteria will help doctors choose antibiotics for better treatment.

According to the survey results, in 11 patients isolated bacteria showed that Streptococcus pneumoniae accounted for the highest percentage (36.36%), followed by Escherichia coli (12%) and Acinetobacter baumannii (12%). The bacteria cause common respiratory and gastrointestinal infections so the patients' part in the study often has respiratory infections (45.33%) and urinary tract (20%). This result is similar to the research results of Tran Do Hung et al (2012) at Can Tho City General Hospital and Nguyen Thi Nhon (2017) at E. Hospital.

2.Current situation of antibiotic use

2.1. Rate and number of antibiotics / antibiotic groups used

During the treatment at the hospital departments, the patients used many antibiotics. The results are shown in Table 3.6.

Table 6. Rate and number of antibiotics / antibiotic groups used

Order No.	Antibiotic groups		Frequency	Rate (%)	Total	Rate (%)
1	Beta-lactam	Amoxiciclin	22	13,25	102	61,45
		Ampicilin	7	4,22		
		Cefalothin	3	1,81		
		Cefepim	1	0,60		
		Cefotaxim	3	1,81		
		Cefoxitin	36	21,69		
		Ceftazidim	9	5,42		
		Ceftezol	9	5,42		
		Ceftriaxol	5	3,01		
		Cefuroxime	6	3,61		
		Piperacilin	1	0,60		
2	Aminoglycosid	Amikacin	28	16,87	39	23,49
		Gentamicin	11	6,63		

3	Macrolid	Vancomycin	3	1,81	3	1,81
4	Quinolon	Ciprofloxacin	3	1,81	10	6,02
		Levofloxacin	2	1,20		
		Moxifloxacin	5	3,01		
5	Co-trimoxazol	Co-trimoxazol	1	0,60	1	0,60
6	Phenicol	Cloramphenicol	1	0,60	1	0,60
7	Nitroimidazol	Metronidazol	9	5,42	10	6,02
		Tinidazol	1	0,60		
Total			**166**	**100**	**166**	**100**

During treatment at the hospital, the patients used many types of antibiotics. The Beta-lactam group was used the most (56.63%), then the Amogoglycoside group (23.49%). Cefoxitin, a second generation Cephalosporin antibiotic with slow intravenous injection, has a broad spectrum of antibacterial activity and is mainly on Gram (-) and Gram (+) most used (21.69%) at In the hospital, Amikacin (accounting for 16.87%), Amoxicilin (accounting for 13.25%) and Gentamicin (6.63%).

This result is different from the research results of Tran The Thai (2010), showing that the new Cefotaxim is the most used antibiotic (35.67%) and according to the research results of Nguyen Thi Hien Luong at the Viet Duc hospital (2012) also showed that Cefotaxim is most used in hospitals with the rate of 34.84%. The cause of this difference is that Cefotaxim recently suspected antibiotic caused ADR the most in 2018 (10.5%) (Drug Alert No. 4, 2018).

At the same time, this result is also consistent with the Ministry of Health's Use of Antimicrobial Guidelines (2015) in combination with Cephalosporin antibiotics and Amogoglycoside antibiotics to treat respiratory infections.

According to the survey, in 100 study patients, there are 7 groups of antibiotics used in treatment.

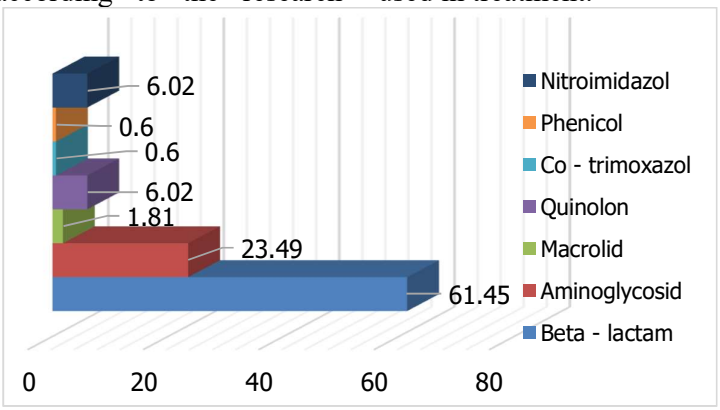

Figure 3.1. Diagram of the distribution of antibiotic groups used in treatment

According to the research results, the group Beta-lactam is most used (accounting for 56.63%), followed by Amogoglycoside group (accounting for 23.49%). The antibiotic group used at least in hospitals in treatment includes: Phenicol (accounting for 0.60%) and Co - trimoxazol (accounting for 0.60%).

2.2 . Antibiotics road

Survey of 100 patients, the results obtained related to the use of antibiotics as follows:

Table 7. Percentage of antibiotics road

Order No.	Antibiotics road	Number of antibiotics	Rate (%)
1	Injection	136	90,07
2	Oral	9	5,96
3	Injection and Oral	6	3,97
Total		**151**	**100**

When choosing antibiotics suitable for the disease, the work to be considered next is the choice of road for that antibiotic to be used appropriately and effectively, (Do Thi Hue, 2010).

According to survey results, injectable antibiotics account for a high proportion (90.07%); oral antibiotics accounted for 5.96%; antibiotics used both for injection and oral administration accounted for 3.97%. This is consistent with the research results of Le Thi Huong at the Internal Medicine Department of Tuyen Quang General Hospital (2010), showing that injectable drugs account for 60.57% and oral drugs account for 39.43%. According to the results of Tran Thi Hong Nhung (2011) research on patients with renal insufficiency in pediatrics, Bach Mai hospital showed that injectable antibiotics accounted for 69.60% and 30.40% oral route.

2.3. Classify patients according to the intended use of antibiotics

Through a survey of 100 patients, the patients were classified according to the purpose of antibiotic use as follows:

Table 8. Classifying patients according to the purpose of antibiotic use

Order No.	Purpose of use	Patients	Rate (%)
1	Use antibiotic treatment	45	30,20
2	Use prophylactic antibiotics	101	67,79
3	Use antibiotics both prophylactic and treatment	3	2,01
Total		**149**	**100**

According to Miles and Bruke's study, proper prophylactic antibiotic use will reduce the risk of infection after surgery by 50% (Le Thi Kim Thanh, 2003; Bruke J.F et al, 1993).

Through a survey of 100 medical records, the results showed that antibiotics used for prevention purposes accounted for the highest rate (67.79%), antibiotics used for treatment purposes accounted for 30.20%. Finally, antibiotics are used for both treatment and prophylactic purposes, accounting for 2.01%.

According to research results, the majority of hospitalized patients are elderly patients, weakened immune systems. Therefore, the antibiotic regimen is used for the purpose of preventing large-scale infection in the study sample.

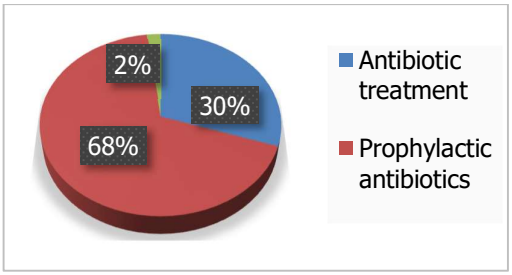

Figure 3.2. Chart of classification of patients according to the purpose of antibiotic use

2.4. The adverse events observed in patients treated with antibiotics

Surveying through the medical records in the study showed that in 100 medical records, there are only 5 medical records with clear information about adverse events occurring during treatment with antibiotics such as allergies and digestive disorders. The results are shown in Figure 3.3.

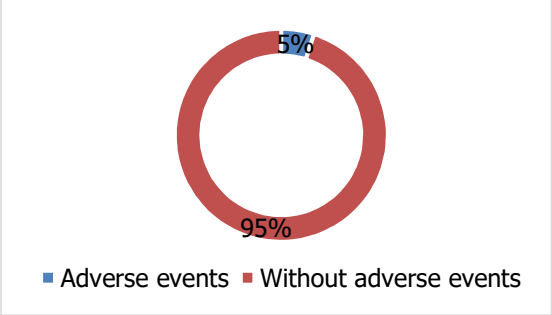

Figure 3.3. Chart of adverse events recorded in patients using antibiotics

According to the research results, most adverse events of the drug during antibiotic treatment were rarely recorded in retrospective medical records, accounting for only 5%. Adverse events occur completely as a mild allergic reaction such as itching, redness.

2.5. Time antibiotics and duration of hospitalization

One of the principles of using antibiotics is to treat the prescribed time. This helps reduce bacterial resistance. Survey results of antibiotic use time and average hospital stay time are shown in Table 3.9.

Table 9. Antibiotic duration and average length of hospital stay

Order No.	Duration of antibiotics and hospital stay	Day
1	Time to use antibiotics	4,32 ± 3,11
2	Hospital stay time	8,11 ± 5,65

The average time of antibiotic use per patient is 4 days and the average length of hospital stay for each patient with antibiotic use is 8 days.

The medical records conducted mainly are respiratory infections and the purpose of antibiotic use is mostly used for surgical prevention, the above research results show that the length of antibiotic treatment is appropriate with the recommendation of the Ministry of Health (Ministry of Health - Guidelines for antibiotic use, 2015).

2.6. Treatment results at discharge

The treatment effect is assessed according to the doctor's decision and is recorded in the medical record. The results are as follows:

Table 10. Treatment results at discharge

Order No.	Treatment results	Patients	Rate (%)
1	Cured	20	20
2	Reduce	78	78
3	Constant	2	2
4	More severe disease	0	0
5	Transfer	0	0
Total		**100**	**100**

The proportion of patients with reduced support accounts for a high proportion (78%), followed by the proportion of patients treated with remission accounting for 20%. There are two cases of patients unchanged (2%). There are no more severe cases or referrals. This may prove that the treatment process in hospitals in general and the use of antibiotics in particular is relatively reasonable at Can Tho City General Hospital in 2018.

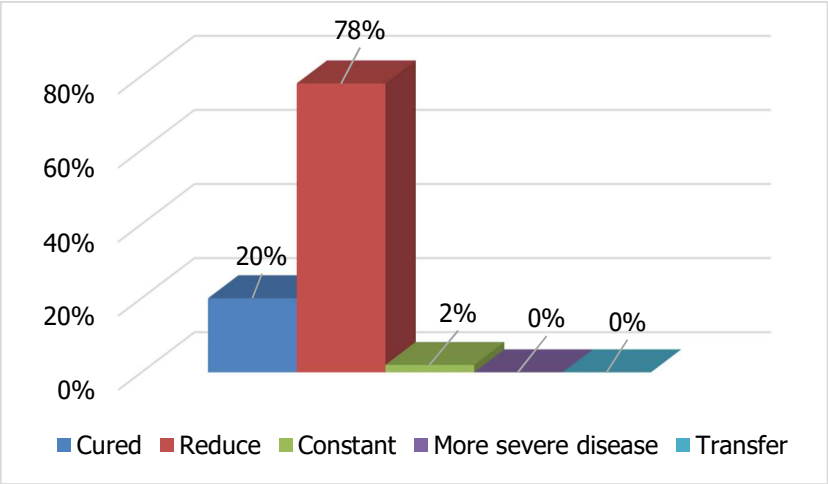

Figure 3.4. Chart of treatment results at discharge

IV. CONCLUSION

Through a retrospective study "Survey on the use of antibiotics at Can Tho City General Hospital" from January 2018 - 3/2019, we draw some conclusions as follows:

1. General characteristics of the research sample

Female patients account for a higher proportion than male patients in both ages from 18-60 and over 60 years old. The majority of female patients (53%) account for a higher rate than men (47%).

Most patients in the study sample had normal renal function (accounting for 63.04%).

Most patients do not have comorbidities (35%).

The proportion of patients with respiratory infections accounted for the highest proportion in the hospital (45.33%), then urinary tract infections (accounting for 20%).

Gram (-) group accounts for a higher rate than Gram (+) group (63.64% compared to 36.36%).

Among the bacteria isolated in the study sample, Streptococcus pneumoniae accounted for the highest percentage (36.36%), followed by Escherichia coli (12%) and Acinetobacter baumannii (12%).

2. Current situation of using antibiotics in hospitals

The most used group of Beta - lactam accounted for 56.63%, followed by Aminoglycoside group, accounting for 23.49%. Cefoxitin is the most used drug (accounting for 21.69%) in the treatment departments in the disease. Institute, followed by Amikacin (accounting for 16.87%), Amoxicilin (accounting for 13.25%), finally Gentamicin (6.63%), Amoxicillin (accounting for 13.25%), finally, Gentamicin (6.63%)

Injection is the most commonly used sugar, accounting for 90.07%.

Antibiotics are used mostly for prophylactic purposes (accounting for 67.79%).

The average time of antibiotic use for each patient is 4 days and the average length of hospitalization / patient is 8 days. At least 1 day for antibiotics, at most 7 days., decreased by 78%; after that, patients treated with 20%.

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RÉSUMÉ:

SURVEILLANCE DE L'USAGE D'ANTIBIOTIQUES À L'HÔPITAL CENTRAL DE LA VILLE DE CAN THO

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Objectifs: Trouver les traits caractéristiques de l'échantillon de recherche à l'hôpital général central de la ville de Can tho.

Sujets et méthode: L'Etude retrospective est portée sur plus de 100 dossiers à l'hôpital général central 1 de Can tho, de Janvier 2018 – Mars 2018, sejournant 2 jours ou plus à l'hôpital, et la prescription est accompagnée au moins d'un type d'antibiotique.

Résultats: Sur les 100 patients étudiés, 53% étaient du sexe féminin, et 47% masculins. Le nombre de femmes était supérieur aux hommes, de 18 à 60 ans : 27% et 25% respectivement, et plus de 60 ans : 25% et 22% respectivement. La fonction rénale est restée normale chez 63.04%. et 35% ne se plaignaient d'aucune affection.

Les patients ayant des affections respiratoires sont à un taux élevé : 45.33%, dont le Streptococcus pneumonia à 36.36%, taux le plus élevé. L'Antibiotique le plus fréquemment utilisé étant le Bêta lactam, à un taux de 56.63%, en particulier la Cefoxitin (21.69%), Les antibiotiques sous forme injectable sont utilisés à 90.07%, et ceux, dans le but prophylactique, étant de 67.79%. Les effets adverses (non voulus) étaient de 5% dans notre étude. La durée moyenne d'administration pour un patient, 4 jours, et la durée d'hospitalisation 8 jours. Le pourcentage de patients nécessitant un support pour le traitement est diminué de 78%.

Conclusion: Ce travail montre que l'usage d'antibiotiques est justifié et raisonnable.

Mots clés: *Antibiotics, antimicrobial use, infection.*

TREATMENT OF DISTAL METAPHYSEAL FRACTURES OF THE TIBIA WITH TITANIUM ELASTIC NAILING (TEN)

Nguyen Duc Binh*

ABSTRACT

Purpose: To determine the radiographic and clinical outcomes for distal metaphyseal tibia fractures treated with TEN. **Design:** Prospective analysis. **Method and materials:** A total of 51 patients with 43 OTA/AO type A and C1 distal metaphyseal tibial fractures (< 3cm) treated with TEN. **Result:** Distal of the fracture from the joint line averaged 2.8 cm (range, 0-3). Mean follow-up was 21,2 months (range, 12-36). There was no osteitis, pseudarthroses. Malunion occurred in 5 fractures (10,4%%) and were significantly associated with open fractures. Final functional outcome average 87,5 (OLERUD score). **Conclusions:** Five years of clinical experience have shown that the TEN can provide reliable fixation for unstable distal metaphyseal tibia fractures. Secondary angulation and nail migration were always related to technical error.

Key words: *distal tibia fracture, titanium elastic nailing.*

I. INTRODUCTION

Distal tibial fractures have historically been treated with open reduction and internal fixation using plates. Although this technique provides predictable reduction quality, it adds the risk of additional soft tissue injury [28] [30]. Wound problems with rates of resultant infection up to 50% have been reported as the main disadvantage associated with this technique [26] [8, 19] [1] [14] [18]. Olerud and Karlstrom [23] reported that delayed healing, infection and implant problem are often associated with plate osteosynthesis of the distal tibia. To less these risk, alternative treatment methods including external fixation, staged fixation and minimally invasive surgery have arisen. Intramedullary nailing (IMN) is considered the treatment of choice for diaphyseal tibial fractures [2] [3] [4] [12] [29] and has been expanded to distal metaphyseal tibial fractures to provide indirect reduction (minimally invasive), stable fixation (load sharing) and multiple fixation points [5] [15] [25]. However, because of metaphyseal widening, short segment fixation and intra-articular extension, IMN can be complicated by malunion, nonunion or implant failure [22] [13].

In view of these concerns, we used TEN (titanium elastic nailing) which combines narrow flexible nails and have curved distal tips [17], [9, 10]. These nails are bent by the surgeon before insertion so that distal locking can be achieved when they spread out and obtain a hold in the distal part of the bone. The combination of two nails is the basic requirement but is insufficient if used alone, one or two additional flexible nails are also inserted into the medullary canal.

Therefore, the purpose of this study was to determine the radiographic and clinical outcomes for distal metaphyseal tibia fractures treated with TEN.

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II. PATIENTS AND METHODS

From January 1014 to December 2018, we treated 51 distal metaphyseal tibia fractures, there was 29 right leg and 22 left leg in 32 men and 19 women with a mean age of 55,1 years (29 to 87).

Among the recorded causes of fracture, road accidents accounted for 35 cases and domestic accident for 15, usually in older patients. None of them had associated fractures. 48 patients were in good health, but in 3 the general condition was poor.

Of 51 fractures, 37 were open; three grade I, nine grade II, and two grade III, according to the Gustilo and Anderson system.

The OTA/AO classification of the fractures included 43-A and 43-C1 with metaphyseal extension. Because OTA/AO 43-B are unicondylar and do not have an unstable metaphyseal-diaphyseal extension that could be treated with a nail, these was excluded. An accompanying fibular fracture was 43/51.

The TEN was used for distal metaphyseal tibia fractures within 1,5 to 3 cm above the ankle.

Operative technique

Patients were submitted to local or total anaesthesia then placed on a fracture reduction table using radioscopic control.

When the fibula fracture was located on its peripheral third (up to 10 cm from the edge of the lateral malleolus), the fibular was fixated with the use of neurtralisation plate. In this way, the reduction of the tibia fracture was facilitated, the length of the limb was maintained and its axis during nailing was ensure. When the fracture line was intra-articular extending towards the ankle joint (type C1), one or more intrafragmentary screw were placed in the lower metaphysis of the tibia before the nailing.

The nails with angle distal ends were introduced through a hole drilled in the centre of the medial-anterior and lateral-anterior aspect of the proximal epiphysis. The procedure was radioscopically controlled, the distal beaks were driven to the distal end of the bone and directed to splay from the midline into the lateral cortex as seen in the frontal plane, to ensure effective distal locking.

Follow-up

Patient clinical and radiographic follow-up was at 6, 12, 24 weeks and more.

Initially, patients were splinted in a neutral position. At 2 weeks postoperatively, patients were changed to removable foot ankle support and advanced with therapy-directed range of motion (ROM). Initiation of weight-bearing depend upon fracture, articular extension and numbers of nail, averaged 2,3 months (range, 07-9). Patients with 3 or 4 nail fixation were allowed partial weight-bearing of about 20 kg until the sixth week and full weight-bearing only after the third month. On the contrary, patients with the malleolar or intraarticular tibial fractures (C1) with 2 nail fixation were not allowed partial weight-bearing until the sixth week.

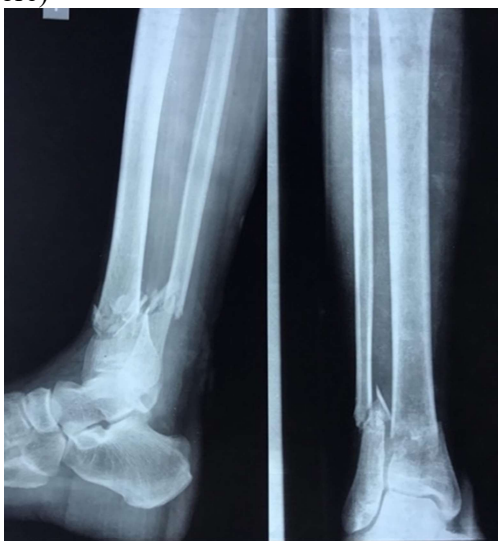
Wound complications were recorded as superficial wound infection without surgical intervention, delayed wound closure or deep infection with surgical intervention.

Radiographic outcomes were evaluated as fracture healing (minimum 3 cortices bridged).

Normal alignment was determined as between 5 degrees varus and 10 degrees valgus. Correlation between malunion, delayed, functional outcomes with open fractures, fracture type, closed injuries of soft

tissue were analyzed. Nonunion was determined as nonunited fractures at 6 months.

Clinical outcome was recorded as final ankle ROM, pain and return to work (Olerud score)



Figue 1. AP and lateral radiograph showing a distal metaphyseal tibia fracture

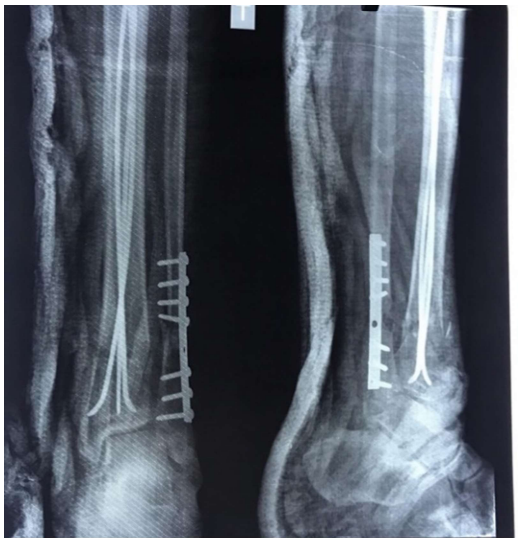


Figure 2. AP and lateral radiograph showing the postoperative reduction and alignment after TEN and plate fixation of the distal fibula were perfomed

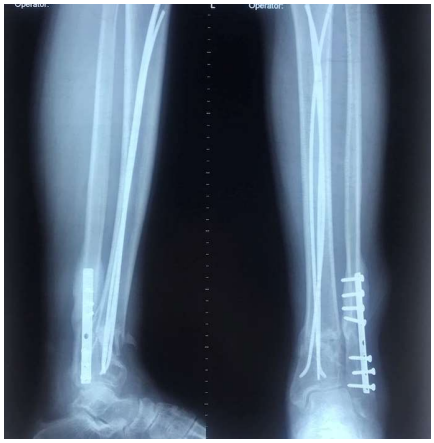


Figure 3. AP and lateral radiograph showing the union at 3rd month.

