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Introduction

The Journal of Southeast Asian Medical Research is a peer-reviewed journal with printing every 6 months. The main goal of this collaboration project is to distribute new knowledge in medical sciences to medical communities and scientists, as well as encouraging scientific collaborations within Southeast Asia and also other nations around the world. The journal publishes original research in the medical sciences: clinical and basic. We welcome original articles from across the world. The editorial board consists of international experts in various fields of medicine, ranging from internal medicine to a variety of surgeries. The full text of the journal is available online at http://www.jseamed.org

It is our aim to publish the most up-to-date and useful research information in medical sciences. In Southeast Asia, there are some unique problems in health care and diseases, such as tropical diseases, and it is crucial that health professionals can access, share and exchange knowledge promptly. In this region, there is still a gap of knowledge in health sciences that needs to be closed by scientific research, which we are hoping to close after this collaboration project. We hope that the journal will fulfill the objectives and will provide benefit to all, both medical practitioners and researchers alike.

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COMPARISON OF THE COBB ANGLE MEASUREMENT BETWEEN MANUAL AND DIGITAL METHODS AMONG FIVE MILITARY HOSPITALS

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Abstract

Background: The Cobb angle measurement of the spine is an important parameter for assessing patients with scoliosis in terms of diagnosis, treatment planning, follow-up for severity and disease progression. This angle can be obtained from a plain X-ray film in an upright posteroanterior view or can be measured from digital images. A 5° curve progression is considered clinically significant.

Objective: This study aimed to compare the accuracy and difference of the Cobb angle measurements between manual and digital methods among 5 military hospitals located in the 1st area of command having orthopedic services and using different Picture Archiving and Communication (PACS).

Methods: Using plain X- ray films of patients diagnosed with scoliosis, a comparative study of the Cobb angle measurement was conducted. A total of 120 images were recorded in a compact disc in the Digital Imaging and Communications in Medicine (DICOM) system and was used to install in computer systems of 5 military hospitals (Hospitals A, B, C, D, and E), and then was interpreted using each hospital digital PACS. The mean difference of 5° is considered clinically significant. The validity of measurements was analyzed using paired t- test for the mean equivalence. The reliability of one time measurement was also performed using Intraclass Correlation Coefficient (ICC).

Results: Both one time and an average of three times of digital measurements among Hospitals A, B, C, D and E revealed significant differences when compared with the manual measurement ($p < 0.01$). However, no clinical significance of both one time and the averaged three measurements were observed when the mean difference was less than 5°. In the combined process group (Hospitals C, D and E), a significant difference of the manual and digital measurements was observed ($p<0.01$). However, no clinical significance using both one time and averaged three time measurements was found when the mean difference was less than 5°. The data of one time digital measurements were reliable (ICC= 0.9).

Conclusion: The use of digital Cobb angle measurement is a convenient practice. A significant difference using manual and digital methods was found using both one and combined processes; however, no clinical significance was observed. One time digital measurement revealed validity as those found in three time averaged measurements.

Keywords: Scoliosis, Cobb angle, Manual measurement, Digital measurement

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Introduction

The Cobb angle measurement is the gold standard to quantitatively measure the lateral deviation of the spine and is usually considered for diagnosis, planning of management and follow-up of patients with scoliosis. This measurement is also used to determine the severity of the curve and estimate its progression which is very helpful among orthopedists especially spine surgeons for planning the most appropriate treatment. Technological advances have allowed and increased the use of digital X-ray images in clinical practices of which the PACS (Picture Archiving and Communication System) has been used in intrahospital computerized systems. This technology offers many advantages, i.e., efficient image storage, rapid data sorting, ease to access and review of studies comparing different follow-up for patients with scoliosis. Varieties of digital systems of PACS that have been designed from various companies are available in many hospitals. However, the accuracy of each digital system of PACS has never been compared among military hospitals in Thailand.

The Cobb angle measurement method has been used in clinical practices as a simple and well known technique using manual measurement. Using a pencil and a goniometer, the doctor draws lines on plain X- ray film in posteroanterior view and calculates the scoliotic or the Cobb angle formed by the most tilting vertebra, from the upper end vertebra to the lower end vertebra. Despite this simplicity, several factors may influence the measurement including the use of different goniometers, size and sharpness of pencils, correction of selected vertebrae and level of experiences with precision of the doctors. Thus, the main principle of digital measurement of Cobb angle is to reduce the impact of human error.

The reliability of the measurement of the Cobb angle using manual versus digital methods have been studied. Brian et al. [1] compared the Cobb angle measurement of scoliosis radiographs with preselected end vertebrae traditional versus digital acquired X-ray images. Tanure et al. [2] also studied the reliability assessment of Cobb angle measurement using manual and digital methods. The results showed that the mean error of the manual method was 3.8 degrees while the digital method was 3.6 degrees. Many related studies have reported mean error ranging from 1.7 degree to 6.5 degrees.[3-6] However, in military hospitals, the efficacy of the digital X-ray system for the Cobb angle measurement used in multi center hospitals comprising different brands of PACS has never been compared. Due to multi-disciplinary management of scoliosis, the X-ray films have been interpreted by different individuals. Decisions regarding surgical interventions and physiotherapeutic or orthotic options can be made based on scoliotic curve progression denoted by the Cobb angle. Hence an accurate, precise, and reliable method is of paramount clinical importance, especially considering even a 5 degree curve progression is potentially clinically different.[7]

Therefore, to demonstrate the reliability and accuracy of a variety of digital methods in multi center hospitals compared with a traditional manual method, the digital measurements among five military hospitals in the first area of command having different PACS were compared and reported in detail for each system.

Methods

To calculate the sample size according to the study of Tanure et al. [2], different measurements of the Cobb angle were 3.85 ± 3.45 degrees using the manual method while those obtained by the digital method were 3.61 ± 3.18 degrees, a minimum of 118 plain X-ray films were necessary to provide a 95% confidence interval at a margin of error of 5%. This study was approved by the Institutional Review Board, Medical Department, Royal Thai Army (IRBRTA 2190/2561).

In this study, a total of 120 plain X-ray films from patients receiving a diagnosis of scoliosis, both idiopathic and degenerative type, were available to assess the validity and reliability of the digital method to assess the Cobb angle. These plain X-ray films were retrospectively randomized chosen from the database of patients with scoliosis attending Phramongkutklao Hospital from 2012 to 2018. The X-ray films were without predilection of age, sex, location, type, or magnitude of the curvature. They were all posteroanterior views of standing whole spine films within 36 inches long.

All 120 images then were recorded in a compact disc in the Digital Imaging and Communications in Medicine (DICOM) system. This compact disc was used to install in five military hospitals computer systems and then was interpreted by each hospital's digital PACS. The study population magnitude of the curve ranging from the smallest one (5 degrees) to a largest one (80 degrees). Each chosen curvature was recorded with preselected end vertebrae to prevent human error from measurement. We endeavored to locate and choose the most obvious margin of the end plates for the upper and lower vertebrae of each plain film. The PACS were: UniWeb viewer in Hospital A, VUE Solutions in Hospital B, medSynapse (former) in Hospital C, medSynapse (new) in Hospital D and TRACS DICOM VIEWER in Hospital E.

Manual and digital measurements were compared as follows: 1) a single pair of each hospital (manual vs. digital measurements conducted in Hospitals A, B, C, D and E) using only the one time measurement; 2) manual vs. digital measurements conducted in Hospitals A, B, C, D and E using the average of three time measurements; 3) manual vs. a single process of measurement groups (Hospitals A and B) both one time and the average of three time measurements; 4) manual vs. combined process of measurement groups (Hospitals C, D and E) both one time and the average of three time measurements; 5) manual vs. subset of combined process of measurement (linear tips; Hospital C and circle tips; Hospital E) both one time and the average of three time measurements.

Only one person used the traditional (manual) method as well as the digital (software based) method to assess scoliotic images obtained from 120 patients.

Manual measurement

One spine fellow performed the Cobb measurement technique using preselected end vertebrae of each plain film obtained from 120 patients. A pencil size HB with sharp pencil lead (for precision of lining) was used to make a straight line. A goniometer then was used to calculate the Cobb angle. To make a precise line and avoid scratches on the X-ray films, all 120 curves were recorded in a set of manual methods using only one time measurement (**Figure1**).

Digital measurement

The compact disc in the DICOM system containing the same images of all 120 patients was provided for digital measurements using the PACS of each military hospital (Hospitals A, B, C, D and E), located at the first area of command. Each hospital data set was individually recorded at the first time measurement as well as the average (mean) of three time measurements. The three time measurements were used to compare with one time measurements.

The differences of measurement processes among these digital PACS were grouped. The first group was a single step measurement, which was used in Hospitals A and B. This single step of measurement of the Cobb angle was automatically calculated and interpreted when only two lines were drawn at both upper and lower end plates. (**Figure 2**)
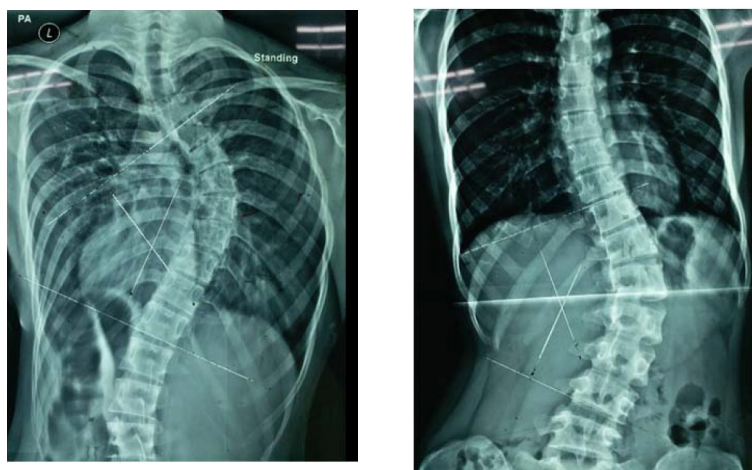
Figure 1. The Cobb angle using a manual measurement

Hospital A

Hospital B

Figure 2. Cobb angle performed at Hospitals A and B using digital measurements.

Hospital C
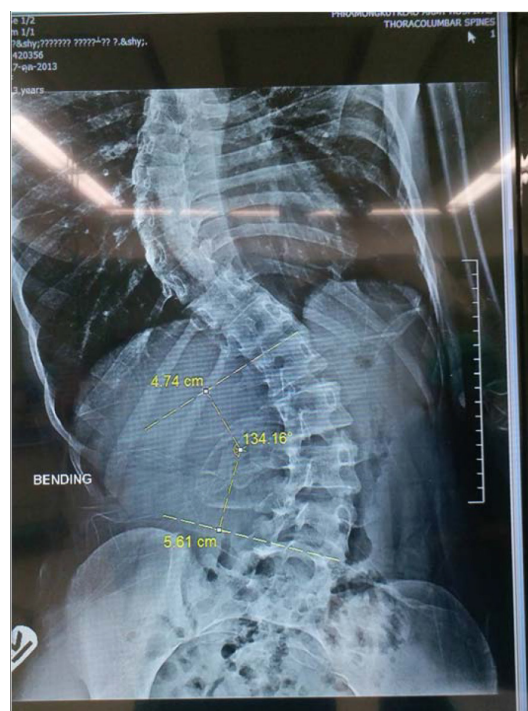
Hospital D

Figure 3. Cobb angle performed at Hospitals C and D using digital measurements

The second group was a combined step of measurements which was used in Hospitals C, D and E. The Cobb angle was automatically calculated and interpreted when two lines were drawn at both upper and lower end plates at first and the angle joining line was drawn in the following part.