III. RESULTS

Of the 51 distal metaphyseal tibia fractures, three were lost to follow-up. Mean follow-up was 21,2 months (range, 12-36).

The average distance from the distal extent of the tibial fracture to the plafond was 2,9 mm (range, 0 to 3 mm).

Fractures were healed at an average of 4,7 months. The nunion were significantly associated with open fractures, grade of closed injuries and pattern of the tibia fractures. The union rate of closed fractures before 12 weeks was 62,9% and 23,1 % of open fractures; of closed injury Tscherne type 0, 1 were 72,4% and Tscherne type 2 were 16,7%; of spiral fractures were 72,2% and tranversal, oblique fractures were 35,5%.

Alignment was normal in 43 cases and there was valgus of less than 8^0 in two, varus in two, recurvatum in one. No signification association between increasing fracture severity (43 AO/OTA type fracture), nail numbers and malunion was noted. 3 of 14 open fractures compared with 2 of 34 closed fractures resulted in malunion, which was significant. There was no secondary external rotation.

Final functional outcome average 87,5 (OLERUD score). There was the correlation between functional outcome and open fractures, grade of closed injuries and alignment.

Complications were superficial infection in one. There was no osteitis, pseudarthroses

IV. DISSCUSION

Secondary angulation and migration were always related to technical error, open fracture not to increasing fracture severity (43 AO/OTA type fracture), age, gender and nail numbers. We had no cases of unexpected implant loosening or leg shortening. The failures occurred mostly during the early trials and were usually due to insufficient spread of the curved nail ends and to the use of the two-nail construct on its own. The basic two-nail should always be complemented with at least one additional nail, using 3.5 mm for tibial.

The TEN appears to be particularly safe for treating open tibial fractures, because no reaming is required. We now use it instead of external fixations except for the Gustilo III-B and III-C type [9] [10].

In a comparison versus plate fixation, our study results demonstrated had a higher mean ankle score (Olerud), shorter union time [6, 24] and were similar to inter locking nail about alignment, weight-bearing [22] [16].

An important aspect is the promotion of osteogenesis in compact bone [7]. Although our clinical study allows no definite conclusions to be drawn about the role of flexibility in osteogenesis, it is notable that all distal metaphyseal tibial fractures showed primary consolidation at about 3 months.

All fibular fractures located up to 10 cm proximal from the edge of the lateral malleolus should be fixed with the use of a neutralization plate [20] [11]. In this way, tibial fracture reduction is facilitated, the limb length can be maintained and its axis during nailing is ensured. This strategy leads to stable osteosynthesis, thus avoiding malunion, rotational deviations of the metaphyseal fragment, limb shortening and material failure [21] [27].

V. CONCLUSION

Five years of clinical experience have shown that the TEN can provide reliable fixation for unstable distal metaphyseal tibia fractures. In our study, anatomic alignment was achieved in the majority of cases, there were no pseudarthroses, deep infection, osteitis., functional outcomes were 87,5. Return to previous work status with or without restriction was common.

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RÉSUMÉ:

TRAITEMENT DES FRACTURES AU NIVEAU DE LA MÉTAPHYSE DISTALE DU TIBIA AVEC LA FIXATION PAR DU TITANIUM ÉLASTIQUE (TEN)

Nguyen Duc Binh*

* *Hôpital Général de Saint Paul*

But: Trouver les résultats radiographiques et cliniques des fractures au niveau de la métaphyse distale du tibia traitée avec le TEN

Type du travail: Analyse prospective.

Matériel et méthode: 51 patients avec fractures au niveau de la métaphyse distale du tibia, dont 43 OTA/AO de type A et C1 (< 3cm) traités avec TEN.

Résultats: La distance de la fracture à l'articulation est en moyenne 2.8cm (0-3cm). La surveillance est en moyenne 21.2 mois (12 – 36). Il n'y avait pas d'ostéite, de pseudarthroses. Chez 5 cas, survient la mauvaise union (10.4%), et ces patients avaient une fracture ouverte. Les résultats fonctionnels sont satisfaisants dans 87.5% de cas. (score d'OLERUD)

Conclusion: Cinq annees d'experience Clinique ont montré que le TEN peut fournir une bonne fixation de fracture instable au niveau de la métaphyse distale du tibia. Les erreurs techniques expliquent l'angulation secondaire et la migration du titanium de fixation.

Mots clés: *Distal tibia fracture, titanium elastic nailing.*

SURVEY ON THE SITUATION OF USING TYPE 2 DIABETES MEDICINE AT ENDOCRINOLOGY DEPARTMENT OF CAN THO CITY GENERAL HOSPITAL

Bui Tung Hiep*

ABSTRACT

Objectives: Suvery on the situation of using type 2 diabetes medicine at Endocrinology Department of Can Tho City General Hospital from March 2018 to September 2018. ***Subjects and research methods*:** descriptive cross-sectional retrospective. The study was conducted on patients diagnosed with type 2 diabetes and inpatient treatment at the Endocrinology Department of Can Tho City General Hospital. ***Results:*** In the study, hospitalized type 2 diabetes patients aged 60 to 69 accounted for the highest percentage of 34%. Female patients who account for 70% are 2.3 times higher than male patients with 30%. The proportion of overweight and obese patients is 38%. Patients with a history of diabetes mellitus account for a high rate of 87%. Hypertension is the most common comorbid disease accounting for 65.2%, dyslipidemia accounts for 21.9%. The average fasting glucose 16.77 ± 9.21 mmol / L, while 9% achieved glycemic targets. The average HbA1c is 10.01 ± 2.93%. Treatment regimens: Monotherapy 77%, 23% multi-therapy. The most used insulin group accounted for 82%. The combination of the two drugs accounted for 20%, the combination of three drugs accounted for 3%. Type of insulin combination + Metformin accounted for the highest rate of 9%. Duration of treatment: Most patients treated <7 days accounted for 41%. After the treatment of any capillary blood sugar of any patient, the average reduction was 137.56 mg / dL. The number of patients reaching the target blood glucose was 151, accounting for 75.5%. *Conclusion:* All drugs in the list of antihypertensive drugs used in the study sample belong to groups of drugs that treat hypertension appropriately as recommended by the Ministry of Health in 2017 and the American Diabetes Association. (ADA) 2018.

Keywords: *Type 2 diabetes, Type 2 diabetes medicine*

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I. INTRODUCTION

Diabetes is a global health problem of the 21st century, considered the fourth pandemic in the world after cardiovascular disease, cancer, HIV / AIDS with increasing incidence. The rate of type 1 diabetes increases slowly, whereas type 2 diabetes increases rapidly. In addition, along with an increase in inappropriate food use, less physical activity in children in many countries, type 2 diabetes is on the rise in both children, becoming a health problem. Serious community. According to the World Diabetes Federation (IDF) in 2017, 425 million people worldwide have diabetes. There will be 629 million people with diabetes worldwide in 2045. Diabetes is a chronic disease with genetic factors, which can lead to acute and chronic complications that can lead to disability or death. (Bui Tung Hiep, 2018).

In recent years, along with the economic development as well as life, the proportion of diabetic patients at Can Tho City General Hospital is increasing inpatient treatment. With the desire to contribute to improving the quality of treatment and use of drugs effectively and safely for diabetic patients, the study "Survey on the use of drugs in

patients with type 2 diabetes in endocrinology Can Tho City General Hospital "is conducted with 2 objectives:

- *Survey of characteristics of patients with type 2 diabetes treated in Endocrinology Department of Can Tho City General Hospital.*

- *Survey on the use of drugs for treatment of diabetes type 2 at the Endocrinology Department of Can Tho City General Hospital.*

II. SUBJECTS AND METHODS

1.Subjects

Including patients diagnosed with type 2 diabetes and inpatient treatment at the Endocrinology Department of Can Tho City General Hospital during the period from March 2018 to September 2018.

Selection criteria

- Select patients who meet all of the following criteria:

- Patients with type 2 diabetes are diagnosed according to the American Diabetes Association (2018) and inpatient treatment in Endocrinology.

- Patients ≥ 18 years or older.

Exclusion criteria

- Patients with type 1 diabetes

- Patients with gestational diabetes

- The patient did not have enough information

- The patient was transferred to another department or referral.

2.Methods

Sampling method

- Sample: 200 medical records.

- Convenient sample selection.

Research Methods

- Descriptive cross-sectional, retrospective non - interference is used to extract information in the medical record.

research location

- Endocrinology Department, Can Tho City General Hospital.

- Research period: March 2018 - 9/2018.

III. RESEARCH AND DISCUSSION

1.Patient characteristics

The study was conducted at Can Tho City General Hospital in the period from 3/2018 to 9/2018 on 200 patients we obtained the following results:

Table 1. Patient characteristics by age and sex

Age group	Gender					
	Male		Female		Total	
	Patients	Rate (%)	Patients	Rate (%)	Patients	Rate (%)
< 40	5	2,5	3	1,5	8	4,0
40 – 49	5	2,5	8	4,0	13	6,5
50 – 59	12	6,0	28	14,0	40	20,0
60-69	22	11	46	23,0	68	34,0
70 – 79	8	4,0	38	19,0	46	23,0
≥ 80	8	4,0	17	8,5	25	12,5
Total	60	30	140	70	200	100
The lowest age	31					
The highest age	92					
The average age	65,27 ± 12,38					

In terms of gender of inpatient patients in the hospital, the survey showed that in the sample of the study, mainly female patients accounted for 70% higher than men accounted for 30%. The results are similar to those of Nhan Khanh Linh (2018) (female 72%, male 28%).

The age group from 60 to 69 has the highest prevalence of type 2 diabetes, accounting for 34.0%. The average age of patients in the study sample was 65.27 ± 12.38 years, similar to the average age in the study of Tran Nguyen Tra Mi (2013) was 64.5 ± 12.7 years.

Table 2. Body mass index (BMI) and patient's condition

Classification	BMI (kg/m^2)	Patients	Rate (%)
Skinny	< 18,5	21	10,5
Normal	18,5 - 22,9	109	54,5
Overweight	23 - 24,9	53	26,5
Obesity degree 1	25 - 29,9	15	7,5
Obesity degree 2	≥ 30	2	1,0
Total		150	100
The average BMI ± SD(kg/m^2)		21,96 ± 2,88	
The Lowest		15,63	
The highest		35,56	

The average BMI value in the study sample is 21.96 ± 2.88 kg / 2, which is relatively close to the average BMI of type 2 diabetic patients in Vietnam is 21.9 ± 3.6 kg / m2. The proportion of overweight and obesity patients is 38% of which overweight accounts for 26.5%, obesity degree 1, obesity level 2 is 10.5% and 1.0% respectively. According to ADA 2017, the diseases Diabetes type 2 with overweight and obesity increases the risk of cardiovascular disease and death, thus needing lifestyle changes, weight loss to reduce blood sugar, HbA1c, tryglyceride and reduce the need for medication.

Table 3. History of patients with type 2 diabetes

Anamnesis	Patients	Rate (%)
Have a history of diabetes	174	87
No history of diabetes	26	13
Total	**200**	**100**

The number of patients with a history of diabetes, high percentage of 87%, the number of patients without a history of diabetes, accounting for 13%. The determination of whether or not the patient has a history of type 2 diabetes to help control blood sugar promptly and effectively, improve the efficiency of treatment.

In addition to the main disease is type 2 diabetes, patients may also have some accompanying diseases. Within the scope of the research topic, the attached diseases are presented below:

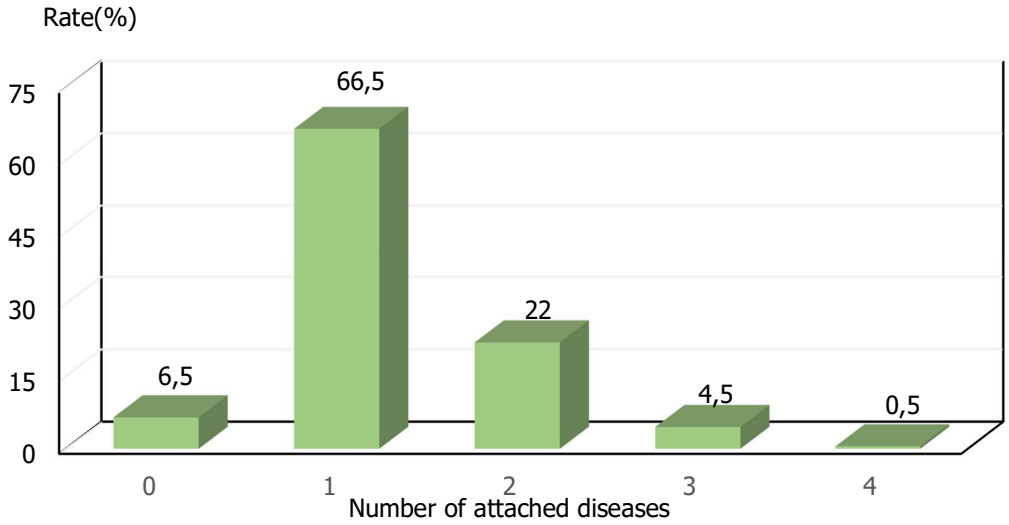

Figure 1. Number of attached diseases

Of the 200 patients, 6.5% of patients did not have comorbidities. The number of patients with 1 attached pathology accounted for the highest proportion, accounting for 66.5%. Patients with 2 to 3 comorbidities accounted for 22% and 4.5% respectively and patients with 4 coexisting diseases accounted for the lowest rate of 0.5%.

Table 5. Attached diseases in research samples

Attached diseases	Patients	Rate (%)
Hypertension	122	65,2
Blood lipid disorders	41	21,9
Local ischemic heart disease	17	9,1
Foot infection	12	6,4
Hepatitis	12	6,4
Urinary infections	11	5,9
Kidney failure	9	4,8
Skin infections	4	2,1
Heart failure	7	3,7
Anemia	6	3,2
Stomach ulcers	5	2,7
Atherosclerosis	3	1,6
Hypokalemia	3	1,6

In the study sample, many associated diseases were encountered, of which the most common hypertension was 122 patients with 65.2%. Blood lipid disorders had a relatively high rate of 21.9%. When treating diabetes, attention should be paid to the associated diseases to avoid complications of blood pressure and cardiovascular disease.

Table 6. Index fasting blood sugar of patients

Blood sugar (mmol/L)	Patients	Rate (%)
Achieving glycemic targets	18	9
Not achieve glycemic targets	182	91
Total	200	100
Smallest	1,40	
Biggest	49,10	
TB ± SD (mmol/L)	16,77 ± 9,21	

Most hospitalized patients with fasting glucose not reach target blood sugar very high percentage of 91% and only 9% achieved glycemic targets under the ADA 2018 (4.4 to 7.2 mmol / L).

Table 7. HbA1c

Numeral	Smallest	Biggest	Medium	Patients achieve target	Rate (%)
HbA_1C (%)	2,8	20,10	10,01 ± 2,93	32	16

The average HbA1c was 10.01 ± 2.93%, 32 patients accounted for 16% of the target. The average HbA1c index increased by more than 10% showed that the patient's blood sugar in the past 3 months was poorly controlled. Similar results with the study of Tong Minh Tam (2017) have the average inpatient HbA1c of 10.0 ± 2.7%.

2. Situation of using type 2 diabetes medicine in the research sample

In the study sample using both monotherapy and polytherapy. Treatments accounted for 77% and multi-therapy accounted for 23%. The groups of medications used for each patient depend on the patient's blood sugar control and response to the medication.

Table 8. Drug classes used in the study

Medicine group	Patients using	Rate(%)
Insulin	164	82
Biguanide	41	20,5
SGLT2 inhibitors	2	1
Sulfonylurea	18	9
α-glucosidase inhibitors	11	5,5
Combination pills	1	0,5

Most patients with type 2 diabetes are treated with insulin, metformin and sulfonylurea. In which insulin storage for the highest rate with 82%. Metformin and sulfonylur are used at a high rate, accounting for 20.5% and 9% respectively. The results differ with the study of Nguyen Khanh Ly (2015), most used group is Biguanide accounting for 45.74%, sulfonylurea accounts for 23.4%, insulin group accounts for 22.34%, SGLT2 inhibitory group is not used.

Table 9. Types of drug combinations used in the study

Type of combination	Number of patients used	Rate (%)
Two drugs	40	20,0
Metformin + Insulin	18	9,0
Metformin + Sulfonylurea	3	1,5
Sulfonylurea + α-glucosidase inhibitors	2	1,0
Insulin + α-glucosidase inhibitors	3	1,5
Insulin + SGLT2 inhibitors	2	1,0
Slow-acting insulin + Fast-acting insulin	12	6,0
Three drugs	6	3,0
Metformin + Insulin + α-glucosidase inhibitors	4	2,0
Metformin + Sulfonylurea + α- glucosidase inhibitors	2	1,0
Total	**46**	**23**

In a multidisciplinary regimen, the combination of the two most used drugs accounted for 20.0%. The combination of Metformin + Insulin accounts for the highest rate of 9.0%. The most commonly used metformin + insulin is 9.0% because it is the most effective combination of this type, with many benefits. Time to reduce the risk of heart attack and death (Katzung, Bertram G et al, 2009).

Table 10. Time of hospital treatment for patients

Treatment time	Patients	Rate (%)
< 7	82	41
7 -14	78	39
15 – 21	26	13
> 21	14	7
Total	200	100
Smallest	2	
Biggest	39	
TB ± SD	10,47 ± 6,68	

In the study sample, the majority of patients with type 2 diabetes had a treatment time of less than 7 days, accounting for 41%, from 7 to 21 days, a high rate of 39%. Overall, the use of drugs in patients with type 2 diabetes effectively through early discharge patients <7 days.

Table 11. The effect of glycemic control of patients

Blood sugar (mg/dL)	Smallest	Biggest	Mean± SD	Patients reaching target blood sugar	Rate(%)
At the hospital	93	598	290,52 ±118,36	34	17,0
At treatment	89	452	213,36 ± 70,50	74	37,0
At discharge	71	347	152,96 ± 47,90	151	75,5

After the treatment of any capillary blood sugar of any patient, the average reduction was 137.56 mg / dL. It can be seen that any blood sugar of patients decreases gradually from the time of admission, at the time of treatment to discharge. This can prove that the treatment process at the Hospital Endocrinology in general and the use of diabetes treatment drugs of type 2 in particular are relatively reasonable at Can Tho City General Hospital in 2018.

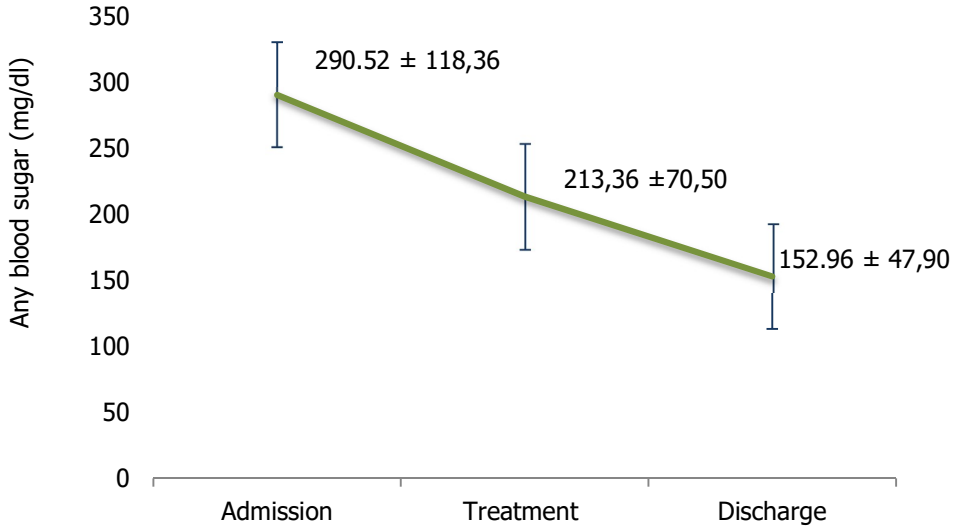

Figure 2. The average capillary blood glucose levels of patients at the time of admission, at the time of treatment to discharge

IV. CONCLUSION

General characteristics of the research sample

- Regarding age and sex groups: Hospitalized type 2 diabetes patients aged 60 to 69 accounted for the highest proportion of 34% and there was a large difference in the proportion of male and female patients. Female patients with 140 people accounted for 70%, 2.3 times higher than male patients with 60 people accounting for 30%.

- Regarding body mass index and patient's condition: The average BMI value in the study sample is 21.96 ± 2.88 kg / m2. The proportion of normal physical patients accounted for the highest proportion, accounting for 54.5%. The proportion of overweight and obese patients is 38%. Thin condition accounted for 7.5%.

- About diabetes history: Patients with a history of diabetes accounted for a high rate of 87%, patients without a history of diabetes accounted for 13%.

- About co-morbidities: The most common hypertension accounts for 65.2%, dyslipidemia accounts for 21.9%. Foot infections 6.4%, hepatitis 6.4%, urinary infections 5.9%, kidney failure 4.8%, other infections 2.1%, heart failure 3.7%, anemia 3. 2%, stomach ulcer 2.7%, atherosclerosis 1.6% and hypokalemia 1.6%.

- Fasting blood glucose: fasting blood glucose averaged 16.77 ± 9.21 mmol / L, only 18 patients (9%) achieved blood glucose target under ADA 2018 (4.4 - 7.2 mmol / L).

- HbA1c: HbA1c average 10.01 ± 2.93%, the lowest is 2.80%, the highest is 20.10%. Among them, 32 patients accounted for 16% of HbA1c according to ADA 2018.

The use of type 2 diabetes medication groups

- All drugs in the list of antihypertensive drugs used in the study sample belong to groups of antihypertensive drugs that are appropriate according to the recommendation of the Ministry of Health in 2017 and the American Diabetes Association (ADA). 2018.

- There are 06 classes of drugs are used to treat are: insulin group, the group biguanide, SGLT2 inhibitors, α-glucosidase inhibitors and group sulfonylurea pills and biguanide combination. In which insulin accounted for the highest rate with 82%.

- Regarding the selection of treatment regimens: Therapy monotherapy accounted for 77%, multi-therapy accounted for 23%.

- In the study sample, the combination of two drugs accounted for 20%, the combination of three drugs accounted for 3%. Type of insulin combination + Metformin accounted for the highest rate of 9%.

- Duration of treatment: Most patients treated <7 days accounted for 41%, 7-14 days accounted for 39%. The average number of hospital stays is 10.47 ± 6.68 days.

- About glycemic control: After the treatment of any capillary blood sugar of the patient, the average reduction was 137.56 mg / dL. The number of patients reaching the target blood glucose was 151, accounting for 75.5%.

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RÉSUMÉ:

SURVEILLANCE DE L'USAGE DE LA MÉDICATION DU DIABÈTE TYPE2 AU DÉPARTEMENT D'ENDOCRINOLOGIE DE L'HÔPITAL GÉNÉRAL DE LA VILLE DE CAN THO

Bui Tung Hiep*

** Université de Médecine Pham Ngoc Thach*

Objectifs: Surveillance de l'usage de la médication du diabète type 2 au département d'Endocrinologie de l'hôpital général de la ville de Can tho de Mars à Septembre 2018.

Sujets et méthodes: Méthode descriptive, rétrospective, cross-sectionnelle. L'Etude est menée sur des sujets diagnostiqués comme ayant le diabète type 2 et des sujets suivis au sein du départment d'Endocrinologie de l'hôpital général de la ville de Can tho

Résultats: Dans l'étude, les patients diabétiques type 2 hospitalisés âges de 60 – 69 occupent 34%, et c'est le plus grand pourcentage. Les patients de sexe féminin forment 70% spnt 2 a 3 fois supérieures en nombre aux hommes qui en forment 30%. Les patients qui excèdent en poids, et qui sont obèses forment 38%. Ceux qui oni une histoire de diabète sucré sont à une grande proportion de 87%. L'Hypertension est la comorbidité la plus rencontrée, est à 65.2%, la dyslipidémie, 21.9%. Le glucose à jeun est en moyenne 16.77 ± 9.21 mmol/l, tandis que 9% ont le but de glycemie recherché. Le HbA1c est de 10.01 ± 2,93%. Les regimes de traitement : Monotherapie : 77%, Multitherapie : 23%. Le groupe utilisant l'Insuline : 82%. Le groupe utilisant deux medicaments combines : 20%, celui de trois medicaments #%. La combinaison de l'Insuline + Metformin occupe la plus grande proportion de 9%. La duree du traiterment : La plupart des patients dont le traitement dure moins de 7 jours (41%). La glycemie capillaire de chaque patient a ete reduite de 137.56 mg/dL après tout traitement. Les patients ayant attaint la glycemie cible de 151, sont de 75.5%

Conclusion: Tous les médicaments antihypertenseurs utilisés dans ce travail appartiennent au groupe recommandé par le Ministère de la Santé en 2017 et L'American Diabetes Association (ADA) 2018.

Mots clés: *Type 2 diabetes, Type 2 diabetes medicine.*

RESULTS OF THE RESPONSE IN TREATING HYPOPHARYNX SQUAMOUS CELL CARCINOMA OF STAGES III - IV (M0) WITH CISPLATIN - TAXANE - 5 FU PRIOR TO SURGERY AND/OR RADIOTHERAPY

Phung Thi Hoa*, Tong Xuan Thang*

ABSTRACT

Summary: Treatment with the chemicals prior to and during the hypopharynx cancer is a the therapy prior to the radiation or surgery that allows to reduce the tumor volume to preserve cases of widespread spreading into the larynx, ensuring the life quality as well as reducing the rate of metastasis and the second cancer**.** **Objectives**: 1. Evaluating the treatment response to Pre-treatment chemicals of treating Hypopharynx cancer of stages III –IV (M0) with TCF; 2. To learn of the Toxicity and undesirable effects of the hypopharynx cancer of stages III-IV with TCF. **Subjects**: including 27 patients diagnosed with the hypopharynx squamous cell carcinoma of the type $T_{3,4}$ (M_0), treated at National Otorhinolaryngology Hospital of Vietnam from September 2016 to September 2018; **Methods:** Self-control clinical intervention. **Results:** 100% were male patients, the average age of 52.6 ± 6.2 years old, tumor mainly in the pyriform sinus 96.3%, widespread spreading into the larynx 74.1%, causing the funnel-shaped cartilage of vocal cords 85.2%, responded to treatment in 5/27 patients (18.5%) changed to T0, 2 patients to T1 (7.5%), 5 patients changes to T2 (18.5%), acomplete response in 5 patients (18.1%), partial response in 15 patients (55.6 %), 6 patients in severe progress (22.2%); Prior to the treatment, 27 patients of low or no surgical ability; After the surgery treatment, 17 patients (63%) with the conservative surgery, 6 patients undergoing the conservative surgery (35.3%), 11 patients undergoing the curative resection (58.8%). 21 patients underwent thelymphadenectomy intervention: Pure and simple lymphadenectomy in 5/21 patients (18.5%), lymphadenectomy combined with the tumor surgery in 16/21 patients (59.3%); the major toxicity found to relieve the hemoglobin flows, no severe hepatic and renal dysfunction leading to the treatment stoppage, the main uncommon side effects of fatigue (100%), fever and digestive disorders with the low rate. **Conclusion:** Pretreatment chemicals help to reduce the tumor volume, lower the disease stage, facilitate surgery and radiation therapy, reduce complications, and limit metastasis.

Keywords: *Hypopharynx cancer, Leading chemicals, Pre-treatment chemicals.*

I. BACKGROUND

Hypopharynx cancer is essentially a squamous carcinoma (SCC, occupied > 95%), the disease is less common than throat cancer and larynx of Ear - Nose and Throat, cancers of the head face and neck - It belongs to the upper gastrointestinal tract and respiratory [1] [2]. In Vietnam, the rate of Hypopharynx cancer in women is 0.3 / 100 000 / year, male is 2.7 / 100 000 / year [3]. Classical treatment is surgery of laryngeal laryngeal section, partially or completely, with dredging neck lymph nodes, radiation combination treatment, or postoperative radiotherapy. Surgery in the late stages will have to remove many groups of Pathological function in the larynx and throat reduces the physiological functions, affecting quality of life of patients.

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In order to thoroughly treat cancer diseases and conserve physiological functions and organs limited to surgical removal of all organs, chemical treatment trends have emerged.Chemotherapy has been applied mostly to stage III-IV in throat cancer since the beginning of the 21st century. Clinical trial studies on chemical treatment In throat cancer and other cancers, there are many results: raw preservation organizational integrity, increasing the response rate of the disease to the next radiation therapy[4] [5] [6] [7] [8].

Treatment of previous adjuvant chemicals in Hypopharynx cancer is the treatment before radiotherapy or surgery, this method helps 60% to 80% regress at Tumor and lymph nodes with an 80% overall response, fully responding to 30-50%. These results show previous adjuvant chemicals for stage III - IV and reduces the stages of disease, facilitates favorable conditions that benefit for radiation therapy and reduce the rate of local recurrence.

In Vietnam so far, the study of the role of previous adjuvant chemicals treatment for head cancer In general, Hypopharynx cancer in particular is minuscule, especially as no research has been evaluated Results of treatment of previous adjuvant chemicals associated with surgery in the treatment of Hypopharynx cancer [5] [7] [9]. Export from the above practice, we carried out the topic: "Results of responses in treating Hypopharynx squamous cell carcinoma of Stage III - IV(M0) with Cisplatin - Taxane - 5 FU prior to surgery and / or radiation therapy ".

With the targets:

1. Evaluating the treatment response to Pre-treatment chemicals of treating Hypopharynx cancer of stages III –IV (M0) with TCF

2. To learn of the Toxicity and undesirable effects of the hypopharynx cancer of stages III-IV with TCF

II. SUBJECTS AND RESEARCH METHODS

2.1. Subjects of the Study: including 27 patients diagnosed with the hypopharynx squamous cell carcinoma of the type $T_{3,4}$ (M_0), treated at National Otorhinolaryngology Hospital of Vietnam from September 2016 to September 2018

2.2. Methods: Self-control clinical intervention.

2.3. Criteria for selecting patients

(1) The patients were diagnosed with segmentation of T3.4 (M0), and no second cancer drive.

(2) Patients are treated for the first time.

(3) Age under 70, both sexes.

(4) Having a good overall status index: from 0-2 on the scale of the cooperative group Eastern mail (ECOG: Eastern Cooperation Oncology Group).

(5) Having clinical diagnosis, exaggerated endoscopy, imaging diagnosis (CT scan, straight chest capture).

Diagnosis of histopathology: Squamous carcinoma, graded Grads from 1 to 4. All of these patients have a definitive diagnosis by histopathology Mesothelioma (SCC) in the Department of Disease Surgery - Central Otolaryngology Hospital. (6) Tests for normal liver and kidney function and spinal cord function. The review of basic experience: + Leukocyte ≥ 4 G / L; Hemoglobin ≥ 125g / l. Platelets ≥ 150G / l + AST / ALT ≤ 40 UI / l. Creatinine ≤ 100 mmol / l

(7) Patients without severe acute and chronic diseases at risk of death, photos take part in treatment.

(8) Prepare a complete treatment profile, monitor the course of treatment, after

treatment follow sample medical conditions and routine visits.

(9) Patients are carefully explained, personal information is kept confidential and we follow medical ethics. All patients confirm the commitment to be treated Pre-treatment chemicals. and follow the research process properly.

2.4. Research content

Chemical transfer regimen: Docetaxel 50mg / m2 body surface area inside 250ml 5% sugar and infused for 1 hour, then infused Cisplatin 75mg / m2 surface area body face, mixed with 200 ml 0.9% saline serum solution for slow intravenous infusion 40 drops / minute day 1; 5-Fluorouracil 750mg / m 2 body area, intravenous infusion day1-5.

- Carry out 3 cycles of treatment, implementation time 1 Cycle: 21 days. Steps to prepare for treatment of Pre-treatment chemicals for 1 cycle: Before chemical transfer 30 minutes, patients take anti-emetic medication through the vein. Then anti-emetic medicine if necessary to minimize vomiting and nausea.
- Evaluation at the end of three cycles: Criteria for evaluating results in about millions Clinical, subclinical, and diagnostic diagnosis to determine the degree of regression local tumors, regional and metastatic lymph nodes choose surgery (or still have to be removed completely sets, or conservative surgery) and postoperative radiation.

- Classification of TNM period according to WHO according to WHO - IARC -2005 [8].

Phase III (T3 N0 N1 M0 / T1, T2, N1M0), IVa (T4a N0 N1 N2 M0 / T1, T2, T3, N2 M0), IV b (T any N3M0 / T4b, any N, M0).

- Evaluate histopathological degeneration after responsive chemical treatment (regressing 50 -100%).

Research chemicals: Cisplatin: EBWE Arzneimittel Ges.m.b.H, Austria. Docetaxel: Sanofi - Aventis Deutschland - Germary. 5FU (Fluorouacil): EBWE Arzneimittel Ges.m.b.H, Austria

III. RESULT

Gender: 100% of men.

Age: from 38 - 61, the common age is from 50 to 60 years old, the average age is 52.6 ± 6.2.

3.1. Features of endoscopic spread and compact response spread later treatment

Table 1: Response table to reduce the spread of tumor spread before - after treatment Endoscopic

The direction of spreading the lesion of Tumor	Before treatment Pre-treatment chemicals.		After treatment Pre-treatment chemicals.		p
	Amount	%	Amount	%	
Larynx	20	74.1	8	29.6	0.001
Front larynx	4	14.8	1	3.7	0.159
Spread to the bottom of the tongue	1	3.7	0	0	0.313
Spread into the spine	0	0	0	0	

Spread into the esophagus mouth	8	29.6	4	14.8	0.190
Spread came close to the mouth of the esophagus	5	18.5	2	7.4	0.224
Spread into the trachea	0	0	0	0	
Spread into thyroid	0	0	0	0	
Spread into the cover of cartilage	1	3.7	0	0	0.313
Fixed hopper cartilage / vocal cords	23	85.2	9	33.3	0.000
Spread into the area behind the funnel ring	1	3.7	1	3.7	1.000
Spread into hopper cartilage / bar hopper splint damage	18	66.7	15	55.6	0.402
Spread entered the side wall / citadel after falling throat	6	22.2			0.009
Appeared on the second cancer drive			3	11.1	0.075

Comment: A tumor can spread to many places, the main tumor spreads into the bar 74.1% administration (20 / 27patients), Fixed funnel cartilage / vocal cords 85.2% (23/27 patients), spread tocartilage hopper / funnel splint is 66.7% (18/27 patients), spread to the esophagus 29.6%(8/27 patients), other widespread sites we encountered at low rates. After tumor therapy there was reduced spread of lesions to the larynx (8/20 cases) (P <0.05), causing trouble planing cartilage funnel funnel (9/23 cases) (P <0.001), spreading into hopper cartilage / funnel splint clearance (15/18 cases), spread to the esophageal mouth (4/8 cases). But there is also tumor progression: 3/27 patients develop a second cancer drive.

3.2. Spillover and response characteristics on Computerized tomography

Table 2. Spillover and tumor response before- after treatment on Computer class cutting

Injury Spreading	**Before treatment (amout)**		**After treatment (amout)**	
	Amount	**%**	**Amount**	**%**
Hypopharynx	8	29.6	13	48.2
Hypopharynx - larynx	19	70.4	9	33.3
No Tumor			5	18.5
Total	27	100.0	27	100.0
p	0.121			

Comment: There is a reduced response to injury before and after treatment on Computerized tomography,19/27 patients (70.4%) had spread to the larynx before treatment, after treatment only 9/27Patients (33.3%), 13/27 patients (48.2%) were confined to the Hypopharynx, and especially 5 patients (18.5%). Do not observe tumor on Computerized tomography.

3.3. T-response after treatment

Table 3: Previous T-segment response - after treatment

T Diagnosis	**Before treatment (Amount)**	**After treatment (amout)**				
		T0	**T1**	**T2**	**T3**	**T4**
T3	21	4	1	4	8	4
T4	6	1	1	1	1	2
Amount	27	5	2	5	9	6
%	100	18.5	7.5	18.5	33.3	22.2
p	0.002					

Comment: There is a clear decrease in the segment T: Before treatment 21/27 patients T3 and 6/27Patients in T4; after treatment from 4 patients from T3 and 1 patient from T4 to T0 - throat tumors all originals are completely gone, no longer found under hard-tube endoscopy, Computerized tomography,and Histopathology about negative after treatment. There was 1 patient T3 and 1 patient T4 decreased to T1, 4 patients T3 and 1 patient T4 on T2, patients who remained in the T segment had compact volume condensation special tumors that spread the esophagus mouth thus facilitating surgical intervention and mouth connection, however, there are 4 patients with severe progression to T4, P< 0.05 means statistical.

3.4. Effectively meet the treatment designation

Table 4. Evaluation of response after 3 waves of preoperative adjuvant chemicals

Response	Amount	%
Meeting part	15	55.6
Complete response	5	18.1
Stable	1	3.7
Progress	6	22.2
Total	**27**	**100.0**

Comment: On 27 patients perform 3 rounds of surgery / and operation or radiotherapy us 20/27 patients were met (74.1%), of which 5 patients responded completely(18.1%) and 15 patients partially responded (55.6%). 1 patient does not have the same response hurt. There were 6 patients (22.2%) who developed severe progression: 3 patients appeared proceed to increase the simple T segment from T3 to T4; 3 patients appear a second cancer drive In the esophagus region, in these 3 patients, 1 patient develops the second cancer and progression of primary tumor from T3 to T4, and 2 patients with fecal lowering T segment of primary tumor (1 patient from T3 lowered to T2, 1 patient from T4 lowered to T2).

Table 5. Change of surgery and lymph node surgery indications

	Conservation surgery		**Surgery for radical erection**		**Lymphadenopathy**		
	Conserve endoscopic	Conserve open surgery	There is a flap big chest muscle	Not created muscle flap big	Dredging Simple	Dredging links combination Tumor	Is not dredging
Amount	1	5	1	10	5	16	6
%	5.9	29.4	5.9	58.8	18.5	59.3	22.2

Comment: A total of 27 patients with initial diagnosis have very little surgical ability or can't be operated. After 3 batches of chemical transfer with TCF regimen, implementation was allowed 17 patients surgery in which 6 patients had conservative surgery (35.3%), 11 patients radical surgery (58.8%). Intervention of lymphadenopathy surgery 21 patients: 5/21 simple curettage Patients (18.5%), Dredging combined with surgery for 16/21 patients (59.3%). There are 10 patients Radiation: in particular, 5 patients respond completely to radiation without surgical intervention, 1 patient has indicated surgery but the patient has not Agreed to radiate, 4 patients with severe progression, incapable of surgery, including 3 patients appear second cancer drive appears in the esophagus.

3.5. Unexpected toxicity and effects

Table 6. Toxic table on hematopoietic system

Index	HC1(Amount)					HC2 (Amount)					HC3 (Amount)				
	Lvl 0	Lvl 1	Lvl 2	Lvl 3	Lvl 4	Lvl 0	Lvl 1	Lvl 2	Lvl 3	Lvl 4	Lvl 0	Lvl 1	Lvl 2	Lvl 3	Lvl 4
haematopoietic	8	19				6	21	0	0		6	19	2		
leukocytes	27					27					26	1			
platelets	26	1				27					24	3			
amout															

Comment: mainly reduce the level 1 of haematopoietic, there are 2 patients who reduce level 2 in the third cycle of the regimen. Current platelets and leukocytes decreased little and at level I.

Table 7. Table of toxicity outside the haematopoietic system

Index	HC1(Amount)					HC2 ()					HC3 (n)				
	Lvl 0	Lvl 1	Lvl 2	Lvl 3	Lvl 4	Lvl 0	Lvl 1	Lvl 2	Lvl 3	Lvl 4	Lvl 0	Lvl 1	Lvl 2	Lvl 3	Lvl 4
ALT/AST	21	6				26	1				25	2			
Creatinin	26	1				26	1				26	1			
amout															

Comment: There are a few patients with reduced liver and kidney function at level I, not any patient with severe damage must stop treatment.

- Unwanted effects we encountered 100% of tired patients, having diseases fever, gastrointestinal disorders with low rates, symptoms of other effects not seen.

IV. DISCUSS

4.1. The feature spreads and responds to tumor treatment through injury reduction and indication treatment after 3 cycles of TCF.

- Age and gender: In this study, we did not see infected female patients Nguyen Dinh Phuc's study [8] ratio of male / female: 14/1. Common age from 50 -60 Age, average age 52.6 ± 6.2. This result is also consistent with author Nguyen Dinh Phuc. Thus, lower throat cancer is mostly seen in middle-aged men.

Spreading: tumor mainly in the piriform sinuses 26/27 Patients (96.3%), spread infiltrated manage 74.1%, fix cartilage hopper 85.2% wire rod, spread to hopper cartilage / splint.

The funnel is 66.7%, spread to the esophagus 29.6%, the other sites spread I met with a low rate. After tumor treatment, there was a decrease in the spread of lesions in the bar also managed (8/20 cases) ($P < 0.05$), causing fixed cartilage cartilage cartilage (9/23 cases)($P < 0.001$), spread into the funnel cartilage / funnel funnel (15/18 cases), spread into esophageal mouth (4/8 cases). But there is also tumor progression: 3/27 patients the second cancer is present. In Computerized tomography, 19/27 patients (70.4%) have spread to the larynx first treatment; After treatment, only 9/27 patients (33.3%), 13/27 patients (48.2 %) were residing in the area throat, and especially 5 patients (18.5%) did not observe tumors on Computerized tomography .

- T response: lowering the segment to T0 with 18.5% - no longer see tumor under Endoscopy Hard tube, Computerized tomography, and Histopathology on post-treatment negative; T2 18.5%, T1 7.5%, severe progression to 4 patients (14.8%) from T3 to T4, P < 0.05 is statistically significant. At the stage most of the cancer lesions have not invaded much, only on those it is difficult to restore the throat tube after removal of the tumor the throat is very narrow, so it is easy to leak the throat tube after surgery, this can be overcome by the surgery to insert the closed skin flap into the throat, but these are large, postoperative surgeries Severe surgery and success rates are not high so with Pre-treatment chemicals can help shrink Primary tumors will facilitate surgery.

- The response of the tumor to the regimen: the response rate is quite high, we have obtained 20/27 patients (74.1%) responded, including 5 patients fully responding (18.1%), and 15 patients (55.6%) partially respond. This result is similar to some authors who treat Hypopharynx cancer.T u Thi Thanh Huong overall response rate was 80.4%, complete response was 25.5% (P <0.05) [9]; Tran Bao Ngoc is: 35.7% fully responsive and 47.6% partially satisfied, author Esscica Bauman: 30% fully responded and 67% partially responded after 3 leading chemical cycles cetuximab, Carboplastin, Palitaxcel regimens [10].

-Circulation surgery for 17 patients, of which 6 patients were preserved surgery (35.3%), 11 patients with radical surgery (58.8%). Intervention of lymphadenopathy 21 patients: simple scraping 5/21 patients (18.5%), Dredging combined with surgery of 16/21 patients (59.3%).

4.2. Toxicity and undesirable effects

- Mainly reduce the haematopoietic level, there are 2 patients reduce the level 2 in the third cycle of the regimen. Platelets and leukocytes decreased less and at level I.

- There are a small number of patients with reduced liver and kidney function at level I, no patients with severe damage have to stop treatment.

- Unexpected effects we encountered 100% tired patients, met patients with fever, gastrointestinal disorders with low rates, other symptoms of symptoms not met.

- In these cases, we actively supplement the prophylactic and toxic drugs to reduce the toxicity and unwanted effects.

V. CONCLUSION

1.The tumor is mainly in the piriform sinuses 96.3%, Spread into 74.1% larynx, Fixed cartilage cartilage rod 85.2%, 5 patients responded completely(18.1%) and 15 patients partially responded (55.6%). There were 6 patients (22.2%) who developed severe progression: 3 patients appear a second cancer drive In the esophagus region

2.Prior to previous adjuvant chemotherapy, 27 patients had low surgical ability or were unable to operate, after 17 previous patients, 63 patients (63%) had surgery (6 patients surgical preservation - 35.3%, 11 patients with radical surgery - 58.8%). Intervention dredging lymphadenopathy 21 patients (simple scraping 5/21 -18.5%), Dredging combined with surgery of 16/21 patients (59.3%);

3.Toxicity is mainly met with a slight decrease in the flow of ecosystems, there is no significant reduction in liver and kidney function to stop treatment, unwanted effects

are mainly tired (100%), fever and digestive disorder with billion low rate

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RÉSUMÉ:

RÉSULTATS DE LA RÉPONSE DANS LE TRAITEMENT DU CARCINOME À CELLULES SQUAMEUSES HYPOPHARYNX DES ÉTAPES III - IV (M0) AVEC CISPLATINE - TAXANE - 5 FU AVANT LA CHIRURGIE ET/OU LA RADIOTHÉRAPIE

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Résumé: Le traitement avec les produits chimiques avant et pendant le cancer de l'hypopharynx est une thérapie avant la radiothérapie ou la chirurgie qui permet de réduire le volume de la tumeur afin de préserver les cas de propagation généralisée dans le larynx, tout en garantissant la qualité de vie et la des métastases et du second cancer.