Moreover, the combined step of the measurement group differed in some details of the angle joining lines. The Cobb angle performed in

Hospitals C and D used a linear tip on the angle joining line (**Figure 3**) while Hospital E used circle tips (**Figure 4**).

Statistical analysis

Validity and reliability of Cobb angle measurements using manual and digital methods were assessed to compare intra-observer differences. The analysis of intra-observer variation calculated for each data set was expressed in Mean $\pm$SD.

A 5 degree curve progression was considered clinically significant. [7] Using the paired -*t* test for the mean equivalence when the difference of measurement was less than 5 degrees, a *p*-value less than <0.05 was considered statistically significant measurements. The reliability of measurements was tested using the Intraclass Correlation Coefficient (ICC).

Results

The mean $\pm$ SD of one time measurement of the Cobb angle using manual and digital measurements conducted at five military hospitals (Hospitals A, B, C, D and E) was demonstrated. The intra-observer analysis and validity of only one measurement is shown in **Table 1**. All digital measurement data revealed significant differences when compared with the manual measurement
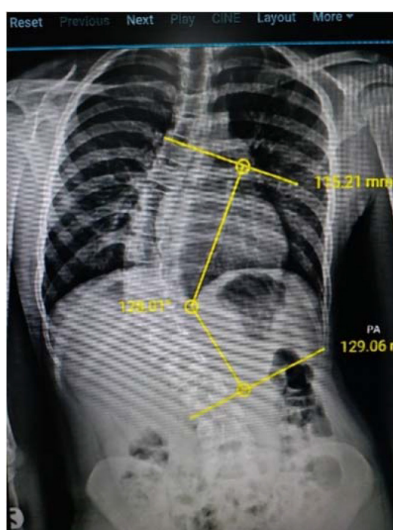
Figure 4. Cobb angle performed at Hospital E using digital measurement

Table 1. Comparison of the Cobb angle using manual and digital measurements conducted in 5 hospitals.

Comparison Manual VS Digital Measurements	The Cobb angle (Mean±SD)	Paired differences of the Cobb angle between manual VS digital measurements (Mean±SD)	*p*-value
Manual measurement	31.68±16.54		
Hospital A	32.84±17.10	1.15±4.76	<0.001
Hospital B	32.40±16.36	0.72±3.81	<0.001
Hospital C	33.26±15.80	1.58±4.85	<0.001
Hospital D	33.20±16.62	1.52±4.25	<0.001
Hospital E	35.65±16.59	3.97±3.87	<0.001
Hospitals A and B	32.62±16.62	0.93±3.83	0.009
Hospitals C, D and E	34.04±16.18	2.35±3.71	<0.001
Hospitals A, B, C, D and E	33.47±16.30	1.79±3.48	<0.001

Using the paired -t test for mean equivalence, *p*-value less than <0.05 was considered statistically significant. Mean differences between the two methods not more than 5 degrees was considered not clinically significant.

Table 2. Reliability of one time measurement of manual and digital measurements using Intraclass Correlation Coefficient (ICC)

Hospital	ICC	95% CI		p-value
		Lower	Upper	
A	0.980	0.971	0.986	<0.001
B	0.986	0.980	0.991	<0.001
C	0.977	0.967	0.984	<0.001
D	0.983	0.976	0.988	<0.001
E	0.986	0.980	0.990	<0.001
A and B	0.986	0.981	0.991	<0.001
C, D and E	0.987	0.981	0.991	<0.001
A, B, C, D and E	0.989	0.984	0.992	<0.001

P-value less than 0.05 was statistically significant.

Table 3. Comparison of the Cobb angle using manual and averaged three digital measurements conducted in 5 hospitals (single and combined measurements)

Comparison Manual VS Digital Measurement	The Cobb angle (Mean±SD)	Paired Differences of the Cobb angle between manual VS digital measurement (Mean±SD)	p-value
Manual measurement	31.68±16.54		
Hospital A	33.23±16.20	1.55±4.15	<0.001
Hospital B	32.42±16.39	0.74±4.30	<0.001
Hospital C	32.73±16.08	1.04±2.77	<0.001
Hospital D	33.27±16.78	1.58±3.89	<0.001
Hospital E	35.53±16.67	3.85±3.26	<0.001
Hospitals A and B	32.83±16.09	1.14±3.36	<0.001
Hospitals C, D and E	33.84±16.39	2.16±2.67	<0.001
Hospitals A, B, C, D and E	33.44±16.21	1.75±2.62	<0.001

Using the paired -t test for mean equivalence, *p*-value less than <0.05 was considered statistically significant. Mean difference between the two methods not more than 5 degrees was considered not clinically significant.

data (p <0.01). However, digital measurements among Hospitals A B, C, D and E revealed no clinical significance within 5 degree variation (**Tables 1 and 3**). All measurements were reliable according to the Intraclass Correlation Coefficient (ICC=0.9) as shown in **Table 2**.

For averaged three time measurements, similar results were observed as only one time measurement (**Table 3**).

Discussion

Although the Cobb angle is an objective 2-dimensional measure of a 3D spinal deformity, and despite its high intra and inter-observer error, it still remains the "gold standard" radiographic parameter to quantify scoliotic curves due to its inherent simplicity. Phramongkutklao Hospital, a tertiary military hospital caring for multi disciplinary treatment of scoliosis, has transferred

patients with scoliosis from other military hospitals. Thus, assessing patients with scoliosis and treatment planning based on the degree of spinal curve measured by the Cobb angle method is important. Traditionally, the manual measurement has been used before the advent of computerized programs. Currently, the PACS has conveniently been used to digitally measure the Cobb angle. Usually, according to Tanure et. al [2], five-degree variations are acceptable having the mean error range from 1.7 to 6.5 degrees. In this study, the manual measurement was used as the reference method to compare with five digital measurement systems. Due to varieties of PACS used among military hospitals, comparisons were divided in two groups. The first group had a single process of digital measurement that used only two lines at both endplates and then the Cobb angle was automatically calculated. The second group used a combined process where the Cobb angle could be automatically calculated after the perpendicular line was applied to both endplate lines. This second group differed in their tools and tip of the perpendicular line. Normally, the perpendicular line has a straight linear line that is easy to precisely apply to the endplate line. In Hospital E, they used the circle tip of the perpendicular line which made the measurement contain more error than that of a linear line. The single process digital measurement (Hospitals A and B) showed significant difference compared with those obtained from the manual method but remained in acceptable ranges with no clinical differences compared with the traditional methods. The combined process of digital measurements of Hospitals C, D and E also showed significant difference where no clinical significance was observed. Additionally, our study showed that the Cobb angle using both one time measurement and average three time measurements was practical. One aspect considered was how many times the Cobb angle should be measured to obtain the most accurate result. Our study revealed that only one time measurement was reliable and quite practical that the result was compatible with the value of both manual and three-time digital measurement methods.

Conclusion

The use of a digital Cobb angle measurement is a convenient practice. A significant difference using the manual and digital methods was found using both one and combined process; however, no clinical significance was observed. One time digital measurement revealed validity similar to those found in three time average measurements. Thus, one time digital measurement using the PACS can be used for the Cobb angle.

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PREVALENCE AND ASSOCIATED FACTORS IN THE DECLINE OF RENAL FUNCTION AMONG OUTPATIENTS ATTENDING A COMMUNITY HOSPITAL, CENTRAL THAILAND

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Abstract

Introduction: Chronic kidney disease (CKD) is recognized as global public health issue especially affecting developing countries including Thailand. The epidemiologic data in the decline of renal function and the risk factors among Thai patients especially in community hospital settings were limited.

Methods: A cross-sectional study was conducted to identify the prevalence and associated risk factors in the decline of renal function among outpatients in Thaluang Community Hospital, Lop Buri Province, central Thailand, between November 1, 2018 and October 31, 2019. The decline in renal function was defined by glomerular filtration rate (GFR) <60 mL/min/1.73m^2. Multivariate logistic regression analysis was performed to obtain the adjusted odds ratios (AOR) and 95% confidence interval (CI) of the factors related to the decline of renal function.

Results: A total of 874 outpatients participated in the study. The overall prevalence in the decline of renal function (eGFR <60 mL/min/1.73m^2) was 20.3% (95% CI; 17.5%-22.9%). Among male participants, the prevalence in the decline of renal function was 21.1% (95%CI; 16.7%-25.5%) while it totaled 19.7% (95%CI; 16.3%-23.1%) among females. The independent associated factors in the decline of renal function included greater age (AOR 1.07; 95% CI=1.05-1.09), history of NSAIDs used (AOR 2.97; 95% CI=1.85-4.79) and elevated pulse pressure (PP) >75th percentile (AOR 1.64; 95% CI=1.07-2.53)

Conclusion: We reported the prevalence in the decline of renal function among outpatients in a Thai community hospital which was comparable with the national level. Advanced age, history of NSAIDs used and PP were related to reduced kidney function. Therefore, effective health interventions should be conducted especially, appropriate NSAIDs used among outpatients.

Keywords: Decline of renal function, Community hospital, NSAIDs, Pulse pressure, Prevalence, Thailand

Introduction

At present, chronic kidney disease (CKD) is recognized as a global public health issue and a major health problem, especially affecting developing countries.[1] In Thailand, many people, particularly in rural areas, experience CKD and its complications; moreover, patients with end stage renal disease face difficulties when it comes to hospital costs.[2] In 2009 one related study in Thailand reported the prevalence of CKD stage III-IV was 7.8 and 9.3% among Thai men and women, respectively; additionally, the study demonstrated that the prevalence of CKD was higher in the Bangkok Metropolitan.[3] A 10-year population-based study in Norway demonstrated that mean estimated change in glomerular filtration rate (GFR) was -1.03 ml/min/1.73 m^2/year; additionally, females was associated with slower decline in GFR.[4] Furthermore, patients with rapid decline measured by eGFR tended to increase risk of cardiovascular diseases and mortality.[5]

The risk factors for the decline of renal function include advanced age, noncommunicable diseases such as type 2 diabetes (T2D), hypertension (HT), hyperuricemia, history of kidney stones and history of using traditional medicine.[3,6,7] Moreover, some factors bring about the rapid decrease of eGFR among patients indicating disease progression. [8]

However, epidemiologic data in the decline of renal function (GFR <60 mL/min/1.73m^2) and the risk factors among Thai patients especially in community hospital settings were limited. Therefore, this study collected data from Thaluang Hospital, Lop Buri Province, central Thailand to determine the prevalence in the decline of renal function and associated factors among outpatients attending this community hospital. The results of the present study emphasized that the decline of renal function should be recognized as a serious health problem in Thailand.

Methods
Study designs and subjects

A hospital-based cross-sectional study was conducted to identify the prevalence and associated risk factors for the decline of renal function among outpatients in Thaluang Community Hospital, located in a rural area of Lop Buri Province, about 190 km from Bangkok. Inclusion criteria for the study consisted of patients aged at least 18 years attending the outpatient department of Thaluang Hospital between November 1, 2018 and October 31, 2019. Any patient not presenting a history of serum creatinine testing and eGFR during the period of study was excluded. The study was reviewed and approved by the Royal Thai Army Medical Department Institutional Review Board (approval number S035h/63_Exp).