Objectif: 1) Évaluer la réponse du traitement aux produits chimiques de prétraitement pour le traitement du cancer à Hypopharynx des stades III-IV (M0) avec du TCF; 2) Connaître la toxicité et les effets indésirables du cancer de l'hypopharynx des stades III à IV avec TCF. Sujets: Il y a 27 patients chez lesquels un carcinome à cellules squameuses de l'hypopharynx du type T3,4 (M0) a été diagnostiqué, traités à l'Hôpital National d'Oto-Rhino-Laryngologie du Vietnam de Septembre 2016 à Septembre 2018;

Méthode: Intervention clinique d'autocontrôle.

Résultats: 100% patients des hommes, la moyenne d'âge était de 52,6±6,2 ans, la tumeur principalement dans le sinus pyramidal 96,3%, une propagation généralisée dans le larynx 74,1%, causant le cartilage en forme d'entonnoir de 85,2%, les cordes vocales 85,2%, ont répondu au traitement chez 5/27 patients (18,5%) sont passés à T0, 2 patients à T1 (7,5%), 5 patients ont changé en T2 (18,5%), réponse complète chez 5 patients (18,1%), réponse partielle chez 15 patients (55,6%)), 6 patients en progression sévère (22,2%). Avant le traitement, 27 patients avec une capacité chirurgicale faible ou nulle. Après le traitement chirurgical, 17 patients (63%) opérés de la chirurgie conservatrice, 6 patients opérés de la chirurgie conservatrice (35,3%), 11 patients opérés de la résection curative (58,8%). 21 patients ont subi une intervention chirurgicale: Adénopathie pure et simple chez 5/21 patients (18,5%), lymphadénectomie associée à une chirurgie tumorale chez 16/21 patients (59,3%); la toxicité majeure constatée pour soulager les flux d'hémoglobine, l'absence de dysfonctionnement hépatique et rénal grave conduisant à l'arrêt du traitement, les principaux effets indésirables peu fréquents de la fatigue (100%), la fièvre et les troubles digestifs à faible taux.

Conclusion: Les produits chimiques de prétraitement aident à réduire le volume de la tumeur, à réduire le stade de la maladie, à faciliter la chirurgie et la radiothérapie, à réduire les complications et à limiter les métastases.

Mots clés: *Cancer de l'hypopharynx, Principaux produits chimiques, Produits chimiques de prétraitement.*

THE FINAL ASSESSMENT OF *NAJA SIAMENSIS* ANTIVENOM IN EXPERIMENTAL TESTS

Le Khac Quyen*, Hoang Anh Tuan*, Trinh Xuan Kiem****

ABSTRACT

Objectives: *Naja siamensis* (*NS*) antivenom produced successfully in Vietnam and in the world. Our study established to assess this *NS* antivenom on safety, efficacy, pyrogens, sterility, pH, thiomersal and sodium chloride concentrations in experimental tests.

Methodology: According to IV Vietnam National Pharmacopoeica, safety and efficacy tests performed based on medium lethal dose (LD_{50}) and medium effective dose (ED_{50}) by mices (18-20g) and guinea pigs (250-350g). Sterility test did on thioglycolate media at 20 - 25ºC and 30-35 ºC and Soybean casein digest at 20 - 25ºC for bacteria and fungi identification. Pyrogens test also did to confirm the quality of our *NS* antivenom. Moreover, *NS* antivenom specificity and titred level were also testified by ELISA technique.

Results: Medium lethal dose (LD_{50}) was 12,59 µg/20g mice. Medium effective dose (ED_{50}) was 100 LD_{50}/ml. No pyrogens and sterilization in *NS* antivenom confirmed. Titred level of *NS* antivenom by ELISA was 1/64,000. An assessment of *NS* antivenom in vitro and in vivo showed specificity with high safety and strong efficacy.

Conclusion: *Naja siamensis* antivenom passed the criteria of Vietnamese National standardizations and WHO recommendations.

Keyword: Naja siamensis *antivenom; safety and efficacy assessment.*

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I. INTRODUCTION

From 1894, Dr. Calmette produced cobra antivenom in Sai Gon Institute firstly in the world. As a result, treatment of snake envenoming spreaded out the new trend by using antidote of antivenom [1]. Theakston demonstrated about an evidence-base for effectiveness of antivenom treatment based on ELISA technique [2]. In Vietnam, Trinh Xuan Kiem and colleagues have produced successfully *Naja kaouthia* antivenom in Cho Ray hospital from 1993 [3]. Then, *Calloselasma rhodostoma*, *Ophiophagus hannah*, *Cryptelytrops albolabris* and *Bungarus candidus* antivenoms are made consequently to reduce mortality rate of snakebites from 20% to 3.1% in Cho Ray hospital [3],[5]. However, 6% *Naja siamensis* (*NS*) envenomed patient of snakebites is still a chanllenge of clinicians for lack of antivenom [6].

In 2009, World Health Organization (WHO) arranged snake bites into neglected tropical dieases and reconfirmed that venomous snake antivenom is an antidote only of the treatment for envenomed patients by snake venom [6], [7]. Unavailable of specific antivenoms to treat the envenoming patients due to many venomous snake species in different areas in the world becomes a seriously medical important problem in the world [7].

NS antivenom production is in great demands in clinical practice recently. This antivenom produced firstly in Vietnam and in the World [8]. The aim of this study is with a

design to assess of *NS* antivenom in vitro and in vivo according to Vietnamese National Standards as well as WHO recommendation for antivenom products.

II. MATERIALS AND METHODOLOGY

2.1. Materials

- 30 out of 157 vials of *NS* antivenom product choosed for the study by randomized [8]

- *NS* venom supplied from KLT Technological Medicine joint-stock Company.

- Thioglycolate and Soybean Casein Digest media supplied by International Research Institute of Gene and Immunology and Nam Khoa Company limitted.

- 144 white mices (18-20grams/mice), 06 Guinea-pigs (250-350grams/cobay) and 03 rabbits (1.75-2.0 kilograms/rabbit) supplied by Institute of vaccine and medical biologicals Nha Trang (IVAC) and Department of Toxicology and Military Radiation, Military Medical University.

- Syring and needle: single use only sterilized syring of Vinahankook, 05ml and 20 ml, Lot 1410, manufactured date 14/01/2019.

2.2. Methodology: In vitro and in vivo animal model:

- An assessment of *NS* antivenom of the safety, efficacy (based on LD_{50} and ED_{50}), pyrogens and sterilize in vitro and in vivo [9].

- Calculation of LD_{50}: based on LD_{50} formula (Spearman-Karber):

$\text{Log } LD_{50} = \text{Log}X_{100} - \{\text{Log Fd}(\Sigma t\text{-}n/2):n\}$ (LD_{50}: medium lethal dose; Log X_{100}: Log of lowest lethal dose; Log Fd: Log of between lethal dose; n: number of mice for each dose; t: numbers of mice death; Σ: SUM all doses, include from X_0 - X_{100}; and X_0: Log of highest dose without mice death).

- Calculation of ED_{50} based on the formula (Spearman-Karber): $\log ED_{50} = Xo + d/2 - d\ x(\Sigma r_i/n)$. (Xo: log of minimum antiserum volume to protect 100% of mice; d: Log of each different volume level; ri: mice death of each volume level to neutrolize; and n: number of mice to inject)

+ Dilute *NS* antivenom, increase gradually from 10µl /ml to 60µl /ml.

+ *NS* Venom solution was diluted into normal saline 0.9% (10mg% = 100µg/ml), mixed well with each *NS* antivenom dilution, same volume, incubation of this solution at 37^0C/1h.

+ Mice-tail vein injection (*NS* venom solution + antivenom), V=0,5 ml/mice.

+ Number of mice: 8 mices /lot x 4 lots

+ Monitor in 24 hours, record the mice death / a live, percent ratio count (%).

- Sterility test: *NS* antivenom is cultured to identify bacteria and fungi by thioglycolate và Soybean Casein Digest media at International Research Institute of Gene and Immunology and Nam Khoa Company limitted.

03ml *NS* antivenom for culture: 01ml insert to Thioglycolate tube, incubation at 20-25°C and 01 ml to another Thioglycolate tube, incubation at 30-35°C and 01ml to Soybean Casein Digest media, incubation at 20-25°C.

Culture for control group with 04ml normal saline (NaCl 0.9%): 02 Thioglycolate tubes (01ml for each one), incubation at 20-25°C and at 30-35°C. 02 Soybean Casein Digest media (01ml for each one), incubation at 20-25°C. Total culture times are 14 days.

- Pyogens test:

Select 03 of healthy rabits (weight: 1.8 - 1.9 - 2.0 kg), living in Animal experimental zone for a week. *NS* antivenom is injected

into ear border vein with volume V= 01 ml/kg x body weight. Rectal temperature is measured before and after an hour intervals during 3 hours. It is normal if the range of lowest and highest temperature was less than 1^0C. If range was over 1^0C, pyrogens substance confirmed reliably.

Rabit living in quiet room, no sound and no light because its may be effected to final results of tests. Temperature of this room is 23 ºC as same as temperature in rabit living zone of IVAC and Department of Toxicology and Military Radiation, Military Medical University. Before 01 day of the test, rabits can drink water but no food. During the test running, rabits cannot drink water. Thermometer: Using the thermometer which high accuracy until 0.1ºC and put it in rectal 5 cm deep, at least 5 minutes.

- Safety test:

06 healthy Guinea pigs are enrolled into 2 groups (control and expericenced). Their body weight are from 250 to 350g. They are in cage and accessed water and food without antibiotics easily for a week. *NS* antivenom is injected into peritonaeum. Volume is calculated by V=1.5 ml/100g x weight. They will be observed during 07 days for toxic envenomation such as body weight and losing their hair. The test is evaluated normally if the Guinea pigs are still normal development, no depilation and gain weight. The *NS* antivenom is safety in animal experiments.

10 white mices are enrolled into 2 groups (control and expericenced). Their body weight are from 18 to 20g. They are in cage and accessed water and food without antibiotics easily for a week. *NS* antivenom is injected into peritonaeum. Volume is calculated by V=0.5 ml/10g x weight. They will be observed during 07 days for toxic envenomation such as body weight and losing their hair. The test is evaluated normally if the white mices are still normal development, no depilation and gain weight. The *NS* antivenom is safety in animal experiments.

- Meassurement of protein concentration of *NS* antivenom

Dilute *NS* antivenom at levels such as 1/2, 1/4, 1/8...Dilute standard protein (Bovine Serum Albumin, BSA) 2mg/ml (Thermo Fisher) into different concentration 1.4 - 1 - 0.5 - 0.25 - 0.125 and negative sample (blank). Standard protein repeated twice but *NS* antivenom must be three times. 10 µl for each wells. Drop color change solution. Wait 30 minutes, OD meassurement at 590nm wavelength. Build standard line based on standard protein OD results. Calculation of protein concentration based on Bradford Method [9].

- Identification of antibody titration of *NS* antivenom by ELISA technique

100µl *NS* venom (2µg/ml) into ELISA plate 96 wells, pH 9.6, incubated one night at temperature 4°C. Wash by Phosphate Buffer Solution –Tween then incubation with BSA 1% for 60 minutes. Wash it by PBS-Tween again for 5 times. Negative control was dropped horse plasma without antibody and anothers by *NS* antivenom with titre antibody going down gradually such as 1/2, 1/4, 1/8..., incubation 30 minutes, wash 5 times by PBS-Tween. 100µl Anti Horse IgG-Horseradish Peroxidase, incubation 30 minutes, wash its. Add 100 µl OPD (O-phenilenediamine) then 50µl H_2SO_4, 2N. Measure Optical Density - OD, by ELISA machine (Beckman Coulter, USA) at wavelength 450 nm or 492 nm. The result is positive if OD of sample higher mean value of negative control +2 SD (Standard Deviation).

- Immuno-elctrophoresis of *Naja siamensis* antivenom F(ab')$_2$

Identification of albumin, globulin, IgG, IgM, IgA concentration at Medic.

- pH, thimerosal and natri chlorid concentrations of NS antivenom performed at Pasteur Bio-Medical pharmacology Company limitted.

2.3. Time and place: The study was performed from 07/2012 to 04/2019 at Department of Toxicology and Military Radiation and Department of Immunology, Military Medical university; Vietnam Institute on Toxinology; International Research Institute of Gene and Immunology; and Nam Khoa Company limitted, Pasteur Bio-Medical pharmacology Company limitted.

III. RESULTS

3.1. Assessment of potency test of *Naja siamensis* antivenom

3.1.1. Identification of the median lethal dose (LD_{50}) Naja siamensis venom of Vietnam

Table 1. Identification of the median lethal dose (LD_{50}) of Naja siamensis venom of Vietnam

No	*NS* Venom titre (µg/ml)	*NS* venom /mice (µg)	Mice monitoring			Death percent ratio (%)
			Live	Death	Total	
1	0	0	4	0	4	0
2	60	6	4	0	4	0
3	70	7	4	0	4	0
4	80	8	4	0	4	0
5	90	9	4	0	4	0
6	100	10	3	1	4	25
7	110	11	2	2	4	50
8	120	12	2	2	4	50
9	130	13	2	2	4	50
10	140	14	1	3	4	75
11	150	15	0	4	4	100
12	160	16	0	4	4	100
13	250	25	0	4	4	100
14	500	50	0	4	4	100

Number of mice/lot = 4 mices. *NS* venom volume injected per mice (ml) = 0.5

Remark: log LD_{50} = log X_{100} – log Fd $(\Sigma t - n/2)/n$= log 15 – (log10+log11+ log12+log13+log14)/4 +log(50x10)/4 = 1.18 - 0.75 - 0.67 = 1.1. LD_{50} = 12.59 µg /mice.

Result: LD_{50} of *NS* venom in Vietnam is 12.59 µg/mice (20g).

3.1.2. Identification of efficacy of Naja siamesis antivenom (Effective dose-ED_{50})

Table 2. Potency test of Naja siamensis anitvenom

No	NS antivenom (ml)	NaCl 0.9% solution (ml)	*NS* venom (100γ/ml)	Number of LD_{50} / mice	Mice monitoring		
					Death	Live	Percent ratio (%)
1	0.050	3.75	1.200	1	0	8	100
2	0.030	3.77	1.200	1	0	8	100
3	0.010	3.79	1.200	1	0	8	100
4	0.000	3.80	1.200	1	4	4	50

Calculation of ED_{50} based on the formula: $\log ED_{50} = Xo + d/2 - d \times (\Sigma r_i/n) = \log 0.010 + 0.010/2 - 0.010 \times 4/8 = -2.00$. $ED_{50} = 0.01$ml

Results:- 01 ml *NS* antivenom is able to neutrolize 100 LD_{50} = 1200 µg *NS* venom.

- 01vial *NS* antivenom (5ml) is able to neutrolize 500 LD_{50} = 6000 µg *NS* venom.

3.1.2. Pyrogen identification of Naja siamensis antivenom (Pyrogen test)

3.1.2.1. Results of preliminary test before pyrogen test assessment

Table 3. Preliminary test before pyrogen test assessment

Rabit No	Weight (kg)	NaCl 0.9% Volume (ml)	Rabit temperature before NaCl 0.9% injected (°C)			Rabit temperature after NaCl 0.9% injected (°C)			Temperature difference (°C)
			0'	30'	Average	60'	120'	180'	
1	1.8	18	38.5	38.5	38.5	38.8	38.7	38.5	+ 0.3
2	1.9	19	38.6	38.6	38.6	38.9	38.8	38.6	+ 0.3
3	2.0	20	38.6	38.6	38.6	38.9	38.8	38.6	+ 0.3

Remark: the temperature of 03 rabbits is stable. The difference is 0.3 °C.

Result: 03 rabits is passed the criteria to enroll the pyrogen test of *NS* antivenom.

3.1.2.2. Results of pyrogen test (main test)

Table 4: Results of* Naja siamensis *antivenom pyrogen test

Rabit No	Weight (kg)	Volume of *NS* antivenom (ml)	Rabit temperature before *NS* antivenom injection (°C)			Rabit temperature after *NS* antivenom injection (°C)			Temperature difference (°C)
			0'	30'	average	60'	120'	180'	
1	1.8	1.8	38.5	38.5	38.5	38.8	38.7	38.5	+ 0.3
2	1.9	1.9	38.6	38.6	38.6	38.9	38.7	38.6	+ 0.3
3	2.0	2.0	38.6	38.6	38.6	39.0	38.8	38.6	+ 0.4

Remark: The difference of rectal rabit temperature before and after *NS* antivenom injection at 60-minute intervals during 3 hours is less than 0.6^0C. Total temperature difference: 0.3 + 0.3 +0.4 = 1.0 °C < 1.3 °C.

Result: Pyrogen test of *Naja siamensis* antivenom is negative.

3.2. Result of identification of safety of *Naja siamensis* antivenom in vivo (Safety test)

3.2.1. Result of sefety test of Naja siamensis antivenom on Guinea pig

Table 5: Result of sefety test of* Naja siamensis *antivenom on Guinea pigs (experienced group)

No	Weight (g)	*NS* antivenom (ml)	Experienced Guinea pig monitoring				Gain weight (g)
			Depilation	Weight			
				1st Day	3rd Day	7th Day	
1	270	4.05	No	270	275	280	+ 10
2	290	4.35	No	290	296	300	+ 10
3	300	4.50	No	300	304	310	+ 10

Table 6: Result of sefety test of **Naja siamensis** *antivenom on Guinea pigs (control group)*

No	Weight (g)	*NS* antivenom (ml)	Control Guinea pig monitoring				Gain weight (g)
			Depilation	Weight			
				1st Day	3rd Day	7th Day	
4	260	3.90	No	260	265	270	+10
5	300	4.50	No	300	307	310	+10
6	300	4.50	No	300	310	320	+20

Remark: Observation 06 Guinea pigs during 2 hours after *NS* antivenom injection: normal eating, normal moving, no depilation or any abnormal symptoms of early antivenom adverse reactions.

+Both groups of Guinea pigs injected *NS* antivenom grew normal, gained weight, no depilated or any diseases.

No different significance both groups (experienced and control) of weight after observation for a week (P>0.05)

Result: *NS* antivenom was safe on Guinea pig in vivo.

3.2.2. Result of sefety test of Naja siamensis antivenom on white mice

Table 7: Result of safety test of **Naja siamensis** *antivenom on white mice (experienced group)*

No	Weight (g)	*NS* AV (ml)	Experimented white mice monitoring				Gain weight (g)
			Depilation	Weight			
				1st Day	3rd Day	7th Day	
1	18	0.90	No	18	20	25	+ 07
2	18	0.90	No	18	20	25	+ 07
3	19	0.95	No	19	21	26	+ 07
4	19	0.95	No	19	22	26	+ 07
5	20	1.00	No	20	23	28	+ 08

Table 8: Result of safety test of **Naja siamensis** *antivenom on white mice (control group)*

No	Weight (g)	NaCl 0,9% (ml)	White mice monitoring				Gain weight (g)
			Depilation	Weight			
				1st Day	3rd Day	7th Day	
1	18	0.90	No	18	19	25	+ 07
2	18	0.90	No	18	20	25	+ 07
3	18	0.90	No	18	21	25	+ 07
4	19	0.95	No	19	21	25	+ 06
5	20	1.00	No	20	23	28	+ 08

Remark: Observation 10 white mices during 2 hours after NS antivenom injection: normal eating, normal moving, no depilation or any abnormal symptoms of early antivenom adverse reactions.

Both groups of white mices injected *NS* antivenom grew normal, gained weight, no depilated or any diseases.

No different significance both groups (experienced and control) of weight of white mices after observation for a week (P>0.05)

Result: *NS* antivenom was safe on white mice in vivo.

3.3. Results of sterilization tests of *Naja siamensis* antivenom (Sterility test)

Table 9: Results of* Naja siamensis *antivenom sterility test

Media	Thioglycolat incubated at 30 -35^{0}C			Thioglycolat incubated at 20 -25^{0}C			Soybean casein digest incubated at 20 -25^{0}C		
Day	3rd Day	7th Day	14th Day	3rd Day	7th Day	14th Day	3rd Day	7th Day	14th Day
Result	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg

Neg: negative

Remark: *NS* antivenom had cultured in Thioglycolate media (20-25ºC), Thioglycolate media (30-35ºC) and Soybean Casein Digest media in Microbiology Department. The samples were monitored during 14 days to find out bacterial and fungal growth.

Aerobic and anaerobic bacteria and fungi did not grow in media that *NS* antivenoms had cultured.

Results: *NS* antivenom is sterilization with bacteria and fungi.

3.4. Results of measurrement of pH, thimerosal and natri chlorid concentration of *Naja siamensis* antivenom

Table 10: Results of meassurement of pH, thimerosal and natri chlorid of* Naja siamensis *antivenom

No	Biochemical values identification	Results	National criteria
1	pH	6.5 ± 0.3	6.0 – 7.0
2	Thimerosal	< 0.01%	< 0.02%
3	Natri chlorid	0.88% ± 0.2%	0.85 – 0.9%

Remark*:* pH of Naja siamensis antivenom: 6.5 ± 0.3.