Data collection

A standardized case report form was used to collect the data from electronic medical records by the investigators. Collected data included (1) demographic data which comprised age, sex, weight, and height (2) risk behaviors and comorbidities including smoking, alcohol consumption, T2D, HT, and dyslipidemia (DLP) (3) systolic blood pressure (SBP), diastolic blood pressure (DBP) and (4) serum creatinine level and estimated GFR. In addition, history of nonsteroidal anti-inflammatory drugs (NSAIDs) used among individuals was reviewed and collected. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. The pulse pressure (PP) was calculated as the difference between SBP and DBP levels. According to the International Classification of Diseases, Tenth Revision Codes (ICD-10), T2D, HT and DLP were determined by E11, I10-I13 and E78, respectively.[9] Isotope Dilution-Mass Spectrometry traceable enzymatic method was used for the measurement of serum creatinine and eGFR was calculate by CKD-EPI equations.[10] The decline of renal function was defined by eGFR <60 mL/min/1.73m^2.[11]

Statistical analysis

Data were analyzed using StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX, USA: StataCorp LLC. Demographic characteristics were presented using descriptive statistics. Categorical data were presented as number and percentage while continuous data were illustrated as mean and standard deviation (SD). Associated factors of the decline of renal

function were analyzed using binary logistic regression analysis. The magnitude of association was manifested by crude odds ratio (OR) with 95% confidence interval (CI). Multivariate logistic regression analysis was performed to obtain the adjusted odds ratios (AOR) and 95% CI of the factors related to the decline of renal function. A p-value less than 0.05 was considered as statistical significance.

Results

A total of 874 outpatients were enrolled in the study. The average age of participants was 60.1±12.9 years. The majority of participants were female (61.6%). The average BMI was 25.3±5.0 kg/m^2. One third of participants (34.4%) had BMI from 25.0 to 29.9 kg/m^2. Among participants, the prevalence of HT and DM were 45.9 and 40.7%, respectively. Almost 14% of the subjects had a history of smoking and alcohol consumption. The demographic data are shown in **Table 1**.

In all 874, 177 outpatients had eGFR <60 mL/min/1.73m^2. The overall prevalence in the decline of renal function was 20.3% (95%CI; 17.5-22.9%). Among male study participants, the prevalence in the decline of renal function was 21.1% (95%CI; 16.7-25.5%) while it totaled 19.7% (95%CI; 16.3-23.1%) among females. The prevalence in decline of renal function, stratified by age groups and sex, is illustrated in **Figure 1.**

Univariate and multivariate logistic regression analysis identifying the associated factors in the decline of renal function are shown in **Tables 2 and 3**. The independent associated factors in the decline of renal function included greater age (AOR 1.07; 95%CI 1.05-1.09), history of NSAIDs used (AOR 2.97; 95%CI 1.85-4.79) and elevated PP >75th percentile (AOR 1.64; 95% CI 1.07-2.53).
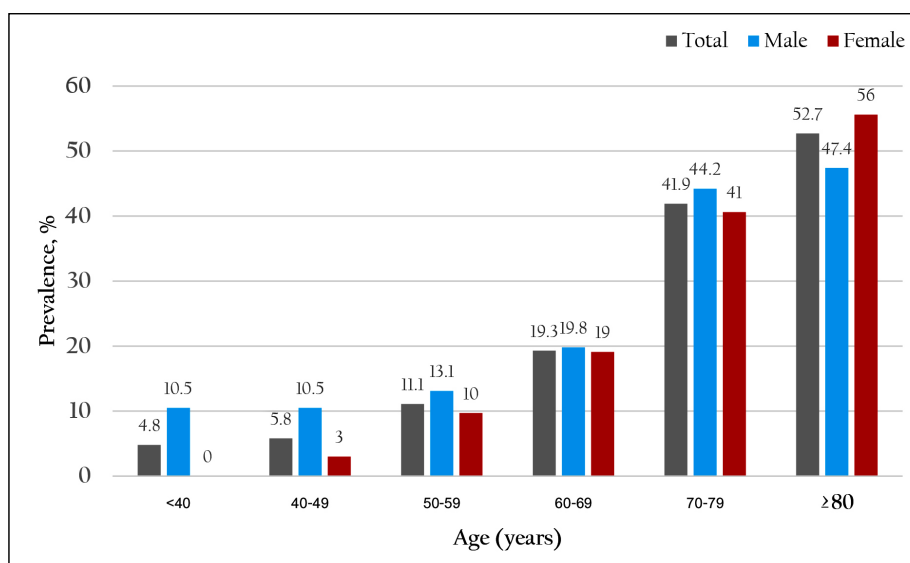
Figure 1. Prevalence of decline of renal function (eGFR<60 mL/min/1.73m^2) stratified by age groups and sex

Table 1. Demographic characteristics of study participants

Characteristics	n (%)
Sex	
Male	336 (38.4)
Female	538 (61.6)
Age (years)	
mean±SD	60.1±12.9

Table 1. Demographic characteristics of study participants (ext.)

Characteristics	n (%)
median (max-min)	60.0 (98-18)
<40	42 (4.8)
40-49	104 (11.9)
50-59	287 (32.8)
60-69	238 (27.2)
70-79	148 (16.9)
≥80	55 (6.3)
Body mass index (kg/m²)	
mean±SD	25.3±5.0
median (max-min)	25.0 (51.6-12.6)
18.4-22.9	231 (28.3)
<18.5	46 (5.6)
23.0-24.9	137 (16.8)
25.0-29.9	281 (34.4)
≥30.0	121 (14.8)
Smoking	
No	755 (86.4)
Yes	119 (13.6)
Alcohol drinking	
No	753 (86.2)
Yes	121 (13.8)
Hypertension	
No	473 (54.1)
Yes	401 (45.9)
Diabetes mellitus	
No	518 (59.3)
Yes	356 (40.7)
Dyslipidemia	
No	854 (97.7)
Yes	20 (2.3)
History of NSAIDs used	
No	528 (60.3)
Yes	347 (39.7)
Glomerular filtration rate (mL/min/1.73m²)	
mean±SD	80.3±24.0
median (max-min)	84.5 (147.3-14.6)
>90	358 (41.0)
60-89	339 (38.8)
45-59	99 (11.3)
30-44	46 (5.3)
15-29	30 (3.4)
<15	2 (0.2)

Table 2. Univariate analysis for factors associated with decline of renal function

Factors	GFR <60 mL/min/1.73 m² n (%)	GFR ≥ 60 mL/min/1.73 m² n (%)	Odds Ratio	95% CI	*p*-value
Sex					
Female	106 (19.7)	432 (80.3)	1.00		
Male	71 (21.1)	265 (78.9)	1.09	0.78-1.53	0.609
Age (years)					
mean±SD	68.2±12.1	58.1±12.3	2.85	2.30-3.54	<0.001
<40	2 (4.8)	40 (95.2)	1.00		
40-49	6 (5.8)	98 (94.2)	1.22	0.24-6.32	0.809
50-59	32 (11.2)	255 (88.8)	2.51	0.58-10.88	0.219
60-69	46 (19.3)	192 (80.7)	4.79	1.12-20.55	0.035
70-79	62 (41.9)	86 (58.1)	14.40	3.36-61.91	<0.001
≥80	29 (52.7)	26 (47.3)	22.31	4.90-101.55	<0.001
Body mass index (kg/m²)					
mean±SD	25.3±4.7	25.3±5.0	1.00	0.96-1.03	0.872
18.4-22.9	52 (22.5)	179 (77.5)	1.00		
<18.5	4 (8.7)	42 (91.3)	0.33	0.11-0.96	0.041
23.0-24.9	33 (24.1)	104 (75.9)	1.09	0.66-1.80	0.729
25.0-29.9	46 (16.4)	235 (83.6)	0.67	0.43-1.05	0.080
≥30.0	21 (17.4)	100 (82.6)	0.72	0.41-1.27	0.258
Smoking					
No	148 (19.6)	607 (80.4)	1.00		
Yes	29 (24.4)	90 (75.6)	1.32	0.84-2.08	0.230
Alcohol drinking					
No	148 (19.7)	605 (80.3)	1.00		
Yes	29 (24.0)	92 (76.0)	1.29	0.82-2.03	0.274
Hypertension					
No	116 (24.5)	357 (75.5)	1.00		
Yes	61 (15.2)	340 (84.8)	0.55	0.39-0.78	0.001
Diabetes mellitus					
No	73 (14.1)	445 (85.9)	1.00		
Yes	104 (29.2)	252 (70.8)	2.52	1.80-3.52	<0.001
Dyslipidemia					
No	177 (20.7)	677 (79.3)	1.00		
Yes	0 (0)	20 (100.0)	N/A	N/A	N/A
History of NSAIDs used					
No	61 (11.6)	466 (88.4)	1.00		
Yes	116 (33.4)	231 (66.6)	3.84	2.71-5.43	<0.001
Pulse pressure (mmHg)					
≤75 percentile (≤63)	113 (16.8)	560 (83.2)	1.00		
>75 percentile (>63)	62 (32.1)	131 (67.9)	2.35	1.63-3.37	<0.001

NSAIDs; non-steroidal anti-inflammatory drugs, CI; confidence interval, SD; standard deviation

Table 3. Multivariate analysis for factors associated with decline of renal function

Factors	Adjusted Odds Ratio	95% CI	*p*-value
Sex			
Female	1.00		
Male	1.06	0.66-1.70	0.815
Age (years)	1.07	1.05-1.09	<0.001
Body mass index (kg/m²)	1.02	0.98-1.06	0.309
Smoking			
No	1.00		
Yes	1.01	0.42-2.44	0.991
Alcohol drinking			
No	1.00		
Yes	2.02	0.83-4.90	0.119
Hypertension			
No	1.00		
Yes	0.96	0.53-1.72	0.879
Diabetes mellitus			
No	1.00		
Yes	1.28	0.66-2.46	0.464
History of NSAIDs used			
No	1.00		
Yes	2.97	1.85-4.79	<0.001
Pulse pressure (mmHg)			
≤75 percentile (≤63)	1.00		
>75 percentile (>63)	1.64	1.07-2.53	0.024

NSAIDs; non-steroidal anti-inflammatory drugs, CI; confidence interval

Discussion

The present study presented that the prevalence in the decline of renal function (eGFR <60 mL/min/1.73 m²) among outpatients was 20.3% which was higher than that of the 2010 national survey conducted in Thailand (9.3%).[3] In addition, compared with the prevalence of eGFR <60 mL/min/1.73 m² in a Canadian community (14.5%), the prevalence of those in this study was relatively high.[9] According to the hospital-based study, the participants of the present study consisted of a high proportion of patients with T2D and HT, approximately 45%; therefore, their comorbidities may have affected the decline of renal function leading to a high prevalence among the study participants. However, the prevalence in the decline of renal function among study participants was comparable with a related study in the UK reporting a prevalence of 18.2%. [12]

Notably, the prevalence in the decline of renal function stratified by age groups significantly differed. We found that outpatients at higher age tended to be at risk in the decline of renal function. Currently, several countries have become aging societies; thus, the relationships between age and CKD have been reported from many studies. One related study conducted in a semi-urban community in Nigeria found that age was a significant factor of developing CKD.[13] Additionally, recent studies in Thailand and Sri Lanka emphasized that the prevalence of CKD related to aging.[3,14] Similarly, GFR measurement using single-nephron GFR, calculated in a healthy adult population in the US, demonstrated that CKD related to advanced age due to decreased glomerular infiltration in the normal aging process. A steep decline is observed after age 50 years. According to physiological processes, age

is claimed to have immense results in decreased GFR.[13] Many reasons explain this phenomenon. Firstly, long term contact with free radicals and oxidative stress results in declining numbers of normal functional podocyte but increasing numbers of sclerosed glomeruli. Secondly, aging kidneys exhibit structural changes in both micro- and macroanatomical aspects. Microanatomical aspects are explained by increasing sclerosis score among aging adults as a result of atrophy of functioning tubular and interstitial fibrosis and arteriosclerosis while macroanatomical changes are due to decreasing kidney volume, thinner kidney parenchymal and abundance of kidney cysts.[15]

We found that almost 40% of participants presented a history of NSAIDs use; additionally, outpatients with a history of NSAIDs use tended to be at risk of significantly declining renal function. Likewise, one related study in China reported that NSAIDs use related to higher risk of CKD; moreover, using NSAIDs more than 48 months led to reduced renal function. [16] Similarly, a community-based cohort study in Canada reported that exposure to high dose NSAIDs increased the risk of rapidly progressing of CKD.[17]

The phenomenon may be explained by the principal mechanism of NSAIDs action via the cyclooxygenase (COX) inhibitor pathway. COX enzyme inhibition disrupts the conversion of arachidonic acid to different prostaglandins such as prostaglandin E2, prostacyclins and thromboxanes, inducing kidney vasodilatation inhibition and reducing renal perfusion. [18]

Additionally, NSAIDs are one of a risk factors contributing to CKD, especially in advance age. Prolong used of NSAIDs leads to chronic interstitial nephritis, known as CIN, papillary necrosis and finally, CKD.[19,20]

Our study suggested promoting effective interventions such as careful consideration before appropriately prescribing NSADs. In addition, health literacy regarding the risk factors in decline of renal function especially NSAIDs use should be provided to patients.[21]

Our study reported that elevated PP was associated with the decline of renal function. Similarly, the National Institute of Diabetes and Digestive Kidney Diseases registry in the US demonstrated that PP significantly correlated to the decline of GFR levels. [22] Additionally, one related cohort study found that among patients with CKD in stages IV and V, PP more than 80 mmHg constituted a significant predictor for disease progression.[23] PP was identified as a strong independent predictor of rising ambulatory arterial stiffness index. The relationship between elevated PP and decline of renal function may be explained by the process of cardiovascular aging as in arterial stiffness at both macrovascular and microvascular.[24–26] Therefore, PP might constitute a noninvasive proxy indicator for the decline of renal function.[27]

The study employed a cross-sectional survey, making it difficult to establish a cause-and-effect relationship between associated factors and decline of renal function. According to secondary data used for analysis, some variables were incomplete. Another limitation was the small sample size in the study; therefore, the association between well-known risk factors such as T2D, HT, smoking status and outcome could not be presented. The results of our study may not be generalized to the whole country but may reflect the real situation of outpatients attending a Thai community hospital.

To our knowledge, this study is the latest study of the decline of renal function among patients attending a Thai community hospital. The results emphasized that Thailand, a developing country, is experiencing a serious public health burden. The decline of renal function including CKDs should be recognized as a serious health problem. The Ministry of Public Health should raise more awareness of this issue among the national population to prevent the disease and alleviate its complications.

Conclusion

The prevalence of the decline of renal function among outpatients in a Thai community hospital was higher than that at the national level. It indicated that this constituted an essential health problem not only in urban areas but also in rural communities. Advanced age, a history of NSAIDs use and PP were related to reduced

kidney function. Additionally, effective health interventions should be conducted especially, to ensure appropriate NSAIDs use among patients.

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PASSIVE LEG RAISING EFFECT AT RESUSCITATION AMONG PATIENTS WITH VASOPLEGIC STATE

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Abstract

Background: Several dynamic parameters have been used clinically to predict volume responsiveness and to guide fluid administration of which passive leg raising (PLR) is one of the most reliable techniques. PLR induces rising in cardiac output attributes through an unstressed volume mobilization from legs to heart causing autologous preload increment. Appropriate fluid resuscitation is essential and can be optimized by hemodynamic-based approach to vasodilatory hypotension.

Objective: This study aimed to evaluate the effectiveness and safety of PLR at early resuscitation among patients with vasoplegia.

Methods: We conducted a comparison study concerning an experimental design using a single blinded assessment of the outcomes that assigned patients with shock to be treated with PLR or flat position at early resuscitation. Forty patients with shock were included in this study. Twenty patients performed PLR at early resuscitation compared with the others that performed in the flat position and were measured for cardiac output (CO), mean arterial pressure (MAP), diastolic blood pressure (DBP), heart rate (HR), central venous pressure (CVP) and systemic vascular resistance (SVR) immediately after the procedures. The primary outcome was to evaluate the effect of early PLR on hemodynamic variables among hypotensive patients by comparing the difference in CO while the secondary outcomes were differences in MAP, DBP, HR, CVP, SVR, survival at hospital admission and the pulmonary complications of chest x-rays between the two groups.

Results: No difference was observed in baseline characteristics between the two groups of patients. Compared with the flat position, PLR at early resuscitation significantly increased CO (3.57 ± 0.27 vs. 2.2 ± 0.18 L/min, $p = 0.037$), MAP (22.48 ± 5.6 vs. 10.83 ± 4 mmHg, $p<0.001$), DBP (19 ± 0.20 vs. 1.23 ± 0.12 mmHg, $p=0.001$) and CVP (4.52 ± 0.19 vs. 2.18 ± 0.13 mmHg, $p=0.002$). However, no differences were observed in HR, SVR, pulmonary complications of chest X-rays [2 (10%) vs. 1 (5%), $p = 0.23$] as well as survival at hospital admission [16 (80%) vs. 13 (65%), $p = 0.48$] between the two groups.

Conclusion: Among patients with shock, PLR at early resuscitation significantly increased CO, MAP, DBP and CVP than that of those performing the flat position. No differences were found in HR, SVR, pulmonary complications; PLR did not improve survival to hospital admission.

Keywords: Vasoplegia, Cardiac output, Venous return, Mean systemic pressure

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INTRODUCTION

Passive leg raising (PLR) is considered to be a maneuver that could promote venous return and increase systemic circulation.[1] PLR at early resuscitation mimics rapid volume expansion and is often used in intensive care units during the hemodynamic assessment of patients.[2] During vasoplegia or patients with shock, tissue perfusion is limited, leading to a low flow state. Increasing the venous and arterial bed resistances can improve myocardial and cerebral blood flow.[3] Early PLR stresses the volume of the venous reservoir, increasing the mean systemic pressure (Pms), which is the driving pressure of the venous return flow.[4] In a series of resuscitated pigs, PLR increased coronary perfusion pressure (CPP) compared with that in a control group. A retrograde volume loading of the aorta from early PLR may raise the intra-abdominal pressure and anterograde blood flow resistance, which increases the CPP gradient.[5] PLR has been developed as a test to predict fluid responsiveness.[6] This maneuver is supposed to transfer a significant volume of venous blood towards the intrathoracic compartment. However, it has been suggested that PLR could have nonsignificant effects on cardiac preload, in particular in the case of intra-abdominal hypertension. This would result in a negative PLR test result in spite of actual fluid responsiveness.

In recent years, concern has been growing about the safety of various interventions performed at early resuscitation. Fluid infusion at early resuscitation has led to worsened clinical outcomes.[7, 8] Another resuscitation body position, such as Trendelenburg, was associated with increased intracranial pressure. Data about the safety of PLR and the beneficial effect of early PLR remain limited. We hypothesized that early PLR could be a safe maneuver and could improve survival at discharge compared with that of patients treated using a standard protocol.

Methods

This study was reviewed and approved by the Ethics Committee of Institutional Review Board, Royal Thai Army Medical Department (IRBRTA 292/2563). The study was conducted in accordance with the Council for International Organization of Medical Science (CIOMS) Guidelines 2012 and Good Clinical Practices.

Sample size was calculated according to the comparison studies of PLR and the flat position in volume expansion.[4,15] At least 26 patients in total were required to compare differences between the two groups. Patients were enrolled on the scene at the initial shock and resuscitation assessment. In this study, patients with shock were included. A single blinded experiment was conducted by randomization of 1:1 ratio using variables of block size, computer-generated sequence and allocation and kept in opaque envelopes.

Participants

Informed consent was obtained from the enrolled patients or their legal representatives. From May 2020 to May 2021, 40 patients admitted in Medical Intensive Care Unit (ICU), Phramongkutklao Hospital, were monitored for invasive arterial blood pressure, peripheral O_2 saturation (SpO$_2$), and electrocardiogram.

Patients were assigned to PLR and the flat position groups. Of these, 20 patients used PLR which was performed within the first 5 min after initial shock and resuscitation assessment and was maintained until the end of resuscitation or until the patients presented stable hemodynamics. The angle of PLR was set at 45° following a related report. [4] To ensure that the legs were lifted at this angle, different assays were made. As a result, all ICU beds were equipped and adjusted to accurately measure this angle.

All patients were measured for CO, mean arterial pressure (MAP), diastolic blood pressure (DBP), heart rate (HR), central venous pressure (CVP) and systemic vascular resistance (SVR) immediately after PLR procedures. The inclusion criteria were patients aged more than 18 years old. The exclusion criteria included patients who had contraindications for PLR, e.g., limb amputation, traumatic patients with suspected pelvic or lower limb fracture, pregnancy, intraabdominal pressure more than 16 mmHg, increased intracranial pressure and pneumothorax. The primary outcome was to evaluate the effect of early PLR on hemodynamic variables among hypotensive

patients by comparing the difference of CO while the secondary outcomes were to compare differences in MAP, DBP, HR, CVP and SVR, survival at hospital admission and pulmonary complications in chest x-rays between the two groups.

Shock was defined as persistent MAP less than 65 mmHg at least 15 min despite adequate volume resuscitation (performed dynamic parameters shows fluid nonresponsive) or required vasopressors to maintain MAP more than 65 mmHg.

Septic shock was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (persistence of infection, and required vasopressors to optimize MAP $\geq$65 mmHg, combined with a serum lactate level >2 mmoL/L (18mg/dL) despite adequate volume resuscitation.

Resuscitation was performed using early intravenous fluid resuscitation with balanced salt solution crystalloid or isotonic crystalloid at least 30 mL/kg according to Surviving Sepsis Campaign guidelines 2018, European Society of Intensive Care Medicine guidelines. Dynamic parameters used to assess adequate fluid resuscitation included pulse pressure variation (PPV), stroke volume variation (SVV) or mini-fluid challenge test when performed dynamic parameters showed fluid nonresponsive, and early use of vasopressor (norepinephrine) to maintain MAP more than 65 mmHg was applied.

General management in ICU

Patients were sedated with fentanyl and mechanically ventilated using pressure-controlled ventilation, aimed to maintain at Pplat <30 cm H_2O, using a tidal volume (V_T) of 6–8 mL/kg of predicted body weight. The faction of inspired oxygen (FiO_2) and Positive-End Respiratory Pressure (PEEP) were titrated to achieve peripheral saturation of oxygen (SpO_2) more than 94%, and RR was set to maintain arterial partial pressure of carbon dioxide ($PaCO_2$), and 35–45 mmHg end-tidal carbon dioxide ($ETCO_2$) was continuously measured.

Hemodynamic monitoring

Radial arterial catheter and central venous catheter were linked to a bedside monitor on one side and to a specific transducer (Philips Intellivue Philips MX600, USA) for blood pressure, DBP, HR and CVP monitoring. The values of CO and SVR were estimated from pulse contour analysis (EV1000 clinical platform, Edwards advanced hemodynamic monitoring tools for an integrated Edwards Critical Care System, USA).