Thimerosal < 0.01%

Sodium chlorid: 0.88% ± 0.2%

Results: pH, thimerosal and sodium chlorid of *Naja siamensis* antivenom passed National standard criteria

3.5. Protein measurrement of Naja siamensis *antivenom*

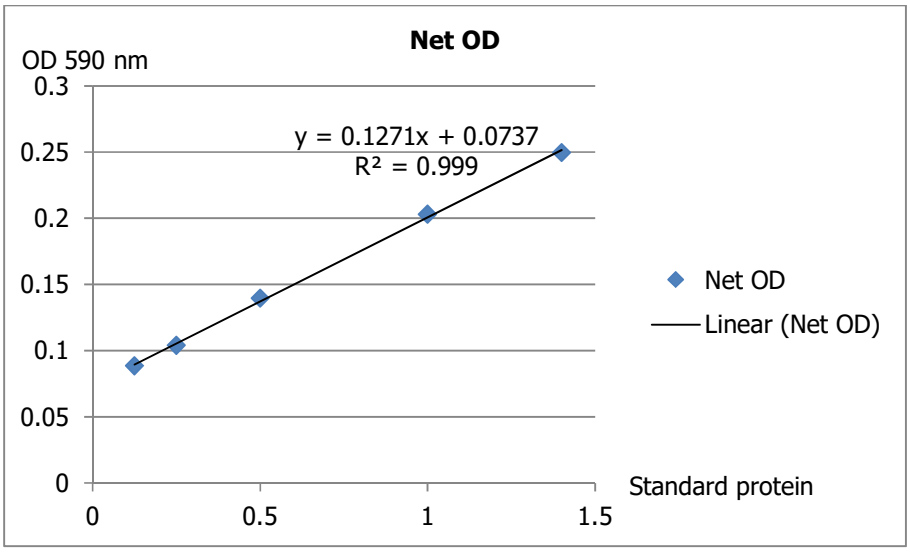


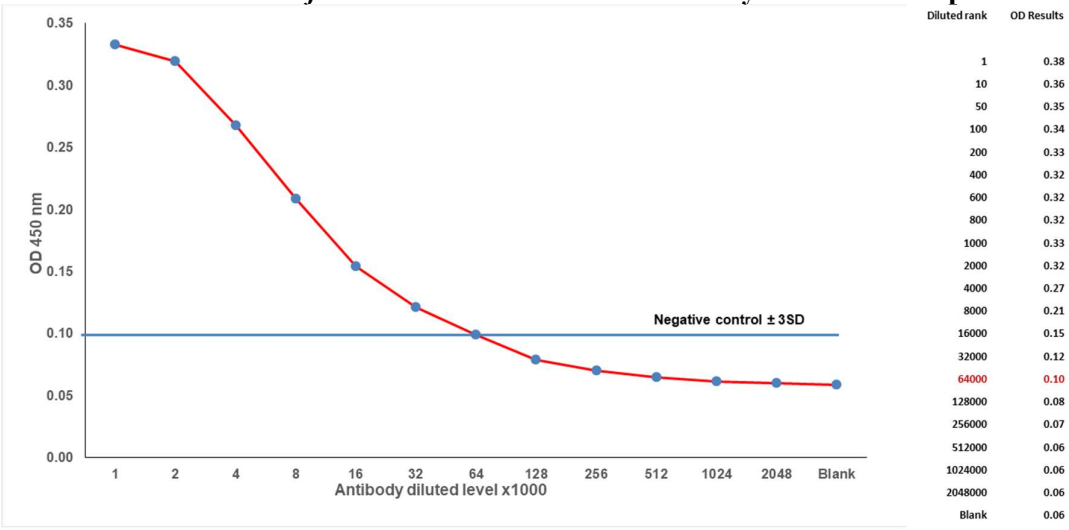
Figure 1. Result of protein concentration of* Naja siamensis *antivenom based on standard line by Bradford Method

Remark: *Naja siamensis* antivenom OD is 0.206 with titred level 64. Protein concentrated calculation of *Naja siamensis antivenom* based on standard protein function:

y = 0.1271x + 0.0737 = (0.206 – 0.073) / 0.127 = 67.2 (mg/ml).

Result: Protein concentration of *Naja siamensis* antivenom is 67.2 mg/ml.

3.6. Identification of *Naja siamensis* antivenom titration by ELISA technique



Diluted rank	OD Results
1	0.38
10	0.36
50	0.35
100	0.34
200	0.33
400	0.32
600	0.32
800	0.32
1000	0.33
2000	0.32
4000	0.27
8000	0.21
16000	0.15
32000	0.12
64000	0.10
128000	0.08
256000	0.07
512000	0.06
1024000	0.06
2048000	0.06
Blank	0.06

Figure 2: Result of specific antibody titration of* Naja siamensis *antivenom by ELISA

Result of OD messured:

- Negative control: 0.076
- SD: 0.002

- Negative control +3SD: 0.082

- The lowest positive dilution of NS antivenom is 0.099 equal 1/64,000 titred level comparison with negative control + 3SD (0.082).

Result: Antibody of *NS* antivenom is confirmed 1/64.000 titrated level by ELISA.

3.7. Results of immuno-elctrophoresis of* Naja siamensis *antivenom F(ab')$_2$

Table 11. Result of* Naja siamensis *antivenom immuno-electrophoresis

The immunoglobuline composition of *Naja siamensis* antivenom	Result	Percent ration (%)	Normal range
Albumin	2.01 g/l	5.74	36.0 – 50.0 g/l
Alpha-1 Globulin	3.25 g/l	9.30	2.10 – 3.50 g/l
Alpha-2 Globulin	0.84 g/l	2.41	5.10 – 8.50 g/l
Beta-1 Globulin	2.17 g/l	6.20	3.40 – 5.20 g/l
Beta-2 Globulin	2.77 g/l	7.90	2.30 – 4.70 g/l
Gamma Globulin	23.96 g/l	68.44	8.0 – 13.5 g/l
Protein	35.0 g/l		60 – 80 g/l
A/G	0.060		1.20 – 1.60
IgG	< 32.00 mg/dl		800 – 1.800 mg/dl
IgM	< 25.00 mg/dl		70 – 330 mg/dl
IgA	< 5.0 mg/dl		90 – 450 mg/dl

Results of immuno-electrophoresis of *Naja siamensis* antivenom F(ab')$_2$: gama globulin (68.44%), beta-1 globulin (2.71%) and beta-2 globulin (2.1%). Albumin is low concentration (5.74%). IgG, IgA and IgM are also low. Protein is 35.0g/l.

IV. DISCUSSION

4.1. Assessment of* Naja siamensis *antivenom of safety test

New antivenom is required safety tests on Guinea pig and white mice. The other tests are also required from National criteria for clinical practice of antivenom treatment such as pyrogens and sterility tests [6],[9]. Our *NS* antivenom is determined safety on Guinea pig and white mice [6]. Safety is the most important issue for antidote treatment. Early and late adverse reactions are relative to antivenom quality [10], [11], [12]. The adverse reactions of other antivenoms producted in the past were low and accepted. For examble, the side effects which *Naja kaouthia* antivenom applied on 54 *Naja kaouthia* evenomated patients, showed anaphylactic shock 3.7%, fever 9.2%, alergy 1.8% [13]. The adverse reaction rate of 32 *Calloselasma rhodostoma* envenomated patients treated by *Calloselasma rhodostoma* antivenom presented anaphylactic shock 3.1%, allergy 9.4% [14]. It was low as same as other countries [4]. Chippaux J.P. và Goyffon M. (1998) [12] suggest that adverse reactions must be reduced less than 5% as WHO (2010) recommendation [6]. To achieve this result, manufacture of antivenom production must be impoved the quality control to reach Good Manufacturing Practice (GMP) [12].

4.2. Assessment of* Naja siamensis *antivenom of potency test

The study determined the median lethal dose (LD_{50}) of *NS* venom of Vietnam. This is a criterion for assessment of efficacy of antivenom as well as other studies about *NS* venom in the future. We have very rare basic studies on *NS* venom in recently. Trinh Xuan Kiem *et al* (2014) studied on LD_{50} of some inportant venomous snakes in Vietnam: *Naja kouthia* 0.4µg/g/tail vein, *Ophiophagus hannah* 1.2µg/g/ tail vein, *Bungarus fasciatus* 1.4µg/g/ tail vein, *Bungarus candidus* 0.1µg/g/ tail vein, *Cryptelytrops albolabris* 0.5µg/g/ tail vein and *Calloselasma rhodostoma* 6.1µg/g/ tail vein [15]. Therefore, determination of the median lethal dose (LD_{50}) of *Naja siamensis* is necessary in venom research in Vietnam. LD_{50} of *Naja siamensis* venom of our study is 12.59 µg/20g mice /peritonized or 0.63 µg/g. It is as same as LD_{50} of *Naja kaouthia.*

The assessment of efficacy of *Naja siamensis* antivenom in experimental model is performed arcording to median effective dose (ED_{50}). This is a gold standard in pre-clinical tests of snake antivenom assessment [6]. Our *NS* antivenom efficacy is evaluated high potency with 500 LD_{50}/vial (05ml). It is able to neutralize 6000µg *NS* venom (6mg/vial) from one vial. This confirmed good quality of resource materials as well as determined good protocols of production of *NS* antigen and immunized horse schedule. *NS* antivenom titration is also determined by ELISA technique at 1/64,000 level. It is also definition of perfect protocol of $F(ab')_2$ purifed *NS* antivenom production. As a result, we will organize the clinical trials for *NS* antivenom as soon as posisible to resolve a lack of *NS* antivenom in Clinical practice in Vietnam.

4.3. Assessment of* Naja siamensis *antivenom of specificity test

ELISA technique on venom research and antigen-antibody reaction was applied by Theakston R.D.G. *et al* firstly in 1977 [16]. Using this method, our study confirmed specificity of *NS* antivenom and it titration.

4.4. Assessment of *Naja siamensis* antivenom of other tests

Our study of pH, thimerosal and sodium chlorid are in normal range as same as National standard criteria. Theses issues are very inportant roles in pre-clinical tests before *NS* antivenom is applied clinical trials.

Pre-clinical assessment is useful for new antivenom but it also has pitfalls in clinical practice. These tests are not predicted new antivenom efficacy in clinical [6]. Therefore, Isblister (2010) suggest that double blind placebo randomized control trials is the best assessment for new antivenom especially ineffective treatment [17].

V. CONCLUSION

The *NS* antivenom product passed the Vietnamese National Quality Control and accorded with WHO snake antivenom guideline. LD_{50} was determined 12.59 µg/20g mice /peritonized or 0.63 µg/g. ED_{50} was calculated 0.10ml. Each *NS* antivenom vial is able to neutralize 500 LD_{50} or 6mg *NS* venom. By experimental animal assessment, *N.S* antivenom is not only no pyrogens and sterilization but also high safety and strong efficacy.

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RÉSUMÉ:

ÉVALUATION FINALE DE L'ANAVENIN *NAJA SIAMENSIS* DANS DES ESSAIS EXPÉRIMENTAUX

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Objectifs: L'anavenin de *Naja siamensis* (*NS*) produit avec succès au Vietnam et au monde. Notre étude visait à évaluer cet anavenin *NS* en ce qui concerne la sécurité, l'efficacité, les pyrogènes, la stérilité, le pH, le thiomersal et les concentrations de chlorure de sodium dans des essais expérimentaux.

Méthode: Selon la Pharmacopée Nationale Vietnamienne IV, les tests de la sécurité et d'efficacité ont été réalisés sur la base d'une dose létale moyenne (DL_{50}) et d'une dose efficace moyenne (DE_{50}) chez les souris (18-20g) et les cobayes (250-350g). Un test de stérilité effectué sur du thioglycolate à 20 - 25°C et 30 - 35°C et de la caséine de soja a été digéré à 20 - 25°C pour permettre l'identification des bactéries et des champignons. Le test des pyrogènes a également permis de confirmer la qualité de notre anavenin *NS*. De plus, la spécificité de l'anavenin *NS* et le niveau titré ont également été attestés par ELISA technique.

Résultats: La dose létale moyenne (DL_{50}) était de 12,59 µg/20g de souris. La dose efficace moyenne (DE_{50}) était de 100 DL_{50}/ml. Pas de pyrogènes et stérilisation confirmée dans l'anavenin *NS*. Le niveau titré de l'anavenin *NS* par ELISA était de 1/64.000. Une évaluation de l'anavenin *NS* in vitro et in vivo a montré une spécificité avec une élevée sécurité et efficacité.

Conclusion: L'anavenin de *Naja siamensis* a satisfait aux critères de normalisation Nationale Vietnamienne et aux recommandations de l'OMS.

Mot-clé: *L'anavenin de Naja siamensis, évaluation de la sécurité et de l'efficacité.*

COST - EFFECTIVENESS OF BIOLOGICAL DRUGS FOR THE TREATMENT OF MODERATE-TO-SEVERE PLAQUE PSORIASIS: A SYSTEMATIC REVIEW

Ha Van Sanh*, Nguyen Thi Thu Cuc, Nguyen Thi Thu Thuy***

ABSTRACT

Objective: This study was conducted to systematically review cost-effectiveness studies of biological drugs for the treatment plaque psoriasis by assessing the quality of the studies and synthesizing cost – effectiveness data from eligible studies. ***Methods:*** A search using MeSH (Medical subject headings) terms and key words was conducted on two databases Pubmed and The Cochrane Library to identify full-text studies written in English that evaluated the the cost – effectiveness of biological drugs for the treatment of moderate-to-severe psoriasis. The quality of selected studies wasassesssed by the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist. ***Results:*** Out of 229 records, 10 publications were included in this review. Based on CHEERS checklist, the quality of studies ranged from 15 to 23 out of the total of 24 with nine studies (90%) of fair to good quality. Overall, etanercef was the most commonly assessed drug in all studies, followed by adalimumab shown in 6 studies. The ICER/QALY values ranged from $2,418 to $188,502. ***Conclusion:*** In most cases, biological drugs were dominant when compared with other therapies including standard care, supportive care, basal treatment, systemic therapy and non-target-immuno drugs.

Key words: *systematic review, cost - effectiveness, biological drugs, plaque psoriasis.*

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I. INTRODUCTION

Psoriasis is a common chronic inflammation disease of the skin.The prevalence ofpsoriasis has been estimated 2% in the worldwide [1] and about 2,2% in Viet Nam[2]. Although there are no severe affections to patient's health, psoriasis can be physically and emotionally debilitating and really have a significant impact on quality of life.

Current main treatments of mild to moderate psoriasis were topical phototherapy and traditional systemic immunosuppressive agents. Regarding to moderate to severe psoriasis, biological drugs help to improve effectively PASI and quality of life of patients. However, the prescription of these drugs was limited by the high price of drugs (costs in treating psoriasis with biological medications ranged from $7,993 to $48,000 per year [3]) which was the burden not only for patients but also for the healthcare system.

As a result, along with the evaluation of the clinical outcomes, the economic analyses are also essential to choose appropriate drugs and allocate rational constrained resources in the healthcare sector. At present, there are a lot of cost – effectiveness studiesabout biological drugs published over the world with thedifference of patient characteristics, research features, clinical protocol, cost value. Therefore, a systematic review about the cost – effectiveness of biological agents in treating psoriasis as well as a studies' quality evaluation were necessary.

The aim of this study was to collect and summarize all data concerning the cost – effectiveness of biological drugs in psoriasis focusing on nine biologics that approval by FDA: etanercept, efalizumab, apremilast, infliximab, adalilumab, ustekinumab, secukinumab, ixekizumab, brodalumab and evaluate the quality of chosen researches by using CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist.

II. MATERIALS AND METHODS

2.1. Literature search

A systematic review was performed on 05 July 2017 in Pubmed and The Cochrane Library to collect data from articles that reported acost-effectiveness evaluation of biological drugsin the treatment ofmoderate-to-severe psoriasis. A PICO scheme including Population, Intervention, Comparison, Outcome was used to describe the objectives of interest (**Table 1**)

Table 1: The PICO scheme

Population	**moderate-to-severe psoriasis patients**
Intervention	Biologicals (etanercept, efalizumab, apremilast, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab)
Comparison	alternative treatments (placebo, standard care, supportive care, basal treatment, systemic therapy and non-target-immuno drugs)
Outcome	incremential cost – effectiveness ratio (ICER)

The search command was ("cost per additional responder" or "cost effectiveness" or "cost efficacy" or "cost-benefit" or "cost consequence" or "cost utility" or "economic evaluation" or "ICER") and ("plaque psoriasis" or "psoriasis" or "moderate to severe") and ("biologic" or "biologic agents" or "biological therapy" or "systemic treatment" or "etanercept" or"efalizumab" or "apremilast" or "adalimumab" or "infliximab" or "ustekinumab" or "secukinumab" or "ixekizumab" or "brodalumab" or "targeted immunomodulators" or "TNF-α" or "IL-12" or "IL-23" or "IL- 17A" or "IL- 17AR" or "CD11a" or "PDE4").

The systematic review was conducted independently by two researchers. In case of disagreement, a discussion between two researchers was carried out to decide the problems and find out the general solutions.

2.2. Study selection

Original studieswritten in English were included if they (1) evaluated the cost – effectiveness of biological drugs for the treatment of moderate-to-severe psoriasis (etanercept, efalizumab, apremilast, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab)in a particular country; (2) used QALY as main outcomes. Unavailable full-text, posters, comments, expert opinions, clinica trials were excluded.

2.3. Data extraction, synthesis and presentation

The articles that met the criteria were extracted information in a table. The following items were recorded including: study features (author' name, country, year of study, population, interventions and comparators, perspective, currency, clinical outcome, economic outcome), study design (study model and modeling features, time horizon, methods of measuring outcomes, discount rates, cost reference date), and results (total costs, total outcomes, ICER value, conclusions concerning cost-effectiveness, sensitivity of uncertainty).

To compare the results of the studies, all costs were converted in USD 2017 based on the reference exchange rate of the World Bank and the consumer price index (exchange rate on 15 December 2017). For ease of comparison, the comparator groups based on the type of biologics and measured outcomes were applied.

2.4. Quality Assessment

Instrumentswas commonly used to assess the quality of health economic studiesas QHES (Quality of Health Economics Studies), CHEC (The Consensus Health Economic Criteria list) and the CHEERS (Consolidated Health Economic Evaluation Reporting Standards). Among them, CHEERS was recommended forhealth economic biomedical studies [4] and it was chosen for this study. The CHEERS checklist contains 24 recommendations subdivided into six main categories: 1) title and abstract, 2) introduction, 3) methods, 4) results, 5) discussion, and 6) other. The process of quality evaluation was independently conducted by two reviewers. The discrepancies were discussed until reaching the consensus. The result was presented as the number of recommendations in CHEERS checklist gained by each article and was classified into four group of quality scale including good (fulfilling 20-24 recommendations), fair (fulfilling 17-19 recommendations), average (fulfilling 14-16 recommendations), below average (fulfilling below 13 recommendations)

III. RESULTS AND DISCUSSION

A total of 229 references were identified through the literature search (198 from Pubmed and 31 from the Cochrane library). After removing duplicates, 207 remaining records were submitted for further selection based on the review of their titles and abstracts. 44 references were recorded to continue screening based on inclusion and exclusion criteria. In this step, the researchers excluded 34 records because of not approaching fulltext (n=9), secondary data (n=4), not reporting ICER/QALY outcomes (n=21). Finally, 10 remaining references were included in this systematic review. The PRISMA flow diagram were shown in **Fig.1.**

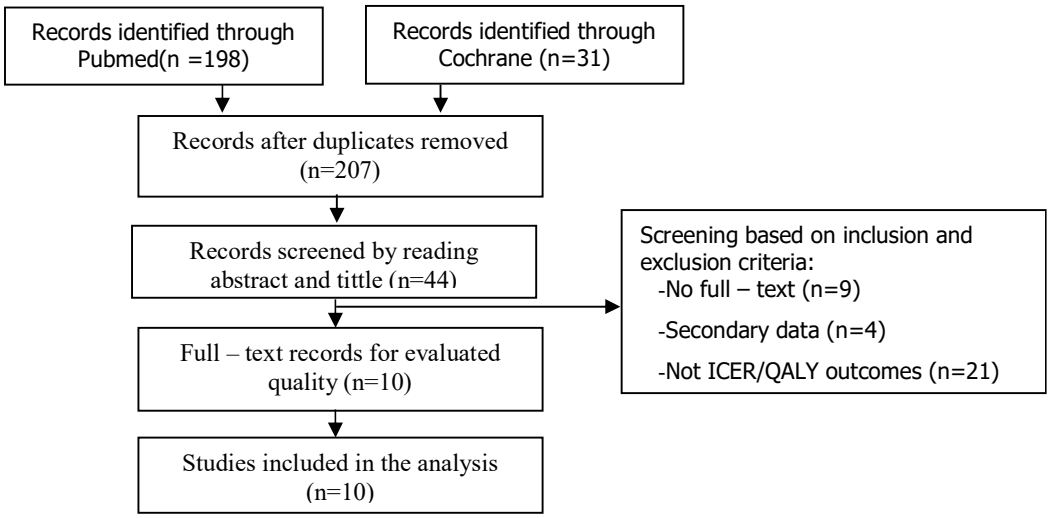

Figure 1: PRISMA flowchart

Using CHEERS checklist, the quality of selected studies has been evaluated. It has been shown that quality of the selected studies ranged from 15 to 23 out of the total of 24. The highest number was 23 in the study of Villacorta 2013 [5] while the lowest one was 15 in the studies of Jeffrey 2016 [14]. Nine studies (90%) gained over 17 recommendations, none had the quality below average. Overall, the quality of selected studies was quite good (**Table 2**).

Table 2: Quality of selected studies according to CHEERS checklist

Quality Scale	Reference	Fulfilling recomendations (n)	Percentage (%)	n (%)
Good	Villacorta 2013[5]	23	95,8	5 (50%)
	Pan 2011[6]	21	87,5	
	Knight 2011[7]	20	83,3	
	Lloyd 2008[8]	20	83,3	
	Sizto 2008[9]	20	83,3	
Fair	Heinen-Kammerer 2007[10]	19	79,2	4 (40%)
	Spandonaro 2014[11]	19	79,2	
	Giorgio 2009[12]	18	75,0	
	Duarte 2017[13]	17	70,8	
Average	Jeffrey 2016 [14]	15	62,5	1 (10%)
Below average	-	-	-	0 (0%)

Out of ten identified economic evaluations, eight articles estimated ICERs from healthcare perspectives [6, 8 – 14] and two studies were from societal perspectives [5, 7]. As far as the treatment cost is concerned, four studies included only direct cost, three included direct and indirect cost, while two mentioned direct cost and adverse event cost, only one references used indirect cost and adverse event cost. Six studies used Markov modelling while two extracted results from clinical trial, one based on the combination of Markov and decision-tree modelling and one used De novo decision-analytic modelling. Time horizon varied from 1 year [9,11], 1-3 years [5] and more than 3 years [6-8, 10, 12-14]. Because there were some differences in the methodology so meta-analysis could not be done, a systematic review was preferred.