Interventions

PLR was performed within the first 5 min after acute circulatory failure at the ICU and was maintained until the end of resuscitation. Procedures involved patients sitting in the 45 degrees, head up, semi-recumbent position, then lowering the patient's upper body to horizontal and passively raising the legs at 45 degrees up then maintaining the maximal effect occurring during resuscitation. To assess postresuscitation pulmonary complications, the report of the attending physician or radiologist on the first X-ray taken at the ICU was evaluated. Lung complications were considered when bilateral lung opacities, edema, pulmonary congestion or bilateral alveolar pattern and survival at hospital admission were described.

Statistical analysis

Results were expressed as mean ± SD when data were normally distributed or median and interquartile range (IQR) if not. Hemodynamic parameters were compared between PLR and the flat position during resuscitation using the independent-t test, paired t-test, Fisher's exact test, Pearson's correlation, and repeated measure ANOVA test. The effects of volume expansion on hemodynamic parameters were analyzed using the Friedman nonparametric repeated measures comparisons. A *p*-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY, IBM Corp.)

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┌─────────────────────────────────────────────┐
│   60 eligible shock patients were assessed    │
└─────────────────────────────────────────────┘
                    │
                    │        ┌──────────────────────────────────────┐
                    │        │  8 had contraindication to PLR        │
                    ├────────│  4 were not randomized                │
                    │        │  3 were not recovered from shock      │
                    │        │  3 were eligible but not enrolled     │
                    │        │  2 had shock interrupted by futility  │
                    │        └──────────────────────────────────────┘
                    ▼
          ┌──────────────────────────┐
          │  40 cases were randomized  │
          └──────────────────────────┘
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40 cases were randomized

20 were treated using PLR | 20 were treated using the flat position

20 received interventions as assigned | 20 received interventions as assigned

0 lost to follow-up in the primary outcome | 0 lost to follow-up in the primary outcome

20 were included in the primary outcome analysis | 20 were included in the primary outcome analysis

Figure 1. Flow chart of patient enrollment and analysis in the trial

Results

Patient characteristics

During the study period, 40 patients with acute circulatory failure were included. Twenty patients performed PLR. All patients were measured for CO, MAP, DBP, HR, CVP and SVR immediately after the procedures. Most patients were female (52%) with average age of 68 years. The most frequent coexisting disease was hypertension while the most frequent etiology of shock was septic shock (**Table 1**).

Regarding adverse effects, the incidence of pulmonary complications of the first chest X-rays were similar between the PLR and flat position groups, (10% vs. 5%, $p = 0.23$).

Clinical outcomes

No significant differences in survival at hospital admission were found [16 (80%) vs. 13 (65%), $p = 0.48$] between the two groups.

Table 1. Demographic data of 40 patients with acute circulatory failure

Demographic data	N = 40
Male, n (%)	19 (47.5)
Female, n (%)	21 (52.5)
Age (yr)	68.25 ± 17.23
Body weight (kg)	58.25 ± 5.38
Co-morbidity, n (%)	
Hypertension	29 (72.5)
Dyslipidemia	18 (45)
Diabetes mellitus	18 (45)
Chronic kidney disease	10 (25)
Chronic liver disease	9 (22.5)
Coronary artery disease	4 (10)
Other diseases	21 (52.5)
IV fluid (mL)	1725 ± 521
Type of shock, n (%)	
Septic	33 (82.5)
Cardiogenic	4 (10)
Hypovolemic	3 (7.5)

Characteristics between the two groups of patients

No significant difference of baseline characteristics was observed between the two groups of patients **(Table 2).**

Table 2. Comparison baseline characteristics between the two patient groups

Characteristics	PLR (n=20)	Flat position (n=20)	*p*-value
Male, n (%)	9 (45)	10 (50)	1.0
Female, n (%)	11 (55%)	10 (50%)	1.0
Age (yr)	66.1 ± 18.5	70.4 ± 16.04	0.437
Body weight (kg)	58.5 ± 5.4	58 ± 5.48	0.773
Coexisting diseases, n (%)			
Hypertension	16 (80)	13 (65)	0.480
Dyslipidemia	10 (50)	8 (40)	0.751
Diabetes mellitus	10 (50)	8 (40)	0.751
Chronic kidney disease	8 (40)	2 (10)	0.065
Chronic liver disease	4 (20)	5 (25)	1.0
Coronary artery disease	4 (20)	0 (0)	0.106
APACHE II Score*	12.7 ± 1.95	12.65 ± 2.23	0.940
Received IV fluid (mL)	1651.5 ± 470.15	1798 ± 570.53	0.381
Fever	6 (30%)	8 (40%)	0.741
Sedation drug			

Table 2. Comparison baseline characteristics between the two patient groups (ext.)

Characteristics	PLR (n=20)	Flat position (n=20)	p-value
Fentanyl	17 (85%)	16 (80%)	1
Heart rate (beat/min)	94 ± 23.25	93 ± 16.76	0.849
MAP on admission (mmHg)	54.95 ± 4.68	57.3 ± 6.5	0.67
DBP on admission (mmHg)	52 ± 5.55	54 ± 4.76	0.139
CVP on admission (mmHg)	7.68 ± 1.49	8.1 ± 1.8	0.73
CO on admission (L/min)	4.4 ± 1.27	4.8 ± 1.1	0.81
SVR on admission (dyn.s/cm^5)	870 ± 43.23	877 ± 45.41	0.576
Blood lactate on admission (mmol/L)	5.0 (4.0–6.9)	4.5 (3.0–7.5)	0.79
Type of Shock			
Septic	17 (85)	16 (80)	1
Cardiogenic	2 (10)	2 (10)	0.605
Hypovolemic	2 (10)	1 (5)	0.231
Dose NE (μg/kg/min)	0.34 ± 0.07	0.35 ± 0.06	0.486
Survival at hospital admission	16 (80)	13 (65)	0.480
Pulmonary complications	2 (10)	1 (5)	0.231
Days in ICU (mean)	5	6	0.63

Values presented as mean ± SD or n (%), p-values corresponded to independent-t test and Fisher's exact test.

*Acute Physiology and Chronic Health Evaluation

Differences of CO, MAP, DBP, HR, CVP and SVR compared between PLR and flat position groups

Changes in hemodynamic variables are shown in **Table 3**. PLR significantly increased CO (3.57 ± 0.27 vs. 2.2 ± 0.18 L/min, $p = 0.037$), MAP (22.48 ± 5.6 vs. 10.83 ± 4 mmHg, $p<0.001$), DBP (19 ± 0.20 vs. 1.23 ± 0.12 mmHg, $p=0.001$) and CVP (4.52 ± 0.19 vs. 2.18 ± 0.13 mmHg, $p=0.002$). PLR increased CO, MAP and CVP during resuscitation from baseline. Compared with the flat position, PLR increased CO, MAP and CVP more. No significant differences were found between the two groups regarding SVR [6 (-27.34, 15.34) vs. 1 (-46.83, 48.83) dyn.s/cm^5 (95%CI), $p = 0.704$] and HR [0.67 ± 0.15 vs. 0.2 ± 0.35 beat/min, $p = 0.98$].

Table 3. Changes in hemodynamic variables from baseline in PLR and the flat position during resuscitation.

Variables	Baseline before PLR (n=20)	PLR (n=20)	Baseline before flat position (n=20)	Flat position (n=20)	p-value
CO (L/min)	4.4 ± 1.27	7.97 ± 1.54	4.8 ± 1.1	7.0 ± 1.28	0.037#
	Mean change from baseline	3.57 ± 0.27	Mean change from baseline	2.2 ± 0.18	
		p<0.001*		p<0.001*	
MAP (mmHg)	54.95 ± 4.68	77.43 ± 7.78	57.3 ± 6.5	68.13 ± 2.5	<0.001#
	Mean change baseline	22.48 ± 5.6	Mean change from baseline	10.83 ± 4	
		p <0.001*		p <0.001*	

Table 3. Changes in hemodynamic variables from baseline in PLR and the flat position during resuscitation (ext.)

Variables	Baseline before PLR (n=20)	PLR (n=20)	Baseline before flat position (n=20)	Flat position (n=20)	*p*-value
DBP (mmHg)	52 ± 5.35 Mean change from baseline	71 ± 5.55 19 ± 0.20 *p* <0.001*	54 ± 4.76 Mean change from baseline	55.77 ± 4.88 1.23 ± 0.12 *p*=0.139	0.001#
HR (beat/min)	94 ± 23.25 Mean change from baseline	93.33 ± 23.4 0.67 ± 0.15 *p* =0.849	93 ± 16.76 Mean change from baseline	93.2 ± 16.41 0.2 ± 0.35 *p* =0.92	0.98
CVP (mmHg)	7.68 ± 1.49 Mean change from baseline	12.2 ± 1.68 4.52 ± 0.19 *p* <0.001*	8.1 ± 1.8 Mean change from baseline	10.28 ± 1.93 2.18 ± 0.13 *p* <0.001*	0.002#
SVR (dyn.s/cm^5)	870 ± 43.23 Mean change from baseline (95%CI)	876 ± 39.26 6 (-27.34,15.34) *p* =0.576	877 ± 45.41 Mean change from baseline (95%CI)	878 ± 45.05 1 (46.83,48.83) *p*= 0.98	0.53

Values presented as mean±SD and mean change presented as mean±SD and interquartile range,
*depicts *p* <0.05 and compared between baseline vs. each intervention
depicts *p*<0.05 and compared between two interventions
 P-values were analyzed using the paired t-test and independent t-test.

Discussion

In this study, baseline characteristics of each group were comparable. We evaluated the effects of PLR on CO, MAP, DBP, HR, CVP and SVR among patients with acute circulatory failure during resuscitation. We found that PLR increased CO, MAP, DBP and CVP during resuscitation from baseline. Additionally, when compared with the flat position, PLR increased CO, MAP, DBP and CVP more. Significantly increased CO, MAP, DBP and CVP confirmed that PLR could actually represent a powerful preload challenge. The increase of venous return was attested to the increase of CO. Interestingly, PLR did not reduce venous return resistance (Rvr) while a decrease in Rvr due to a reduced sympathetic tone could have been expected from an improvement in CO. PLR resulted in a larger increase in Pms than in CVP. This increase in the pressure gradient for venous return was associated with an increase in

CO. PLR effected increased venous return; thus, CO, MAP and CVP values increased when CO and MAP increased. This could improve tissue perfusion, tissue oxygenation and promote recovery of shock.

A Swedish research group reported that PLR was performed more often in cases involving a worsened clinical scenario and early PLR could improve its benefit on survival.[9] The idea of a transient effect of PLR over time has been described among patients with septic shock and is attributed to capillary leak.[10] During acute circulatory failure, maintained tissue perfusion which could favor the shortened effect of PLR on CO.[11] Optimizing venous return is the key to improve survival outcomes.

Experimental data support the distinct hemodynamic effect of PLR and volume load during resuscitation. Volume loading has been associated with decreased CPP due to the detrimental effect

of the increase in right atrial pressure (RAP) during the decompression phase.[12] However, PLR seemed not to alter RAP and has been associated with an increase in CPP. [13] It should be considered that the greatest change in CO due to PLR occurred after 1 min of the procedure.[14]

In the present study, we aimed to assess how hemodynamic variables changed during PLR among patients with shock. In particular, we aimed to investigate whether the absence of increased CO during PLR was due to an absence of increase in venous return, resulting in the absence of a significant increase in cardiac preload, or to a preload independence per se, that is, to an absence of increased CO to a significant increase in cardiac preload.

Laurent Guerin et al.[15] conducted a passive leg raising study among patients with shock and hemodynamic effects of PLR showing thatPLR increased cardiac index (CI) by $17 \pm 20\%$. During PLR, CVP and CI significantly increased. PLR did not change the intra-abdominal pressure among the whole subjects (14 ± 6 mmHg before vs. 13 ± 5 mmHg during PLR, $p = 0.26$) or among patients with intra-abdominal hypertension at baseline (17 ± 4 mmHg before vs. 16 ± 4 mmHg during PLR, $p = 0.14$). Considering the whole subjects, the PLR-induced changes in CI predicted fluid responsiveness with an area under the receiver operator characteristic (ROC) curve of 0.98 ± 0.03. Our results confirmed the results to a related study showing 54% of increased CO. PLR could be used as a test for predicting fluid responsiveness. The test assumes that it increases the stressed blood volume by inducing the gravitational transfer of venous blood from the inferior limbs and the splanchnic compartment toward the cardiac cavities. [18] Nevertheless, the effects of PLR on the determinants of venous return have been investigated in only one study. [19] PLR test significantly shifts intravascular fluid from the legs to the abdomen, suggesting that this dynamic test may not be appropriate among patients with risk of intra-abdomenal or intrathoracic hypertension and also patients at risk of high intracranial pressure. Moreover, other studies have suggested that the PLR test would not be reliable in the case of intraabdominal hypertension because it would compress the inferior vena cava.[20, 21] However, in this study, we excluded patients with intra-abdominal hypertension.

In these regards, our study provides some interesting issues on the hemodynamic effects of PLR that PLR induced significantly increases in CO and CVP among all patients, confirming that it could actually represent a powerful preload challenge. These results agree with those of Keller et al.[19], who reported that PLR increased CVP from 4 to 6 mmHg. One of major interests of the study was to analyze the effects of PLR depending on the fluid responsiveness status. Increasing the pressure gradient for venous return was associated with an increase in CO. Physiologically, Pms depends on vascular compliance and on the volume of venous blood that is submitted to the strain of the venous reservoir walls, i.e., stressed blood volume.[22] As fluid infusion is assumed not to alter vascular compliance, our results suggested that fluid infusion increased Pms and cardiac preload by increasing the stressed blood volume, confirming the results by Keller et al.[19] Our results suggest that PLR also increased the stressed blood volume. CVP did not increase as much as Pms during PLR. This was probably related to the fact that in these fluid responsive patients, the heart was working on the steep part of the Frank-Starling curve. Therefore, a rightward shift on the venous return curve induced by the increase in Pms resulted in a smaller increase in CVP. Interestingly, PLR did not reduce venous return resistance (Rvr), while a decrease in Rvr due to a reduction in the sympathetic tone could have been expected from an improvement in CO.

Another physiological advantage was significantly higher diastolic blood pressure induced by PLR; the major determinant of coronary blood flow. One potential benefit is the combined increased diastolic blood pressure and steady heart rate theoretically allows more balance in myocardial oxygen demand and supply among patients with septic shock. The rapid effect of PLR as internal volume resuscitation has gained more attentions in its effectiveness and safety for out-of-hospital cardiopulmonary resuscitation (CPR) setting, however current evidence has not revealed clinical benefits.

A related study on PLR revealed significant sustained effects on cardiovascular parameters even at 10 min after the start of PLR.[23] Out of the parameters observed in this study, CO showed the largest and most stable sustained increase during the entire PLR time course. CO promptly returned to pre-PLR values at the end of PLR. This increase was believed to be primarily a passive response to the increase in preload due to PLR, which increases CVP, resulting in increased right ventricular CO and subsequently that of the left ventricular preload. This increase in CO presumably caused increases in the other parameters, including MAP, SBP and DBP during PLR. Wong et al. [24] reported that patients whose 500 mL blood was extracted before PLR showed a significantly greater increase in CO than that of the control. These results, together with our present observation, suggested that PLR could be an effective procedure for patients with relatively normal cardiac functions who are in hypovolemic shock and the vasoplegic state. HR tended to decrease in response to PLR. Among normal patients, strong homeostatic mechanisms work to maintain constant blood flow to vital organs. The increase in CO caused by PLR may have induced a blood pressure increase that was sensed by carotid or cardiopulmonary baroreceptors; and thus, decreased HR through a negative feedback system [25-27]. The decrease in HR during PLR was interpreted as the result of a compensatory reflex evoked by the increased CO in response to PLR. SVR is another important parameter of cardiovascular function. Although SVR gradually increased after a transient decrease at the start of PLR, no significant changes in SVR were observed at any time. This SVR response to PLR appeared to be transient and compensatory to the rapid increase in CO, which decayed in a relatively short time and caused no significant differences at any time.

Our study revealed the potential role of PLR in ICU that is probably not only the test of volume responsiveness but also an intervention for volume resuscitation among patients in the vasoplegic state even though the hemodynamic effect may last only a short period.

Study limitations are discussed below. Firstly, CO was monitored using the EV1000 clinical platform, performed by analyzing the radial artery pressure waveform. For rapid changing of intravascular volume or when using vasopressors, monitoring of femoral artery pressure has been recommended. Secondly, our study was conducted in a single center and confined only to patients with shock, so our findings could not be applied for other critically-ill patients without need of circulatory supports. Third, the time between shock with initial resuscitation and the PLR was not recorded which could be a potential confounder. Finally, PLR could have stimulated sympathetic tone and interfered with hemodynamic interpretation.

In this study, PLR was considered to be a maneuver that could promote venous return and improve hemodynamic variable among patients with shock. Some situations, i.e., CPR during cardiac arrest, can increase venous return and artificial circulation during chest compressions. During CPR, CO is limited; increasing the venous and arterial bed resistance that can improve myocardial and cerebral blood flow. PLR stresses the volume of the venous reservoir, increasing the mean systemic filling pressure, which is the driving pressure of the venous return flow. Use of coronary perfusion pressure (CPP) is a good predictor of the return of spontaneous circulation (ROSC) because a retrograde volume loading of the aorta from the PLR may occur, raising the intra-abdominal pressure and the anterograde blood flow resistance, which increases the CPP gradient. Further study about safety of various interventions performed by emergency teams during resuscitation would be very helpful. Data about the safety of PLR during CPR, and the beneficial effect of PLR performed during CPR remains very limited. It can be hypothesized that PLR performed at the beginning of out-of-hospital cardiac arrest treatment would be a safe maneuver and improve survival at discharge with good neurological outcomes compared with those of patients treated using a standard protocol.

Conclusion

Among patients with acute circulatory failure, PLR at early resuscitation significantly increased

CO, MAP, DBP and CVP more than those using the flat position. No differences in HR, SVR and pulmonary complications have been found; PLR did not improve survival to hospital admission.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests

No potential conflict of interest relevant to this article was reported.

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COMPARISON OF PERCUTANEOUS PEDICLE SCREW FIXATION AND PEDICAL SCREW FIXATION IN CONVENTIONAL INCISION IN THORACOLUMBAR FRACTURE

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Abstract

Background: Originally, patients with unstable thoracolumbar spine fracture were treated using pedicle screw fixation, a conventional incision. However, the small incision percutaneous pedicle screw fixation (PPSF), a new device, has been recently introduced which could save surgery time, reduce blood loss and improve clinical recovery.

Objective: This study aimed to evaluate postoperative outcomes of the PPSF, compared with the open pedicle screw fixation (OPSF) in conventional incision among patients with thoracolumbar fracture.

Methods: A retrospective study of 54 cases of patients with thoracolumbar spine fracture without neurological deficit was included in the study. The data were collected from medical records of patients admitted to Rayong Hospital from January 2017-December 2019.

Results: Patients aged from 18-46 years (32.35 ± 8.52) were mostly males (59.2%). Types of fracture included burst (72.22%). The most common level of thoracolumbar spine fracture was L1 (37.04%). Mostly, the cause of injury was fall from height (53.70%). The mean postoperative stays in the PPSF and OPSF groups were significant, $3.09\pm.59$ and 6.16 ± 1.003 days, respectively ($p<0.05$). The mean intraoperative blood losses of the PPSF and OPSF groups significantly differed, 44.35 ± 15.02 and 466.13 ± 87.92 mL, respectively ($p < 0.01$). However, the mean kyphotic angle reduction of the PPSF (24.43 ± 2.74 degrees) and OPSF (24.87 ± 2.55 degrees) groups did not significantly differ ($p > 0.1$). The mean postoperative pain score (VAS) at the first day in the PPSF and OPSF groups were $6.43\pm.94$ and $6.61\pm.98$, respectively, which did not significantly differ ($p > 0.1$).

Conclusion: PPSF spinal fracture treatment could reduce the amount of bleeding during surgery and reduce the length of hospital stay. However, the results of both types of surgery did not differ regarding postoperative pain, decreased kyphotic angle and surgical time.

Keywords: Thoracolumbar Fracture, Percutaneous pedicle screw fixation, Open pedicle screw fixation

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Introduction

Spine fracture has been found especially at the thoracolumbar junction level (T10-L2) where biomechanical transferred area and considerable motion are involved. [1,2] The incidence of this injury in North America was 160,000 persons per year which caused abnormal spine structure (kyphotic deformity) with neurological injury.

The classification of injury at this area used the three-column concept as described by Denis F. [3] This concept divided patients in four groups under biomechanical theory, namely, compression fracture, burst fracture, flexion-distraction injury and fracture dislocation. In 2005, Vaccaro et al. [4] proposed the thoracolumbar injury and severity score (TLICs) considering three aspects, i.e., biomechanical spine fracture combined with the context of Denis's theory, injury at the posterior ligamentous complex and neurological spinal injury. All of these aspects have been applied and used as guidelines for patterns and treatment methods.

The unstable fracture or TLICs ≥4 with neural injury was treated using the open conventional incision. Pedicle screws were applied to fix at the spinal body and reduction & decompression followed the standard treatment. [5,6]

On the other hand, the unstable spine fracture without neurological injury could be treated using percutaneous pedicle screw fixation which saved time during surgery. In addition, this approach reduced blood loss, decreased dissection tissue and improved clinical recovery faster than the old method. [7,8]

The important instrument assisting percutaneous pedicle screw fixation was a guide wire and a cannulated screw to apply insertion at the pedicle only. Fluoroscope assisted evaluating the proper site and direction of screw during surgery. Open surgery splinted the muscles between the multi fidus and longissimus (Wiltse's approach).[14-16] This retrospective study considered the appropriateness, safety and efficacy of both techniques.

Methods

The retrospective study was conducted at Rayong Hospital and approved by the Ethics Committee of Rayong Hospital (RYH REC No. E030/2563). The inclusion criteria included thoracolumbar and unstable fractures. The exclusion criteria included TLICs <4 scores, neurological deficit, and multiple organ injuries. From January 2017 to December 2019, 54 thoracolumbar fractures operated at Rayong Hospital were enrolled in the study. The data were searched from the patients' medical records, i.e., age, sex, levels of spinal fracture, and causes and outcomes of treatment. The participants presenting TL spine fracture were measured using kyphotic or Cobb angle and identified configuration of fracture from a plain film (TL spine AP-lateral).

The patients were divided in two groups. The percutaneous pedicle screw fixation or the PPSF group constituted the study group while the open splint muscle long segment pedicle screw fixation or the OPSF group constituted the control group. Neither group showed decompression or posterior spinal fusion, and both used an indirect reduction technique in the prone position. A distraction device was applied in the field of surgery and controlled precise operation using fluoroscopy.