Out of nine biological dugs evaluated in this study, etanercef appeared in all ten refereneces, adalimumab included in six ones, ustekinumab was in four, infliximab was in two and secukinumab, ixekizumab, brodalumab were in one referenece while efalizumab, apremilast were none. Secukinumab, ixekizumab and brodalumab were only evaluated in one study, the reason may be that these drugs were just approved by FDA for plaque psoriasis treatment in 2015, 2016, 2017 respectively so there were not many studies about cost - effectiveness of these drugs. Moreover, there was no study about efalizumab, apremilast with ICER/QALY as outcome measure which made the result of this review not fulfilled.

Summary of results of these studies has been illustated in **table 3**. Almost studies were conducted in European countries, out of them, three were carried out in the UK,

two were in Italia, one was in Germany and one was in Sweden. Meanwhile, there were two articles conducted in USA and one in Canada. Besides, the systematic review recorded the differences in years of publications (2005 to 2017), currencies (USD, Pound, Euro, Canadian Dollar).Therefore, in order to evaluate and compare the cost – effectiveness of biologicals in psoriasis treatment, ICER/QALY outcomes were extracted and then converted into USD 2017 by using consumer price index (CPI) and exchange rate in 15 December 2017. The converted ICER/QALY results varied in the wide range from $2,418 to $188,502.

As can be seen from **Table 3**, the ICER values varied in a wide range among the studies acording to the comparators. When comparing entanercept directly to other therapies such as standard care, supportive care, basal treatment, systemic therapy and non-target-immuno drugs, the ICER/QALY ranges from $7,397 to $ 120,277[10, 8, 9, 14, 11, 13, 12, 7]. In addition, when patients started treatment with etanercept at different PASI and DLQI values, the ICER/QALY value obtained was also varied from $33,641 to $63,25310, 12. When comparing to other biologicals, etanercept was more cost-effective than adalimumab in the case of comparing to non–system treatment with an ICER value of etanercept less than the ICER of adalimumab ($12,526/QALY versus $58,164/QALY, respectively).

Table 3: The results of selected studies

Reference	Intervention and comparation	Treatment cost	QALY	ICER - original values	ICER - 2017 (USD)	Conclusion
Villacorta, 2013[5]	Etanercept 50 mg	$54,845	2.109	UST 45 vs. ETA 50= Dominant UST 90 vs. UST 45= 384,401	UST 45 vs. ETA 50: Dominant UST 90 vs. UST 45=$41,889	- Ustekinumab 90 mg is not cost effective compared with etanercept 50 mg - Ustekinumab 45 mg dominates etanercept 50 mg
	Ustekinumab 45 mg	$50,926	2.149			
	Ustekinumab 90 mg	$82,103	2.180			
Pan, 2011[6]	Ustekinumab 45 mg	C$16,807	2,718	UST 45 vs. ETA 50 = C$2,718	UST 45 vs. ETA 50 = $2,418	Ustekinumab is more cost-effective than Etanercept
	Etanercept 50 mg	C$19,525				
Heinen-Kammerer, 2007[10]	Etanercept [(a)]	€47,554	0.96	ETA[(a)]vs BT= €45,491	ETA[(a)] vs BT= $63,253	Etanercept is more cost-effective than basal treatment
	Basal Treatment	€41,045	0.82			
	Etanercept [(b)]	€47,945	1.34	ETA[(b)]vs BT= 32,058	ETA[(b)] vs BT= $44,575	
	Basal Treatment	€41,045	1.13			

Reference	Intervention and comparation	Treatment cost	QALY	ICER - original values	ICER - 2017 (USD)	Conclusion
	Etanercept [(c)]	€54,994	1.74	ETA[(c)]vs BT= 18,151	ETA[(c)] vs BT= $25,238	
	Basal Treatment	48,363	1.37			
Knight, 2011[7]	Non-Systemic Therapy	€37,549	5.97	ETA 50 vsNST= €9,925 ADA 40 vsNST= €46,087 ADA 40 vs ETA 50 = €165,354	ETA 50 vs NST= $12,526 ADA 40 vs. NST= $58,164 ADA 40 vs ETA 50 = $208,683	Etanercept 50 mg is more costeffective than adalimumab and non-systemic standard of care.
	Etanercept 50 mg	€56,850	6.56			
	Adalimumab 40	€90,306	6.74			
Lloyd, 2008[8]	Non-Systemic Therapy	41 985	0.70	ETA 50 vsNST = 6217; ETA 25 vsNST= 4297 ETA 50 vs ETA 25 = 11 710	ETA 50 vs NST = $7,397 ETA 25 vs NST = $10,701 ETA 50 vs ETA 25 = $20,157	Etanercept 50 mg is more costeffective than etanercept 25 mg and non-systemic therapy
	Etanercept 50	47 587	1.61			
	Etanercept 25	44 855	1.37			
Sizto, 2008[9]	Supportive Care	0	0	ETA 25 vs. SC = 37 284 ETA 50 vs. SC=38 358 ADA vs. SC=30 538 ETA vs. SC= 37 676 IFX vs. SC= 42 492	ETA 25 vs. SC = $62,764 ETA 50 vs. SC=$64,572 ADA vs. SC=$51,408 ETA vs. SC= $63,424 IFX vs. SC= $71,531	ADA was most cost effective
	Etanercept 25 mg	0.110	4114			
	Etanercept 50 mg	0.123	4699			
	Adalimumab	0.164	4993			
	Etanercept	0.134	5058			
	Infliximab	0.182	7736			
Jeffrey, 2016[14]	Non-Targeted	$88,086	5.531	ADA vs. NT= $108,040 BRD vs. NT= $94,030 ETA vs. NT= $117,769 IFX vs. NT= $92,715 IXK vs. NT= $100,389 SCK vs. NT= $89,843 UST vs. NT= $129,904	ADA vs. NT= $110,341 BRD vs. NT= $96,033 ETA vs. NT= $120,277 IFX vs. NT= $94,690 IXK vs. NT= $102,527 SCK vs. NT= $91,757 UST vs. NT= $132,671	Secukinumab is the most cost-effective agent versus non-targeted therapy
	Adalimumab	$208,881	6.649			
	Brodalumab	$240,398	7.151			
	Etanercept	$198,519	6.469			
	Infliximab	$203,532	6.776			
	Ixekizumab	$254,287	7.187			
	Secukinumab	$221,704	7.018			
	Ustekinumab	$269,843	6.930			

Reference	Intervention and comparation	Treatment cost	QALY	ICER - original values	ICER - 2017 (USD)	Conclusion
Spandonaro, 2014[11]	Supportive Care	-	-	ETA vs SC= 25,839.79	ETA vs SC= $33,845	
	Etanercept	-	-	ADA vs SC= 29,285.34	ADA vs SC= $38,358	
	Adalimumab	-	-	IFXvs SC= 53,525.38	IFXvs SC= $70,108	
	Infliximab	-	-			
Duarte, 2017[13]	Children And Young People Aged 6–11 Years					
	Supportive Care	36,406	8.710	ETA vs. SC=71,903	ETA vs. SC=$98,891	Biological treatments may not be cost-effective for the management of psoriasis in children and young people at a willingness-to-pay threshold of £30,000 per quality-adjusted life-year
	Etanercept	43,808	8.813	ADA vs. SC= 115,825	ADA vs. SC= $159,298	
	Adalimumab	57,251	8.890			
	Children And Young People Aged 12–17 Years					
	Supportive Care	21,749	4.804	ETA vs. SC=137,059	ETA vs. SC= $188,502	
	Etanercept	33,199	4.887	ADA vs. SC= 110,430	ADA vs. SC= $151,878	
	Adalimumab	37,852	4.950	UST vs. SC= 116,568	UST vs. SC= $160,320	
	Ustekinumab	39,975	4.960			
Giorgio, 2009[12]	Etanercept [(d)]	€40,051	6,778	ETA[(d)]vs BT= €33,216	ETA[(d)]vs BT= $43,844	- Etanercept is a cost – effective therapeutic option compared with non systemic therapy - For patients with PASI≥20, cost-effectiveness of etanercept is even greater.
	Basal Treatment	€32,441	6,549	ETA[(e)] vs. BT= €25,486	ETA[(e)] vs. BT= $33,641	
	Etanercept [(e)]	€55,959	6,332			
	Basal Treatment	€50,045	6,100			

(a): Initial ScorePASI&DLQI(N) > 10 (479), (b): Initial ScorePASI&DLQI(N) > 15 (192), (c): Initial ScorePASI&DLQI(N) > 20 (87), (d): IntialPASI Score ≥ 10, (e): IntialPASI Score ≥ 20.Etanercept - ETA, Etanercept50mg - ETA 50, Etanercept25mg - ETA 25, Adalimumab - ADA, Adalimumab50mg - ADA, Ustekinumab - UST, Ustekinumab45mg - UST 45, Ustekinumab 90 - UST 90, Brodalumab - BRD, Infliximab - IFX, Ixekizumab - IXK, Secukinumab - SCK, Standard Of Care -Soc, Supportive Care - SC, Basal Treatment - BT, Non-Targeted - NT, Non-Systemic Therapy - NST.

In particular, the ICER value is up to $208,683/QALY when comparing the cost-effectiveness of adalimumab with etanercept [7]. Whereas, etanercept was less cost-effective than ustekinumab [5, 6] so studies concluded that ustekinumab 45mg was more cost-effective than etanercept 50mg. In addition, the study of Lloyd et al [8] concluded that etanercept 50 mg was more cost effective than etanercept 25 mg with an ICER value of $20,157/QALY.

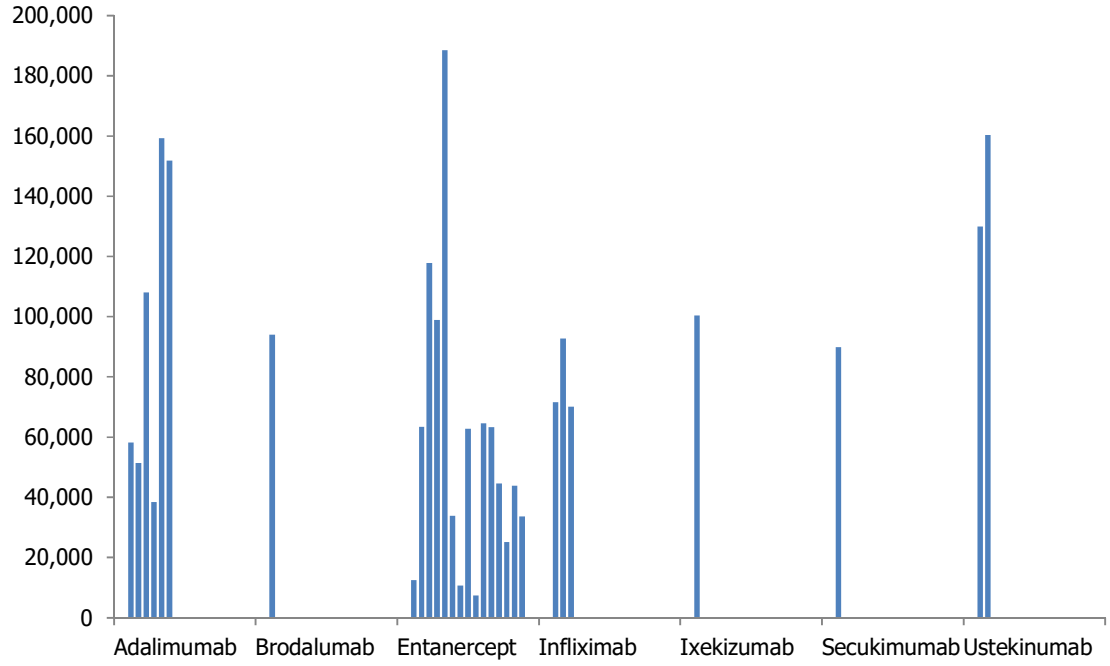

Figure 2: The ICER when comparing biological drugs to other treatments

Adalimumab in the study of Sizto 2008 [9] was more cost-effective than etanercept at both 25mg and 50mg doses, which was against to the study of Knight 2011. Also in this study, the cost for each QALY of adalimumab was also lower than infliximab for $51,408/QALY - $71,531/QALY. The study of Jeffrey 2016 [14] represented the cost-effectiveness in comparison of the most biological drugs including adalimumab, brodalumab, etanercept, infliximab, ixekizumab, secukimumab and ustekinumab; out of them, usecukimumab was the drug used for moderate to severe psoriasis with the lowest cost per QALYcompared to non-targeted therapy with $91,757/QALY.

IV. DISCUSSION

In most cases, biologicals were more cost - effective than other therapies including standard care, supportive care, basal treatment, systemic therapy and non-target-immuno drugs, except for study of Duarte 2017 which surveyed on children and young people [13]. Their result showed that biological were not cost - effective when comparing to supportive care in management of moderate-to-severe psoriasis with Willing-To-Pay (WTP) £30.000/QALY.

The conclusions from selected studies indicated that biologicals were more cost-effective than standard care, supportive care, basal treatment, systemic therapy and non-target-immuno drugs in psoriasis treatment. However, the comparison of conclusions in the included studies is difficult to conduct because of different threshold values in different countries. For instance, the threshold value of the United Kingdom is £20,000 to £30,000while that of USA is $50,000 [15]. Additionally, the research perspective (healthcare perspective, societal perspective) and type of cost (direct cost, indirect cost, adverse event cost) in each study were also different.

Some reviews concerning the cost - effectiveness of the biologicals in psoriasis were found in processing research. Zhang et al evaluated all treatment options for psoriasis, focusing on the quality of studies and methods of the studies [16]. This study found low quality studies, but it did not conclude which drugs were the most cost-effective one. The study of Mauskopf et al [17] focused on the synthesis of features of cost-effectiveness studies about psoriasis medications and their methods but it did not compare the cost-effectiveness of drugs. Whereas, Gutknecht et al. only focused on defining characteristics and heterogeneity in study design [18]. Moreover, the systematic review of Kromer et al analyzed the cost-effectiveness of biologicals in the treatment of psoriasis (adalimumab, alefacept, apremilast, efalizumab, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab) [19]. This study broadly summerized the ICER/QALY, ICER/PASI, ICER/DLQI MID. As far as the ICER/QALYwas concerned, the review mentioned 5 biological drugs (adalimumab, efalizumab, etanercept, infliximab, secukinumab) but it did not evaluate and compare with ustekinumab, ixekizumab, brodalumab.

Comparing to the studies mentioned above, our systematic review concentrated on assessing the quality of selected studies by CHEERS instrument and synthesizing the updated data about ICER/QALY of biologicals in the moderate to severe psoriasis treatment including etanercept, efalizumab, apremilast, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab. The limitation was only searching in 2 databases with the articles written in English, so the was the exclusion many relevant publications from other databases and languagues. Moreover, the conclusion about which drug was the best cost – effective onein moderate to severe psoriasis treatment was not approached. Besides, there are no official rules about quality scale in CHEERS checklist so we suggested a point scale with four quality levels according to fulfilling recommendations.

IV. CONCLUSIONS

Etanacept was the most assessed drug in economic analysis while secukinumab, ixekizumab, brodalumab, efalizumab,

apremilast was evaluated in one study. As a result, there is a need for further economic evaluations of these drugs in the future.

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RÉSUMÉ:

EFFICACITÉ DES COÛTS DES MÉDICAMENTS BIOLOGIQUES POUR LE TRAITEMENT DU PSORIASIS EN PLAQUES MODÉRÉ À SÉVÈRE: UNE REVUE SYSTÉMATIQUE

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Objectif: Cette étude visait à examiner systématiquement les études d'efficacité des coûts des médicaments biologiques pour le traitement du psoriasis en plaques en évaluant la qualité des études et en synthétisant les données d'efficacité des coûts des études éligibles.

Méthodes: Une recherche à l'aide de termes et de mots clés MeSH (Medical subject headings) a été effectuée sur deux bases de données Pubmed et The Cochrane Library afin d'identifier des études en texte intégral rédigées en anglais évaluant l'efficacité des coûts des médicaments biologiques pour le traitement du modéré à sévère psoriasis. La qualité des études sélectionnées a été évaluée par la liste de contrôle CHEERS (Consolidated Health Economic Evaluation Reporting Standards).

Résultats: Sur 229 enregistrements, 10 publications ont été incluses dans cette revue. Selon la liste de contrôle de CHEERS, la qualité des études variait de 15 à 23 sur un total de 24 avec neuf études (90%) étaient de qualité passable à bonne. Dans l'ensemble, l'étanercef était le médicament le plus couramment évalué, suivi de l'adalimumab dans 6 études. Les valeurs ICER / QALY allaient de 2.418 $ à 188.502 $.

Conclusion: Dans la plupart des cas, les médicaments biologiques étaient dominants par rapport aux autres traitements, notamment les soins standard, les soins de soutien, le traitement de fond, le traitement systémique et les médicaments à non ciblés immuno.

Mots clés: *Revue systématique, coût - efficacité, médicaments biologiques, psoriasis en plaques.*

TREATMENT COST OF HEPATITIS C BY DIFFERENT REGIMENS IN VIETNAM: AN ANALYSIS BASED ON TREATMENT GUIDELINES

Nguyen Thi Thu Thuy*, Tran Nguyen Nhat Ha*, Le Manh Hung**

ABSTRACT

Objective: This study aimed to evaluating treatment cost of hepatitis C by different regimens in Vietnam based on Vietnamese treatment guideline. ***Methods:*** Tree decison models based on the treatment guideline were constructed to determine the direct medical costs from begining to finishing with the intire course of treatment, include in: drug costs, and healthcare service costs of each regimen. The regimens of Chronic Hepatitis C Virus, genotype 1 have be used in Vietnamese, such as: Peg-Interferon/Ribavirin Regimen and Direct Acting Antivirals (DAAs) Regimens. Input data for models was retrieved from medical history of HCV patients, experts' opinions, systematic review. ***Results:*** Overall, 09 tree dicision models were built to evaluating medical direct cost of HCV, genotype 1 treatment. The highest of medical direct cost for Peg-INF/RBV Regimen and it was 2,85 times as high as the lowest of medical direct cost for SOF/LDV (141.46 VND million; 49.58 VND million, respectively). In the structure of medical direct cost, the drug cost had predominated. This shows role of the drug throughout the course disease. The highest of drug cost for GZR/EBR+RBV regimen and GZR/EBR (136.22 million VND; 135.00 million VND, respectively). The healthcare service cost of Peg-INF/RBV Regimen was 6.50 million VND that higher than the healthcare service cost of DAAs (4.63 million VND). ***Conclusions:*** The drug cost was the majority part of total medical direct cost. With the rising trend of hepatitis C chronic in Vietnam and the high cost burden of treatment, healthcare policies and national medical programs should be considered.

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I. INTRODUCTION

According to the World Health Organization reports, about 130-150 million of the world population have chronic hepatitis C (CHC) infection [9]. In addition, 3-4 million new cases of HCV infection emerge globally each year [3], [4]. The chronic infection might result in cirrhosis, hepatic failure, or HCC, which are responsible for approximately 350000 to 500000 deaths per year [2],[9], [8], [7]. HCV has a high rate of genetic heterogeneity, therefore, no vaccine or immunoglobulin exist to prevent this infection [7]. Recent advances in HCV therapy have led to the development of new antiviral drugs for treatment of HCV infection, including NS5A inhibitors ledipasvir, daclatasvir, and ombitasvir; the nucleotide analog NS5B polymerase inhibitor sofosbuvir [6], [5], [1]. These new therapies are well-tolerated and safer and much more effective than the previous therapies pegylated interferon (IFN)/ribavirin [1].With chronic infectious characteristics and severse consequences such as cirrhosis and liver cancer, HCV causes high economic and disease burden for both society and healthcare system.

This study aimed to evaluating treatment cost of hepatitis C by different regimens in Vietnam: an analysis based on approach.

II. MATERIALS AND METHODS

2.1. Materials: Medical direct cost in hepatitis C treatment by many regimens.

- The Diagnosed and treatment Guideline of hepatitis C in 2013 and 2016 of Vietnam Ministry of Health.
- Medical tender's result of many central hospital in 2016 – 2017 of Vietnam Social Insurance.
- Cost of health care services in country's clinic, regulated by Circular number 37 in 2015 of Ministry of Health and Ministry of Finance.
- Many clinical specialists in many big hospitals in Ho Chi Minh City.
- Outpatient medical records of genotype 1 hepatitis C patients in Ho Chi Minh Tropical Hospital.

2.2. Methods:

Modeling by decision tree model

To analyze medical direct cost in hepatitis C treatment by many regimens, decision tree model was used to describe treatment process with treatment regimens. In that, Peg-interferon/Ribavirin (Peg-IFN/RBV) was simulated by diagnosed and treatment hepatitis C guideline of Ministry of Health in 2013; direct acting antivirals (DAAs) were simulated by diagnosed and treatment hepatitis C guideline of Ministry of Health in 2016.

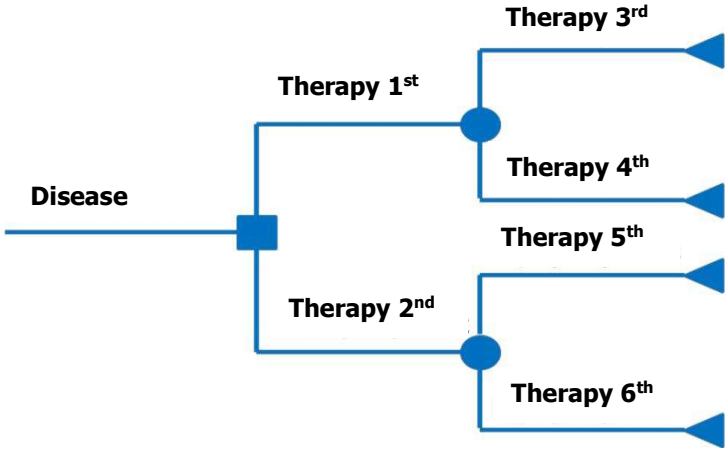


Figure 1: Decision tree model

Analytical cross - sectional study based on retrospective data

Frequency of options in decision tree model, simulated hepatitis C treatment process by Peg-IFN/RBV regimen, was extracted from analytical cross – sectional study based on retrospective data of all of medical records in 2015 of Ho Chi Minh Tropical Hospital accepted selection criteria and exclusion criteria.

Inclusion criteria

- Patients were diagnosed genotype 1, chronic hepatitis C.
- Patients were treated with Peg-IFN/RBV regimen.