The incision using the PPSF technique was nearly out bounder of pedicle 15 mm in length and was checked with fluoroscope in the AP view. The next step was splitting the paraspinal muscle using a small incision to check position of the facet joint. Then a cannulated awl was applied at the outer cortex to insert a guide wire. The guide wire was passed through inside the bone and rechecked with fluoroscopy in the AP and lateral views. When it stayed in a precise position, cannulated tap was applied to make the entry point at the pedicle. The pedicle screw was inserted after removing the guide wire and its position was checked using fluoroscopy. When all pedicle screws were inserted, the proper lengths rod of both sides were replaced. After rechecking the lordotic curve of rods, the nuts were locked above all pedicle screws.

For the OPSF technique, the standard midline longitudinal posterior approach was applied from the upper to lower levels of the pedicle. Wiltse's approach was used to split between the longissimus and multifidus muscles. The screw was inserted using a normal technique and the screw was rechecked using fluoroscopy in AP

and lateral views. The proper lengths of rods were bended and applied, then a nut was inserted.

The measurement technique was used to evaluate the magnitude of the kyphotic deformity, measuring the angle between the inferior endplate of the vertebrae above and the superior endplate of the vertebrae below the fracture vertebrae body.

The data were collected from patients' medical records such as blood loss, length of stay and postoperative pain days 1 and 3 using the visual analogue scale (VAS). The pre- and postoperative kyphotic angles were measured and calculated for kyphotic angle reduction. Data were presented in mean, standard deviation (SD), frequency, percentage and the independent t-test was used to test between the two approaches.

Results

From January 2017 to December 2019, demographic data of 54 thoracolumbar fractures operated at Rayong Hospital showed the mean of age was 32.35 years (SD=8.52), mostly male (29, 59.2%). In addition, configurations of spinal fractures were burst (39, 72.22%), and compression (15, 27.78%). In addition, the levels of the TL fractures were as followed: T11 level (7, 12.96%), T12 level (19, 35.18%), L1 level (20, 37.04%) and L2 level (8, 14.82%). Finally, causes of fractures included fall from height (29, 53.70%), traffic accident (19, 35.18%) and machine contusion (6, 11.12%). Patient demographic data between the PPSF and OPSF groups did not significantly differ (**Table 1).**

Table1. Patient demographic data of the percutaneous pedicle screw fixation and open pedicle screw fixation groups (N=54)

data	PPSF (N=23)	OPSF (N=31)	*p*-value*
Age(year)	31±9	34±8.16	0.56
Gender			
male	11 (47.82%)	23 (74.19%)	0.13
female	12 (52.18%)	8 (25.81%)	
Characteristic of fracture			
Burst Fracture	17 (73.91%)	22 (70.96%)	0.63
Compression Fracture	6 (26.09%)	9 (29.04%)	
Level of fracture			
T11	1 (4.35%)	6 (19.36%)	0.13
T12	10 (43.48%)	9 (29.03%)	
L1	9 (39.13%)	11 (35.48%)	
L2	3 (13.04%)	5 (16.13%)	
Causation of fracture			
Fall from height	11 (47.82)	18 (58.06)	0.51
Traffic accident	10 (43.47)	9 (29.03)	
Machine contusion at back	2 (8.71)	4 (12.91)	

Percutaneous pedicle screw fixation (PPSF), Open pedicle screw fixation (OPSF) *Independent t-test

Preoperative kyphotic angle of the PPSF and OPSF groups were 27.52±2.92 degrees and 27.97±2.76 degrees, respectively with no significant difference. Postoperative kyphotic angles of the PPSF and OPSF groups were 3.09±0.79 and 3.10±0.79 degrees, respectively, without significant difference (Table 2). The average kyphotic angle reduction of the PPSF and OPSF groups was equal at 24 degrees.

As shown in Table 3, using VAS, postoperative pain was evaluated at the first post-operative day of both groups. The VAS of the PPSF and OPSF groups were 6.43±0.94 and 6.61±0.98, respectively. Furthermore, the pain levels at day 3 of both techniques were 2.78±0.90 and 2.94 ±0.85, respectively. As a result, the average pain level of both groups between days 1 and 3 did not significantly differ. In addition, the length of stay of the PPSF and OPSF groups were 6.04±1.10 and 10.90±0.97 days, respectively (p=0.98). On the other hand, duration of post-operative day of both groups significantly differed at 3.09±0.59 and 6.16±1.00 days, respectively.

For intraoperative period, operative time of both groups were 68.3±7.32 and 66.71±6.59 min, respectively (p=0.23). However, blood loss of both groups significantly differed at 44.35±15.02 and 466.13±87.92 mL, respectively.

Complications

Complications occurring among surgery cases included improper screw in the PPSF group (three cases) but none occurred in the OPSF group. However, this problem could be solved using fluoroscopy assisted without neurological deficit.

Discussion

Fixation of the thoracolumbar spinal fracture using OPSF has been used substantially and constitutes a standard method. However, a new procedure to fix comprises the PPSF a considerably popular technique to correct deformity of the spine including unstable thoracolumbar fracture. The advantage of this new method includes minimizing injury to the musculo-tendinous

Table2. Results of kyphotic angle comparing between the PPSF and OPSF groups

data	PPSF (N=23) mean±SD	OPSF (N=31) mean±SD	p-value*
Pre-operative kyphotic angle	27.52(2.92)	27.97(2.76)	0.90
Post-operative kyphotic angle	3.09(0.79)	3.10(0.79)	0.88
Kyphotic angle reduction	24.43(2.74)	24.87(2.55)	0.79

Percutaneous pedicle screw fixation (PPSF), Open pedicle screw fixation (OPSF) *Independent t-test

Table3. Results of outcome comparing between the PPSF and OPSF groups

data	PPSF (N=23)	OPSF (N=31)	p-value*
Postoperative pain at Day 1	6.43±0.94	6.61±0.98	0.56
Postoperative pain at Day 3	2.78±0.90	2.94±0.85	0.94
Length of stay (day)	6.04±1.10	10.90±0.97	0.98
Duration of post-operative day	3.09±0.59	6.16±1.003	0.04
Duration of surgery (min)	68.3±7.32	66.71±6.59	0.23
Blood loss during surgery (mL)	44.35±15.02	466.13±87.92	0.01

Percutaneous pedicle screw fixation (PPSF), Open pedicle screw fixation (OPSF) *Independent t-test

unit, reducing blood loss, decreasing length of stay and lessen postoperative pain. [7-13]

This study compared the PPSF with OPSF techniques wherein reduced blood loss was significantly observed ($p<0.01$). Moreover, the number of postoperative days decreased significantly ($p< 0.05$) as in other related studies. [9, 10, 18, 19] However, lengths of stay of both groups did not differ due to insufficient operative rooms. For this reason, pre-operative time differed for each person.

Regarding the measured kyphotic angle, the PPSF group was corrected 27.52 to 3.09 degrees while the OPSF group was corrected 27.97 to 3.10 degrees. Both were not divergent as in related studies. [9,10,18,22] In addition, duration of surgery of both methods did not differ similar to those of Dong et al. and Grossbach et al. [20,24] In contrast to other studies [9,18,25], the PPSF revealed shorter operative time than that of the OPSF group; nonetheless, duration of surgery might have been related to experiences of surgeons as well as the use of applied instruments.

Pain levels reported at the first operativeand third operative day did not differ although a related study reported that the PPSF group had pain scores lower than those of the OPSF group. [10,12,18,20]

However, McAnany et al.[9] showed similar results as this study. This study encountered some limitations, i.e., the small sample size could not clarify the difference of postoperative pain which could have occurred. In addition, the instrument used for percutaneous fixation could have increased surgery costs; however, benefits were obtained, i.e., reduce blood loss and lower duration of hospital stay.

Conclusion

The PPSF technique reduced blood loss and decreased length of hospital stay. Nevertheless, both techniques did not differ in terms of postoperative pain, kyphotic angle reduction and surgery duration.

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ACTIVITY OF TRIAZOLES AND ECHINOCANDINS AGAINST CANDIDA BLOODSTREAM ISOLATES AT PHRAMONGKUTKLAO HOSPITAL, THAILAND

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Abstract

Background: Candidemia is a major cause of morbidity and mortality which can be treated using antifungal agents, triazoles and echinocandins.

Objectives: We aimed to determine *Candida* species and their sensitivities to triazoles (fluconazole, itraconazole, voriconazole, and posaconazole) and echinocandins (caspofungin, micafungin, and anidulafungin) among patients with candidiasis to guide future treatment of patients with candidemia or invasive candidiasis.

Methods: All firstly isolated *Candida* spp. from patients admitted at Phramongkutklao Hospital, Bangkok, Thailand from January 2012 to December 2013 were included in this study. The antifungal susceptibility testing of *Candida* spp. isolates was assessed based on micro-dilution method.

Results: During the 24-month study period, a total of 66 *Candida* isolates from 66 patients were identified. Of the 66 isolates, 35 (53%) were *C. albicans*, 18 (27.3%) were *C. tropicalis*, 10 (15.2%) were *C. glabrata* and 3 (4.5%) were *C. parapsilosis*. Fluconazole resistant *Candida* isolates were found in *C. glabrata* (100%), *C. albicans* (14.3%), *C. tropicalis* (22.2%) and *C. parapsilosis* (66.7%). Most *Candida* spp. isolates were mainly susceptible to echinocandins (>90%). Notably, 10%-20% of *C. glabrata* isolates showed resistance to echinocandins.

Conclusion: Fluconazole, an empirical therapy, has been cautiously used due to resistant non-albicans *Candida* species especially, *C. glabrata*, *C. tropicalis* and *C. parapsilosis*. However, the emerging echinocandins resistant *C. glabrata* isolates need to be closely monitored.

Keywords: Triazoles, Echinocandins, *Candida* spp., bloodstream infection

Introduction

At present, the incidence of fungal infections has been increasing due to an increase of immunocompromised patients regarding cancer, organ transplantation and human immunodeficiency virus (HIV). *Candida* is one of the most common pathogenic fungi causing invasive and noninvasive infections.[1] A meta-analysis of epidemiological studies from Europe from January 2000 to February 2019 showed that invasive candidiasis, particularly candidemia, was associated with high morbidity and mortality rates.[2] A 30-day mortality rate of candidemia among hospitalized patients was approximately 40%. Candidiasis may cause infection in the liver, spleen and brain. *Candida* infections of the liver or spleen have been major complications among patients with neutropenic cancer.[1]

C. albicans is the most common *Candida* species isolated from clinical specimens. However, prevalence of nonalbicans *Candida* species has been increasing during the past decade. Among nonalbicans *Candida* species, prevalence of *C. glabrata* and *C. krusei* infections remained unchanged while those of *C. parapsilosis* and *C. tropicalis* infections have been increasing.[3] Prevalence of *C. glabrata* and *C. krusei* which harbor intrinsic resistance to triazole antifungul drugs, such as fluconazole [1] have been increasing from 4.9% in 2001 to 12.3% in 2010.[4] Thus, changing etiological agents may affect empiric treatment of invasive candidiasis.

From 1999 to 2002, a study at Siriraj Hospital, Thailand, revealed *Candida* infections totaled 44.6% while nonalbicans *Candida* infections totaled 55.4%.[5] The study showed that *C. albicans*, *C. tropicalis* and *C. parapsilosis* isolates were universally susceptible to fluconazole. However, itraconazole resistant isolates were detected from 16.7 to 19.8% whereas *C. glabrata* isolates were predominately resistant to fluconazole. From 2013 to 2015, a multi-center prospective observational study was conducted in seven countries in Asia/Pacific region; the results showed approximately one fourth of *C. tropicalis* isolates was not susceptible to fluconazole and voriconazole.[6] Moreover, approximately 5% of *C. glabrata* were nonsusceptible to caspofungin, micafungin and anidulafungin.