Exclutive criteria

- Patients were diagnosed hepatitis C with many genotypes, included genotype 1.
- Patients were not Vietnamese or not living nor working in Vietnam.
- Patients have not finished treatment yet.
- Medical records were torned, blurred or not enough information.

Interview specialists

Adversed effects of Peg-IFN/RBV regimen consist of anemia, depression and rash. Assumption of treatment cost for adversed effects of Peg-IFN/RBV was conducted by modeling therapy based on interviewing specialists about solutions and used resources. Interviewed specialists consisted of 5 experienced clinical experts in hepatitis C treatment of Ho Chi Minh Tropical Hospital and Central Tropical Hospital.

Data overview

To find the frequences of each options in each regimens, study researched studies in the world that analyze the proportion of successful hepatitis C treatment by DAAs regimens through Pubmed, Google Scholar, Cochrane with keywords: Chronic hepatitis C, DAAs Regimens with statement ("Chronic hepatitis C, genotype 1" AND "DAAs Regimens). According researching, study recognized 8 studies that reported exactly the proportion of hepatitis C, genotype 1 patients with HCV RNA (-) and HCV RNA (+) result after treated by DAAs regimens in 12 weeks.

Data input of models

The data input used in model were illustrated in table 1.

Table 1: The resource parameters used in model

Parameter	Assessing method	Resource
Proportion of option in model	Retrospective medical report, overview research	- 140 retrospective medical records that accepted selection and exclusion criteria. - Overview researched the proportion of hepatitis C, genotype 1 patients with HCV RNA (-) and HCV RNA (+) result after 12 weeks treatment by many regimens.
Medical direct cost of option in model	Based on treatment regimens	- Medical tender's result of many central hospital in 2017 of Vietnam Social Insurance. - Cost of health care services in country's clinic, regulated by Circular number 37 in 2015 of Ministry of Health and Ministry of Finance.
Adversed effects treatment cost	Interview clinical specialists	- Many clinical specialists in big hospitals in Ho Chi Minh City.

III. RESULTS

3.1. Decision tree model

Peg-Interferon/Ribavirin regimen

According to theDiagnosis and Treatment Guideline of Hepatitis C in 2013 of Ministry of Health's Vietnam (issued in conjunction with Decision No. 4817/QD-BYT dated 28/11/2013 by the Minister of Health), the patients who are diagnosised hepatitis C virus, genotype 1, stage F0-F4, are indicated for 4 weeks with Peg-IFN/RBV regimen. After 4 weeks, the

patient will be re-examined and the following treatment will be indicated based on the follow-up results:

- If HCV-RNA is negative and HCV-RNA <4x10^{5}IU/ml (RapidVirological Response - RVR), patients continue treating with Peg-IFN/RBV for 24 weeks.

- If HCV-RNA is negative and HCV-RNA> 4x10^{5}IU/ml (Rapid Virological Response - RVR),patients continuetreating with Peg-IFN/RBV for 48 weeks.

If HCV-RNA is positive, patients should be continued treating with Peg-IFN/RBV for 8 weeks. Then follow up and review the treatment based on re-examined results as:

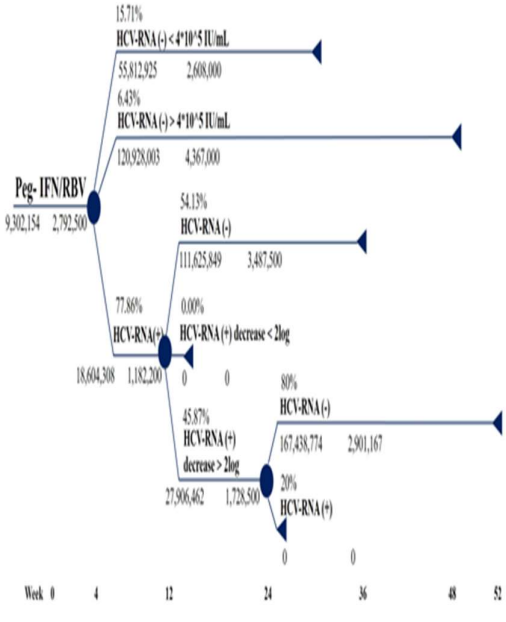
+ If HCV-RNA is negative (Early Complete Virological Response - cEVR), patients continue treating with Peg-IFN/RBV for 36 weeks.

+ If HCV-RNA is positive, but HCV-RNA is decreased lower 2 logs than the 4st week result(Late Virological Response - DVR), the patient should be stopped treating.

+ If HCV-RNA positive and HCV-RNA is decreased higher2 logs than the 4st week result (Partial Early Virological Response - pEVR), patients should be continued treating with Peg-IFN/RBV for 12 weeks.

Subsequently, if HCV-RNA is negative (pEVR (-)), patients continue to receive Peg-IFN/RBV for 28 weeks. If HCV-RNA is positive (pEVR (+)), patientsdoesn't response to the drug, treatment should be discontinued.

The whole treatment process wasmodeled using the tree decision model and was shown in Figure 2.



	P	Drug cost	Health service cost	p*Drug cost	p*Health service cost	Total
	0.16	65,115,079	9,684,500	10,229,579	1,521,434.95	11,751,015.90
	0.06	130,230,157.5	16,537,500	8,373,799.1	1,063,361.3	9,437,162.1
	0.42	139,532,311.7	15,142,200	58,806,755.1	6,381,773.8	65,188,540.8
	0.00	139,532,311.7	4,862,700	0.0	0.0	0.0
	0.29	223,251,698.6	16,284,366.7	63,786,371.6	4,652,688.7	68,439,073.3
	0.07	55,812,924,7	8,289,200	3,986,648.2	582,087.3	4,578,736.3
	1.00			**145,183,182.4**	**14,211,346**	**159,394,529.4**

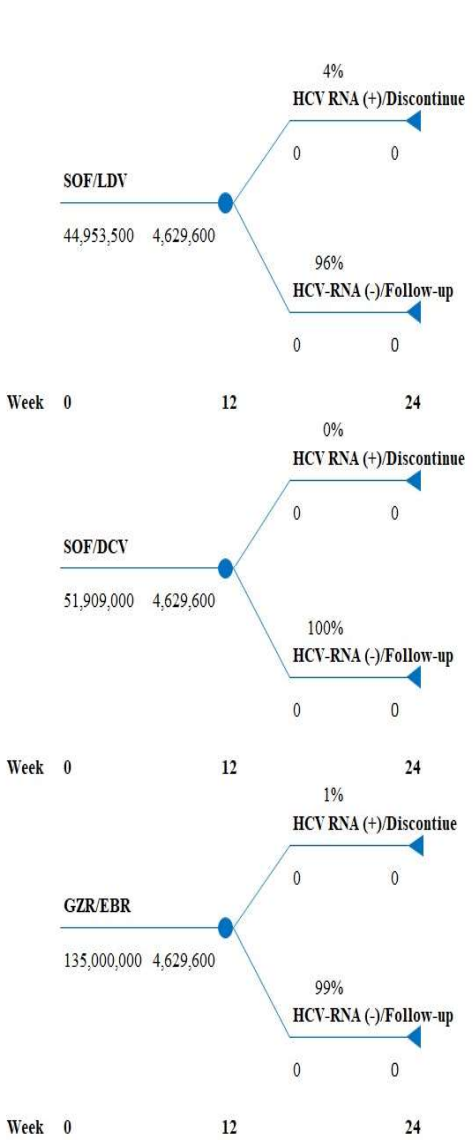
Figure 2: Model of process treatment in chronic hepatitis C with Peg-IFN/RBV regimen

DAA Regimens

According to the Guidelines for the Diagnosis and Treatment of hepatitis C in 2016 of MOH-VN, the patient was diagnosed chronic hepatitis C and was assigned a DAA regimen every 4 weeks. After 12th week, the course of treatment will depend on the results of the test:

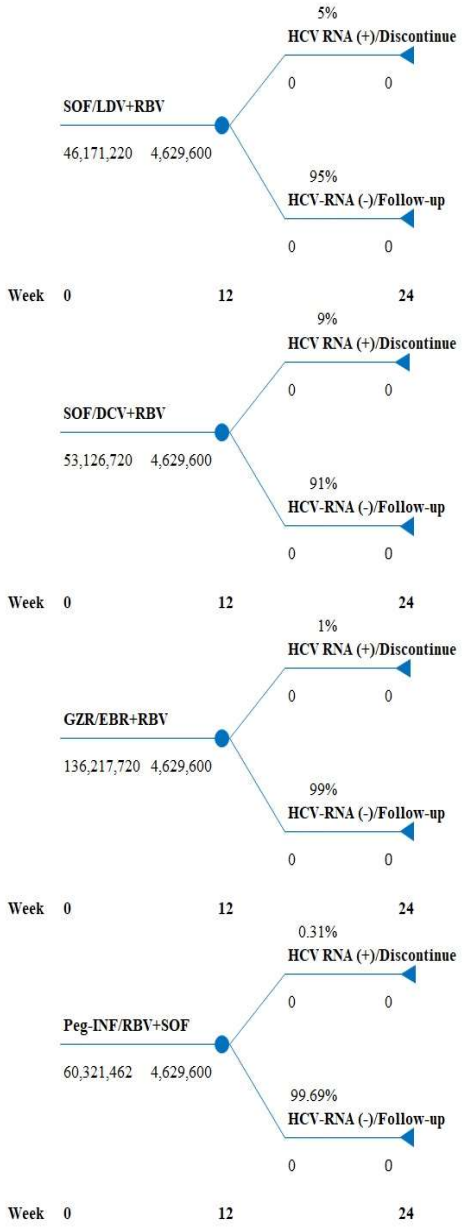
- If HCV-RNA is positive, discontinue treatment.
- If HCV-RNA is negative, the patient was monitored periodically.

The whole treatment process wasmodeled using the tree decision model and was shown in Figure 3 and Figure 4.



	p	Drug cost	Health service cost	p*Drug cost	p*Health service cost	Total
	0.04	44,953,500	4,629,600	1,663,280	171,295	1,834,575
	0.96	44,953,500	4,629,600	43,290,221	4,458,305	47,748,525
	1			**44,953,500**	**4,629,600**	**49,583,100**
	0.00	51,909,000	4,629,600	0	0	0
	1.00	51,909,000	4,629,600	51,909,000	4,629,600	56,538,600
	1			**51,909,000**	**4,629,600**	**56,538,600**
	0.01	135,000,000	4,629,600	1,350,000	46,296	1,396,296
	0.99	135,000,000	4,629,600	133,650,000	4,583,304	138,233,304
	1			**135,000,000**	**4,629,600**	**139,629,600**

Figure 3: Desicion model in CHC treatment with DAAs regimen none RBV



	p	Drug cost	Health service cost	p*Drug cost	p*Health service cost	Total
	0.05	46,171,220	4,629,600	2,308,561	231,480	2,540,041
	0.95	46,171,220	4,629,600	43,862,659	4,398,120	48,260,779
	1			**46,171,220**	**4,629,600**	**50,800,820**
	0.09	53,126,720	4,629,600	4,781,405	416,664	5,198,069
	0.91	53,126,720	4,629,600	48,345,315	4,212,936	52,558,251
	1			**53,126,720**	**4,629,600**	**57,756,320**
	0.01	136,217,720	4,629,600	1,362,177	46,296	1,408,473
	0.99	136,217,720	4,629,600	134,855,543	4,583,304	139,438,847
	1			**136,217,720**	**4,629,600**	**140,847,320**
	0.0031	60,321,462	4,629,600	186,997	14,352	201,348
	0.9969	60,321,462	4,629,600	60,134,466	4,615,248	64,749,714
	1			**60,321,462**	**4,629,600**	**64,951,062**

Figure 4: Desicion model in CHC treatment with DAAs regimen and RBV

3.2. Treatment costs

Peg-Interferon/Ribavirin Regimen

The average cost of drug use per week for both Peg-IFN/RBVregimens was VND 2,325,539; ranging from VND 2,267,211 to VND 2,431,128. Of which, cost of Peg-IFN was significantly and higher 21.92 times than cost of Ribavirin (VND2,224,062 vs VND101,477; respectively).

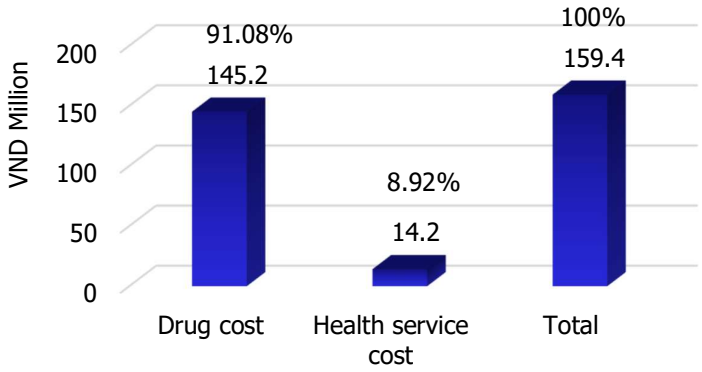


Figure 5: The medical direct cost in CHC treatment with Peg-IFN/RBV regimen

This study found that the mean of medical direct costs was 159.39 million VND per patient with Peg-IFN/RBV Regimen.In which, the cost of drugs accounting for the majority (145.18 million VND). This was explained by the long duration of treatment (28-52 weeks) and the drug cost was much higher than the cost of health services.

In the structure of health services costs, the cost of laboratory test was highest with 13.25 million VND; accounting for 93.47%. The cost of visit and diagnostic imaging were equally valid (0.43 million VND and 0.49 million VND; respectively) and represented a negligible proportion (3.06% vs 3.46%; respectively). This shows that the role of the test in the course of treatment with routine testing services include blood tests, HCV RNA measurements, liver function tests **(Figure 6).**

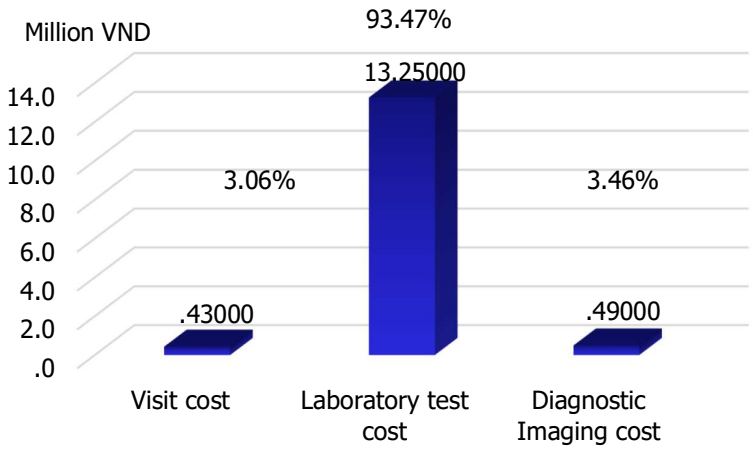


Figure 6: Structure of health service cost

DAA Regimens

Basically, there were 7 DAA regimens for chronic hepatitis C, genotype 1. Based on these models, the medical direct cost for each treatment regimen include drug cost and health care cost. The results were shown in Figure 7.

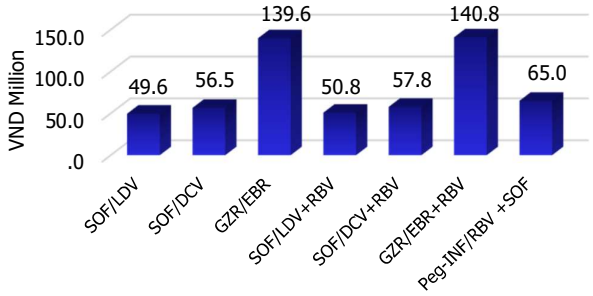


Figure 7: Medical direct cost in CHC treatment with DAA regimens

The lowest medical direct cost in the SOF/LDV regimen (49.58 million VND) and gradually increasing in the order: SOF/LDV+RBV regimen (50.80 million VND); SOF/DCV regimen (56.54 million VND); SOF/DCV+RBV regimen (57.76 million VND); Peg-IFN/RBV+SOF regimen (64.95 million VND); GZR/EBR regimen (139.63 million VND); and GZR/EBR+RBV regimen (140,85 million VND). Thus, the highest medical direct cost in GZR/EBR+RBV regimen and higher was 2.84 times than the lowest cost in SOF/LDV regimen (140.85 million VND; 49.58 million VND, respectively).

Analyzing the structure of medical direct cost in each treatment regimen by percentages, the results are shown in Figure 8.

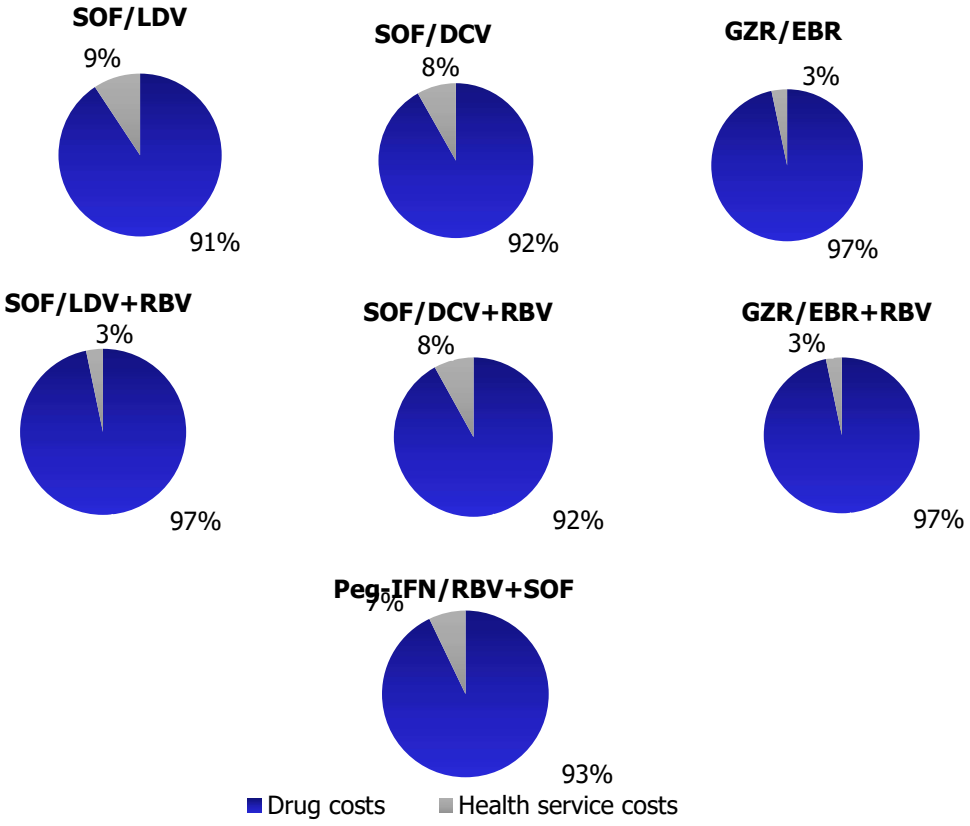


Figure 8: Structure of medical direct cost

In all regimens using DAAs, drug cost were still dominant in total cost and higher 9.71 - 29.12 times than health service cost. This showed the role of the drug in the treatment of chronic hepatitis C. In addition, the topic noted a large difference in the structure of medical direct cost in the SOF/LDV regimen compared with the GZR/EBR regimen, or the GZR/EBR+RBV regimen with increasing percentage of drug cost (90.66%; 96.68%; 96.71%, respectively) and decreasing percentage of health service cost (9.34%; 3.32%; 3.29%, respectively). While in other treatment regimens such as SOF/LDV+RBV, SOF/DCV, SOF/DCV+RBV, Peg-IFN/RBV+SOF, the structure of medical direct costs weren't significantly different from the currently most preferred (SOF/LVD) regimen.

Drug costs

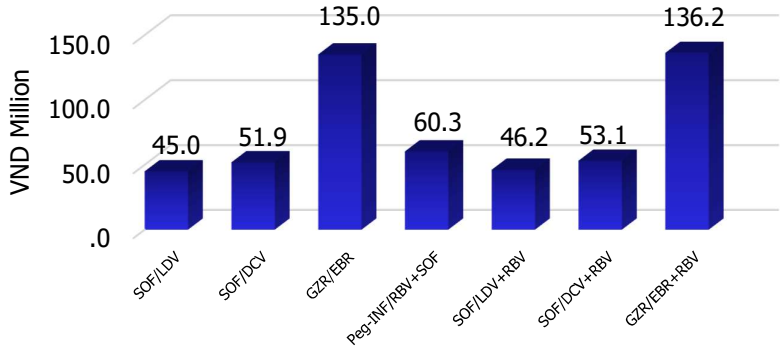


Figure 9: Drug cost in CHC treatment with DAA regimens

The lowest drug cost in the SOF/LDV regimen (44.95 million VND) and increased in the following order: SOF/LDV+RBV regimen (46.17 million VND); SOF/DCV regimen (51.91 million VND); SOF/DCV+RBV regimen (53.13 million VND); Peg-IFN/RBV+SOF regimen (60.32 million VND); GZR/EBR regimen (135 million VND); and GZR/EBR+RBV regimen (136.22 million VND). This study found that the highest drug cost in the GZR/EBR+RBV regimen and was higher 3.03 times than the lowest drug cost in the SOF/LDV regimen (136.22 million VND;44.95 million VND, respectively).

Health service costs

Based on the developed models, this study found that although DAA regimens consits of multiple drug combinations, the overall duration of treatment for these regimens were similar (12 weeks), resulting in equal value of health service cost of DAAs (4,629,600 VND).

Structure of health service cost

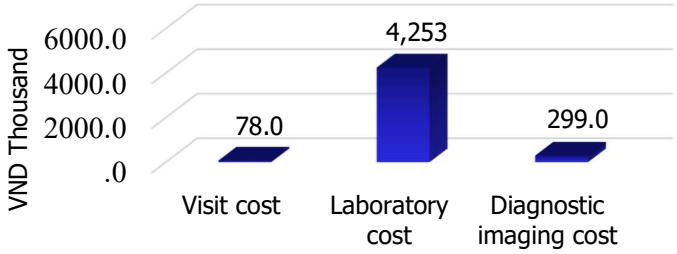


Fig 10. Structure of health service cost

This study found that the laboratory test cost was highest with 4,253,000 VND; the visit cost and the diagnostic imaging cost were lower (78,000 VND vs 299,000 VND, respectively).

Treatment cost

Comparing themedical direct costs in chronic hepatitis C treatment with different regimens, the results were shown in Table 2. It has been shown that the highest medical direct cost was in the Peg-IFN/RBV regimen and was 3.25 times the lowest in the SOF/LDV regimen (161,374,014 VND vs 49,583,100 VND, respectively). Of which, the highest drug cost was in the Peg-IFN/RBV regimen and was 3.23 times higher than the lowest drug cost in the SOF/LDV regimen (145,183,182 VND vs 44,953,500 VND, respectively). The health service cost in the Peg-IFN/RBV regimen was higher with 14,211,336 VND and was higher 3.07 times in the health service cost of DAA regimens (4,629,600 VND). In DAA regimens, the highest medical direct cost was in the GZR/EBR+RBV regimen with 140,847,320 VND and washigher 2.5 times than the other DAA regimens.

Tab 2. The medical direct costs in chronic hepatitis C treatment with different regimens

	Peg-IFN/RBV Regimen	DAA Regimens						
		SOF/LDV	SOF/DCV	GZR/EBR	SOF/LDV +RBV	SOF/DCV +RBV	GZR/EBR +RBV	Peg-IFN/RBV +SOF
Drug cost (VND)	145,183,182	44,953,500	51,909,000	135,000,000	46,171,220	53,126,720	136,217,720	60,321,462
Health service cost (VND)	14,211,346	4,629,600	4,629,600	4,629,600	4,629,600	4,629,600	4,629,600	4,629,600
Total (VND)	159,394,528	49,583,100	56,538,600	139,629,600	50,800,820	57,756,320	140,847,320	64,951,062

IV. CONCLUSIONS

Estimating the medical direct costs in chronic hepatitis C treatment in different regimens vary greatly depending on study methodology but any standards must be considered a substantial burden on society. Such studies may be helpful in determining appropriate allocation of healthcare resources devoted to this condition.

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RÉSUMÉ:

COÛT DU TRAITEMENT DE L'HÉPATITE C PAR DIFFÉRENTS RÉGIMENS AU VIETNAM: UNE ANALYSE BASÉ SUR DES DES LIGNES DIRECTRICES DE TRAITEMENT

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Objectif: Cette étude visait à évaluer le coût du traitement de l'hépatite C par différents schémas thérapeutiques au Vietnam basé sur des des lignes directrices de traitement au Vietnam.

Méthodes: Des modèles des arbres de décision basés sur les lignes directives de traitement ont été construits pour déterminer les coûts médicaux directs du traitement au traitement initial, y compris: les coûts des médicaments et les coûts des services de santé de chaque régime. Les schémas thérapeutiques du génotype 1 du virus de l'hépatite C chronique ont été utilisés au Vietnam, tels que: les schémas posologiques Peg-Interferon/Ribavirin et les schémas thérapeutiques antiviraux à action directe (AAD). Les données d'entrée pour les modèles ont été extraites des antécédents médicaux des patients atteints du VHC, des avis d'experts et d'une revue systématique.

Résultats: Au total, 9 modèles d'arbres de décision ont été construits pour évaluer le coût médical direct du traitement du VHC, génotype 1. Le coût médical direct le plus élevé pour le traitement Peg-INF / RBV et il était 2,85 fois plus élevé que le coût médical le plus faible pour les FOS / LDV (141.46 millions VND; 49.58 millions VND, respectivement). Dans la structure du coût direct médical, le coût du médicament avait prédominé. Cela montre le rôle du médicament tout au long de la maladie. Le coût du médicament le plus élevé pour le schéma thérapeutique GZR / EBR + RBV et GZR / EBR (136.22 millions de VND; 135.00 millions de VND, respectivement). Le coût des services de santé du schéma thérapeutique Peg-INF / RBV était de 6.50 millions de VND, montant supérieur au coût des services de santé des AAD (4.63 millions de VND).

Conclusions: Le coût des médicaments représentait la majeure partie du coût total des soins médicaux. Avec la tendance à la hausse de l'hépatite C chronique au Vietnam et le coût élevé du traitement, les politiques de santé et les programmes médicaux nationaux doivent être pris en compte.

ANALYSING THE BRAND STRENGTH OF DRUGSTORE CHAINS IN HO CHI MINH CITY - USING AVERAGE BRAND STRENGTH INDEX

Le Hien Trang*, Nguyen Thi Thu Thuy*

ABSTRACT

Objective: The aim of this study is to evaluate the ABS index (Average Brand Strength) of the drugstorechains, in order to explore the brand image in customers's mind. ***Materials And Methods:*** Across-sectional descriptive study was designed to evaluate the ABS index of eight selected drugstore chains in HCMC, including Phano, Pharmacity, My Chau, Medicare, Phuc An Khang, ECO, SPG, Vistar. The data was collected from consumers in Ho Chi Minh city (HCMC), satisfied the selection criterias. The interviewers were trained to interview consumers about the awareness, trial, familiar and coverage. The survey questionnaire were utilized to record the consumer's answers. Microsoft Excel 2010 and SPSS 20.0 were used to analysed these results. ***Results:*** The study sample included 467consumers -the clients of drugstore chains in HCMC with 46.9% of men and 53.1% of women; 38.1% with the age of 18 to 29; with over 50.0% had university degree; 46.0% office worker and civil servant. All the selected brand had the awareness rate lower than 20.0%; with the highest rate was Medicare – 19.8%. The ABS index of all 8 drugstore chains were lower than 0.4. Pharmacity brand had the highest ABS index with 0.38; because of a large number of well-established stores, considered as a strong competitor to other drugstore chains. Following, My Chau and Medicare had the similar ABS index with 0.34. They were considered as potential brands with the ability to access the customer's belief. Besides,Vistar was the brand with the lowest ABS index (0.19). ***Conclusion:*** In general, the brand strength of drugstore chains in HCMC were still low; therefore, in order to achieve consumer's satisfaction, these brands required further strategies in improving quality as well as increasing the number of stores.

Key words: *drugstore chains, brand, strength, ABS index, average brand strength.*

I. INTRODUCTION

Nowadays, branding plays a key role in the development and survival of enterprises in all economic sectors, including drug retail area. In Vietnam, besides the traditional forms of drug retailer, in recent years, the business form of drugstore chain has become more and more popular. Differing from single pharmaceutical retail facility, the branding strategies of the drugstore chains are invested professionally. Therefore, there is a great number of drugstore chains established in Viet Nam among traditional retail drugstores. However, drugstore chain still meet certain difficulties because pharmacies competed mostly on location and convenience. Having a good brand strength will help drugstore chains to improve the satisfation and trust of their customers, which is an essential key for success in drug retail. Thus, this study was conduct to evaluate ABS index (Average Brand Strength) of 8 selected drugstore chains in Ho Chi Minh city as well as explore the brand image in customers's mind with 2 following objectives:

- Describing the characteristics of consumers in Ho Chi Minh city, Viet Nam.

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- Analysing the brand strength of drugstore chains in Ho Chi Minh city, Viet Nam.

II. MATERIALS AND METHODS

2.1. Research objects

Eight drugstore chains in Ho Chi Minh city included: Phano, Pharmacity, MyChau, Medicare, Phuc An Khang, ECO, SPG, Vistar.

2.2. Study design

A cross-sectional description was designed based on questionnaire interviews of consumers about 4 factors included: awareness index, trial index, familiar index and coverage.The ABS index was calculated according to the following formula:

ABS = (A + T + F + C) / 4 [2]

Inside:

ABS: Average brand strength

A: Awareness index

T: Trial index

F: Familiar index

C: Coverage.

2.3. Methods

According to previous survey, the minium size of the sample must be 384. With estimating about 20%, the study determined to survey 480 participants. Customers in HCMC were divided into three groups based on living area. According to the data form Market Research Company - Nielsen, three selected districtsrepresentative for Ho Chi Minh city were district 7, district 8and Binh Thanh district [3]. The sample of each area were equal to ensure unbiasedness in the study. The participants involve in the survey should meet the criteria as follow: Vietnamese people, over 18 years old, living in Ho Chi Minh city, could decide where to buy drugs when needed, have purchased products from any of eight selected drugstore chains and agree to join the research. Microsoft Excel 2010 and SPSS 20.0 were used to analyse these results.

III. RESULTS AND DISCUSSIONS

3.1. Characteristics of consumers in Ho Chi Minh city, Viet Nam

Out of the total 480 participants who were interviewed in the study, there are 467 valid answers which were included in the analysis. Characteristics of study sample has been shown in table 1.

Table 1: The characteristics of consumers in Ho Chi Minh city

Variable		Frequency (%)
Sex	Male	219 (46.9)
	Female	248 (53.1)
Age	18 – 29 years old	178 (38.1)
	30 – 44 years old	173 (37.0)
	45 – 59 years old	74 (15.8)
	Over 60 years old	42 (9.9)
Education	Lower than high school	38 (8.1)
	High school	65 (13.9)
	College	67 (14.3)
	University	274 (58.7)
	Higher than university	23 (4.9)
Job	Office worker/ civil servant	215 (46.0)
	Bussiness man	83 (17.8)
	Houseworker/ unemployee	46 (9.9)
	Freelancer	42 (9.0)
	Others	81 (17.3)

Variable		Frequency (%)
Income per month	No income	54 (11.6)
	Lower than 3 millions VND	16 (3.4)
	3-5 millions VND	71 (15.2)
	5-10 millions VND	177 (37.9)
	Over 10 millions VND	149 (31.9)
Distribution	District 7	153 (32.8)
	District 8	155 (33.2)
	Binh Thanh district	159 (34.0)

VND: Vietnamese Dong

The respondents of drugstore chains in HCMC included 46.9% of man and 53.1% of women. More than one-third (38.1%) of the consumers had the age between 18 and 29; with more than half had graduated from university. Office worker and civil servant were the highest rate of job with 46.0%. The salary per month of respondents were quite high with 37.9% whose salary from 5 to 10 millions VND and 31.9% higher than 10 millions VND per month.

3.2. Analysing the brand strength of drugstore chains in Ho Chi Minh city, Viet Nam

Awareness index (A) of drugstore chains in Ho Chi Minh city

The awareness index was evaluated based on the proportion of consumers's awareness of drugstore chains in 3 different levels included: first awareness, next awareness and awareness with suggestion. The results was shown in table 2.

Table 2: Awareness index (A) of drugstore chains in Ho Chi Minh city

Drugstore chains	First awareness		Next awareness		Awareness with suggestion		Awareness index (A)
	N	%	N	%	N	%	%
Medicare	77	16.5	42	9.0	158	33.8	**19.8**
Pharmacity	109	23.3	44	9.4	104	22.3	**18.3**
My Chau	76	16.3	46	9.9	100	21.4	**15.9**
Phuc An Khang	16	3.4	20	4.3	95	20.3	**9.4**
ECO	34	7.3	26	5.6	65	13.9	**8.9**
Phano	31	6.6	36	7.7	42	9.0	**7.8**
Vistar	3	0.6	4	0.9	34	7.3	**2.9**
SPG Pharma	2	0.4	1	0.2	24	5.1	**1.9**

In general theawareness index of all eight brand were lower than 20% and there was a remarkable difference between these drugstore chains. With an outstanding rate of awareness with suggestion, Medicare had the highest rate of awareness index (19.8%), which was 21 times more than SPG (had lowest rate with 1.9%). Following, Pharmacity and My Chau were second and third position of awareness index with 18.3% and 15.9%, respectively. There were three drugstore chains having awareness index lower than 10%, included Phuc An Khang (9.4%), ECO (8.9%) and Phano (7.8%). Vistar and SPG had particularly low level of awareness with 2.9% and 1.9%, respectively.

Brand trial index of drugstore chains in Ho Chi Minh city

The level of brand trial index was calculated by the ratio of the percentage of consumers have used the brand to the percentage of total brand awareness (including first awareness, next awareness and awareness with suggestion). The result of brand trial index was presented in figure 1.

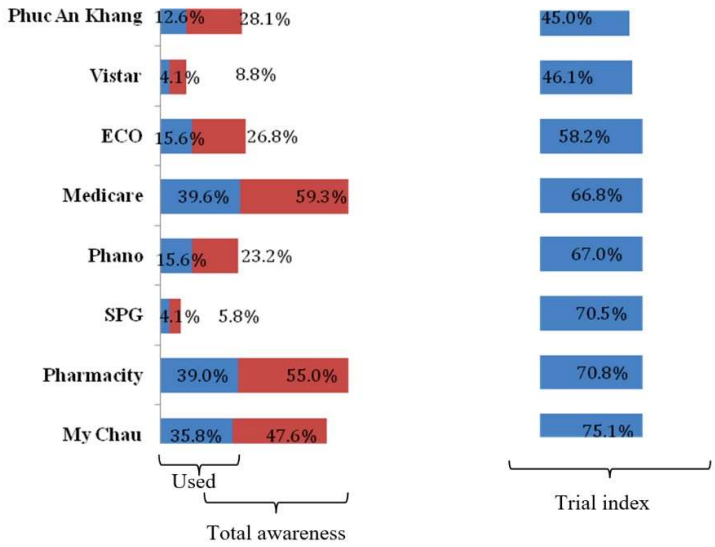

Figure 1: Brand trial index of drugstore chains in Ho Chi Minh city

Overall, the brand trial propotion of eight drugstore chains were higher than 45.0%. The brand having the highest rate was My Chau with 75.1%, which was about 2 times more than Phuc An Khang (had the lowest brand trial index rate with 45.0%). Following, the brand trial index of Pharmacity was 70.8%. In spite of having lowest brand awareness (5.8%),SPG had the third highest level of trial index with 70.5%. SPG brand made a great impression for most customers who have gone to their drugstores. The brand trial index of Phano, Medicare, ECO and Vistar were 67.0%, 66.8%, 58.2%, 46.1%; respectively.

3.3. Brand familiar index

The level of brand familiar index was calculated by the ratio of the percentage of consumers's main using of brand to the percentage of consumers have used the brand. The result of brand familiar index was presented in figure 2.

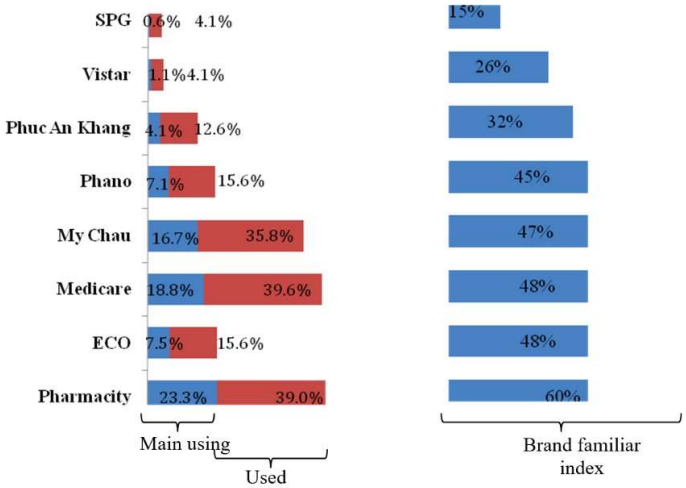

Figure 2: Brand regularity of using index

As shown in Figure 2, Pharmacity was the brand with the highest brand familiar index (59.9%), more than four times to SPG (with 14.7%), due to the relatively high percentage of Pharmacity's customers with 23.3%. Despite having a high percentage of people using the service of drugstore chain (15.6%), ECO had the second highest brand regularity of using index, indicating that consumers who have used the product of ECO would continue using. The following high-performing brands followed were Medicare, My Chau, Phano, Phuc An Khang and Vistar (47.6%, 46.7%, 45.2%, 32.2%, and 26.3%, respectively). Pharmacity, ECO and Medicare were the brands with the highest brand familiar.

Brand coverage of drugstore chains in Ho Chi Minh city

The population of Ho Chi Minh citywas 6.616.684 by 2015 [1]. According to Ministry of Health, each 2000 citations should had 1 drugstrore near by. Therefore, the number of pharmacies required for HCMC residents could be calculated below:

$$N = \frac{6{,}616{,}684}{2000} = 3{,}308 \text{ drugstores}$$

Brand coverage was calculated by the ratio of the number of brand's drugstores to the number of pharmacies required for HCMC residents. Based on the number of drugstores of each brand, the brand coverage rate were measured and presented in table 3.

Table 3: Brand coverage of drugstore chains in Ho Chi Minh city

Drugstore chain	The number of drugstore	Coverage (C) (%)
Pharmacity	39	1.2
Phano	33	1.0
Medicare	27	0.8
Vistar	20	0.6
SPG	17	0.5
Phuc An Khang	16	0.5
ECO	8	0.2
My Chau	7	0.2

Generally,the coverage index of eight selected drugstore chains were particularly low (lower than 2%). With 39 drugstores in Ho Chi Minh city, Pharmacity was the brand having the highest rate of coverage index with 1.2%. Phano had 33 pharmacies which led to its brand coverage was 1.0%. Medicare- with 27 pharmacies - had 0.8% of coverage propotion. Vistar, SPG and Phuc An Khang had similar brand coverage with 0.6%; 0.5% and 0.5%, respectively. With 7 and 8 drugstore among Ho Chi Minh city, ECO and My Chau had the lowest brand coverage (0.2%). In recent years, the population of HCMC as well asthe health care demand of residents had increased dramatically, the number of pharmacies required for all residents was pretty high (over 3000 pharmacies). Therefore, among numerous traditional retail drugstores, the percentage of drugstore chains in Ho Chi Minh city were still low, including strong brands such as Pharmacity, Medicare and Phano. In summary,drugstore chains could enhance their brand strength by increasing the numbers of drugstores. Although it could take a lot of money and employees, which required large investment of drugstore chains.

The ABS index (Average Brand Strength index)of drugstore chains in Ho Chi Minh city

The ABS index was evaluated through four factors: brand awareness index, brand trial index,brand regularity of using index and coverage. The results was shown in figure 3.

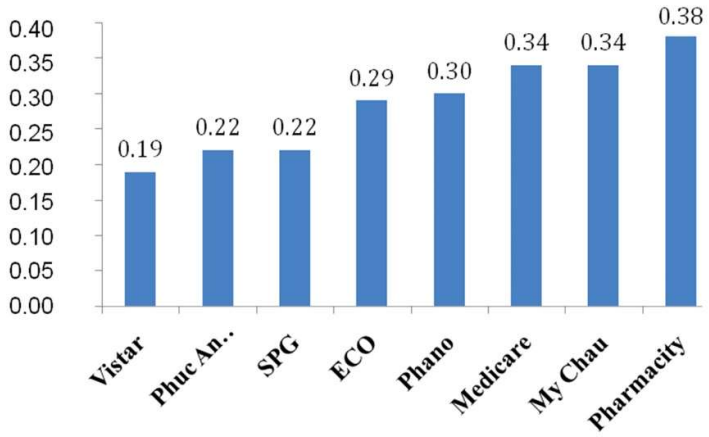

Figure 3: Brand strength index

The ABS index of all 10 drugstore chains are lower than 0.4. Pharmacity is the brand has the highest ABS index with 0.38; it shows that with the well-established and a large number of stores. Pharmacity built up a strong brand. Following. My Chau. Medicare and Long Chau have the similar ABS index with 0.34; 0.34 and 0.33; respectively. These are high potential drugstore chains. their ABS index are nearly the same with highest one - Pharmacity. The next group is included Minh Chau, Phano, ECO which have lower ABS index with 0.31; 0.30; 0.29; respectively. Phuc An Khang and SPG have the same ABS index with 0.22. Vistar is the brand that has the lowest ABS index – 0.19. With the suitable bussiness strategies. Pharmacity has a good position in the pharmaceutical retail market and is considered as a strong competitor to other drugstore chains. On the other hand. the brands which have lower result requires further plan in improving quality and extending size such as increase the number of stores.

IV. CONCLUSION

In general the brand strength of drugstore chains in HCMC were still low due to low brand coverage and low brand awareness. Therefore, in order to success in drug retail industry, these brands required further strategies in building up brand strength by improving quality and facilities as well asincreasing the number of stores.

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RÉSUMÉ:

ANALYSE DE LA FORCE DE LA MARQUE SUR LES CHAÎNES DE LA PHARMACIE À HO CHI MINH VILLE - UTILISATION DU MOYEN INDICE DE FORCE DE LA MARQUE

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Objectif: Le but de cette étude est d'évaluer l'indice ABS (Force moyenne de la marque) des chaînes de pharmacies, afin d'explorer l'image de marque dans l'esprit des clients.

Matériels et méthodes: Une étude descriptive transversale a été conçue pour évaluer l'indice ABS de huit chaînes de pharmacies sélectionnées dans Ho Chi Minh-Ville (HCMV), notamment Phano, Pharmacity, My Chau, Medicare, Phuc An Khang, ECO, SPG et Vistar. Les données ont été collectées auprès des consommateurs de HCMV, répondant aux critères de sélection. Les intervieweurs ont été formés pour interroger les consommateurs sur la sensibilisation, l'essai, la familiarité et la couverture. Le questionnaire de l'enquête a été utilisé pour enregistrer les réponses du consommateur. Microsoft Excel 2010 et SPSS 20.0 ont été utilisés pour analyser ces résultats.

Résultats: L'échantillon de l'étude comprenait 467 consommateurs - les clients des chaînes de pharmacies de HCMV avec 46.9% d'hommes et 53.1% de femmes; 38,1% entre 18 et 29 ans; avec plus de 50.0% avaient un diplôme universitaire; 46.0% employé de bureau et fonctionnaire. Le taux de notoriété de toutes les marques sélectionnées était inférieur à 20.0%; le plus haut taux était Medicare - 19.8%. L'indice ABS des 8 chaînes de pharmacies était inférieur à 0.4. La marque Pharmacity avait l'indice ABS le plus élevé avec 0.38; en raison d'un grand nombre de magasins bien établis, considérés comme un concurrent puissant par rapport aux autres chaînes de pharmacies. Ensuite, My Chau et Medicare avaient un indice ABS similaire avec 0.34. Elles étaient considérées comme des marques potentielles capables d'accéder aux convictions du client. De plus, Vistar était la marque avec l'indice ABS le plus faible (0.19).

Conclusion: En général, la force de la marque des chaînes de pharmacies à HCMV était encore faible; par conséquent, pour obtenir la satisfaction du consommateur, ces marques nécessitaient d'autres stratégies visant à améliorer la qualité et à augmenter le nombre de magasins.

Mots clés: *Chaînes de pharmacies, marque, force, indice ABS, force moyenne de la marque.*