As described above, the study of antifungal susceptibility in Thailand was limited, so this study aimed to determine *Candida* species and activity of triazoles and echinocandins against *Candida* spp. bloodstream isolates to represent the situation of antifungal options for invasive candidiasis treatment.

Methods

This study was reviewed and approved by the Ethics Committee of the Medical Department of the Royal Thai Army (approval no. S029b/57).

Fungal strains

All strains of *Candida* spp. isolated from blood specimens of patients admitted at Phramongkutklao Hospital, Bangkok, Thailand from January 2012 to December 2013 were obtained. All firstly isolated clinical *Candida* spp. isolates in each patient were included. *Candida* isolates were cultured on blood agar at 35^{0}C and species of *Candida* colonies were identified using colony characteristics, germ tube test, and differentiation on CHROMagar accompanied with biochemical tests using a conventional method. In addition, all isolates were processed for matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) identification. The pure clinical *Candida* isolates were kept at -70^{0}C until the antifungal susceptibility test. The regrowth of kept isolates for further testing were cultured on blood agar at 35^{0}C from 24 to 48 hours to obtain a pure colony.

Determining antifungal susceptibility

Antifungal susceptibility testing of *Candida* spp. isolates was assessed using Sensititre® YeastOne (Thermo Scientific, IL, USA) based on micro-dilution method. The Minimal Inhibition Concentration (MIC) values of tested antifungals obtained from commercial kit test consisted of triazole antifungul drugs (fluconazole, itraconazole, posaconazole, voriconazole) and echinocandins, a class of antifungal drugs (caspofungin, micafungin and anidulafungin). The MIC that inhibited the growth of *Candida* spp. isolates was determined by changes in the Alamar blue color. For the quality control antifungal test, *C. parapsilosis*

ATCC 22019 and *C. krusei* ATCC 6258 were used as the reference strains according to the Clinical and Laboratory Standards Institute (CLSI) Version M27.

For the MIC breakpoint regarding susceptibility interpretation, we used the epidemiologic cut-off values (ECVs) and clinical breakpoints based on the CLSI M59 2nd edition and CLSI M60 version, respectively. In the case of lacking breakpoints based on CLSI, we used the clinical breakpoints and ECVs based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2019 guidelines.

Results

During a 24-month study period, 66 *Candida* specimens were clinically isolated. Of these, 35 (53%) were *C. albicans*. Other nonalbicans *Candida* isolates comprised the following: *C. tropicalis* (18, 27.3%), *C. glabrata* (10, 15.2%) and *C. parapsilosis* (3, 4.5%). Generally, *C. glabrata* isolates were mostly resistant to triazoles such as fluconazole (susceptible rate 0%) and posaconazole (susceptible rate 40%), except itraconazole (susceptible rate 90%) and voriconazole (susceptible rate 90%). *C. tropicalis* was resistant to fluconazole and itraconazole with resistant rates of 22.2 and 33.3%, respectively. However, *Candida* spp. isolates were mainly susceptible to echinocandins with susceptible rates from 80 to 100% (**Table 1**).

Not all *C. albicans* isolates were susceptible to fluconazole. The results of MIC range, MIC50 and MIC90 for fluconazole against *C. albicans* were as follow: 0.12 to >256 µg/mL, 1 µg/mL and 128 µg/mL, respectively. Moreover, MIC range, MIC50 and MIC90 for fluconazole against *C. tropicalis* were: 0.12 to 8 µg/mL, 1 µg/mL and 4 µg/mL, respectively. **Table 1** shows the ranges of antifungal MIC values against each *Candida* spp. isolate**.**

Discussion

Studies of *Candida* bloodstream isolates among patients admitted in tertiary care hospitals have been reported in Thailand. From 1999 to 2002, the prevalence of *C. albicans* comprised 44.6% while nonalbicans *Candida* spp. isolates accounted for 55.4% [5] Additionally, from 2004 to 2009, *C. albicans* and nonalbicans *Candida* accounted for 40.3 and 59.7%, respectively.[7] Prevalence of non-albicans *Candida* species over *C. albicans* was also similar to recent reports among countries in the Asia-Pacific region[6, 8]

This study reported on the species distribution of *Candida* bloodstream isolates among patients admitted in Phramongkutklao Hospital and their antifungal susceptibilities from 2012 to 2013. During the study period, 66 *Candida* isolates were identified. Our study showed that *C. albicans* was the most predominant species followed by *C. tropicalis*, *C. glabrata* and *C. parapsilosis*. In contrast to a study of *Candida* species isolated from patient blood samples at Siriraj Hospital, Bangkok, Thailand from January 2016 to December 2017, *C. tropicalis* was the most predominant, followed by *C. albicans*, *C. glabrata* and *C. parapsilosis*. Species distribution of *Candida* spp. directly affected the optimal candidemia treatment. Thus, the close monitoring and surveillance in each hospital setting was important to appropriately design institutional guidelines for empiric treatment of invasive *Candida* infection.

According to 2016 clinical guidelines to manage candidiasis by the Infectious Diseases Society of America, either nonneutropenic or neutropenic patients, receiving a diagnosis of invasive candidiasis, are strongly recommended to undergo echinocandins treatment as first line empirical therapy. However, fluconazole should be used as an alternative drug in the case of non-critically ill or nonsuspected infection with fluconazole-resistant *Candida* spp., especially *C. krusei* or *C. glabrata* infections.[10] Our study showed that *C. glabrata*, accounted for 15% of all *Candida* bloodstream isolates, and was universally resistant to fluconazole. Moreover, fluconazole-resistant *Candida* spp. were detected in *C. albicans* (14.3%) and *C. tropicalis* (22.2%) isolates. Additionally, a recent study using *Candida* spp. isolated from blood samples collected from 2016 to 2017 reported that fluconazole resistance was significantly increased in *C. tropicalis* (37.8%). [11] Thus, treatment using fluconazole was concerned for fluconazole-resistant *C. tropicalis*.

Table 1. Minimum Inhibitory Concentration (MIC) distribution and susceptible rate (%) among *Candida* spp. isolates (N=66)

Antifungals	MIC (µg/mL)																	Susceptible rate (%)	Susceptible breakpoint (µg/mL)
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256		
Fluconazole																			
Candida albicans (n=35)	-	-	-	-	3	12	1	10	4	-	1	-	1	-	1	-	2	85.7	≤2 [a]
Candida tropicalis (n=18)	-	-	-	-	2	1	2	9	-	3	1	-	-	-	-	-	-	77.8	≤2 [a]
Candida glabrata (n=10)	-	-	-	-	-	-	-	-	-	-	-	4	4	2	-	-	-	0	≤0.002 [b]
Candida parapsilosis (n=3)	-	-	-	-	1	-	-	-	-	2	-	-	-	-	-	-	-	33.3	≤2 [a]
Itraconazole																			
Candida albicans (n=35)	-	1	10	10	7	6	1	-	-	-	-	-	-	-	-	-	-	60	≤0.064 [b]
Candida tropicalis (n=18)	-	1	-	4	7	3	3	-	-	-	-	-	-	-	-	-	-	66.7	≤0.125 [b]
Candida glabrata (n=10)	-	-	-	-	-	-	2	7	-	-	-	1	-	-	-	-	-	90	≤4 [c]
Candida parapsilosis (n=3)	-	1	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	66.7	≤0.125 [b]
Voriconazole																			
Candida albicans (n=35)	17	3	3	8	3	-	-	1	-	-	-	-	-	-	-	-	-	97.1	≤0.12 [a]
Candida tropicalis (n=18)	3	-	3	8	4	-	-	-	-	-	-	-	-	-	-	-	-	100	≤0.12 [a]
Candida glabrata (n=10)	-	-	-	-	-	3	6	-	-	-	1	-	-	-	-	-	-	90	≤1 [d]
Candida parapsilosis (n=3)	1	-	-	1	-	-	1	-	-	-	-	-	-	-	-	-	-	66.7	≤0.12 [a]
Posaconazole																			
Candida albicans (n=35)	1	12	5	1	8	3	-	4	1	-	-	-	-	-	-	-	-	54.3	≤0.064 [b]
Candida tropicalis (n=18)	1	-	-	1	5	7	-	4	-	-	-	-	-	-	-	-	-	11.1	≤0.064 [b]
Candida glabrata (n=10)	-	-	-	-	-	-	-	4	-	4	1	-	-	-	-	-	-	40	≤1 [d]
Candida parapsilosis (n=3)	1	-	-	1	-	-	1	-	-	-	-	-	-	-	-	-	-	66.7	≤0.064 [b]
Caspofungin																			
Candida albicans (n=35)	-	-	15	15	5	-	-	-	-	-	-	-	-	-	-	-	-	100	≤0.25 [a]
Candida tropicalis (n=18)	-	-	13	1	4	-	-	-	-	-	-	-	-	-	-	-	-	100	≤0.25 [a]
Candida glabrata (n=10)	-	-	-	3	5	1	-	1	-	-	-	-	-	-	-	-	-	80	≤0.12 [a]
Candida parapsilosis (n=3)	-	-	1	-	1	-	1	-	-	-	-	-	-	-	-	-	-	100	≤2 [a]

Table 1. Minimum Inhibitory Concentration (MIC) distribution and susceptible rate (%) among *Candida* spp. isolates (N=66) (ext.)

Antifungals	MIC (µg/mL)																	Susceptible rate (%)	Susceptible breakpoint (µg/mL)
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256		
Micafungin																			
Candida albicans (n=35)	12	10	11	1	-	-	1	-	-	-	-	-	-	-	-	-	-	97.1	≤ 0.25[a]
Candida tropicalis (n=18)	1	9	4	4	-	-	-	-	-	-	-	-	-	-	-	-	-	100	≤ 0.25[a]
Candida glabrata (n=10)	-	9	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	90	≤ 0.06[a]
Candida parapsilosis (n=3)	-	-	1	-	-	-	-	1	1	-	-	-	-	-	-	-	-	100	≤ 2[a]
Anidulafungin																			
Candida albicans (n=35)	-	8	11	4	9	0	0	2	1	-	-	-	-	-	-	-	-	91.4	≤ 0.25[a]
Candida tropicalis (n=18)	-	7	5	5	1	0	0	0	0	-	-	-	-	-	-	-	-	100	≤ 0.25[a]
Candida glabrata (n=10)	-	0	9	0	0	1	0	0	0	-	-	-	-	-	-	-	-	90	≤ 0.12[a]
Candida parapsilosis (n=3)	-	0	0	1	0	0	1	0	1	-	-	-	-	-	-	-	-	100	≤ 2[a]

For the MIC breakpoint for susceptibility interpretation, [a] clinical breakpoints were based on the Clinical and Laboratory Standards Institute (CLSI); [b] epidemiologic cut-off values were based on CLSI; [c] clinical breakpoints were based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST); [d] and epidemiologic cut-off values were based on the EUCAST.

Consequently, this study showed over 80% of *Candida* spp. isolates remained susceptible to caspofungin, micafungin, and anidulafungin. As a result, echinocandins seemed to be the preferable choice for *Candida* bloodstream infection. However, 20% of *C. glabrata* isolates were resistant to caspofungin compared with 5% reported from countries in the Asia/Pacific region.[6] Thus, further studies need to closely monitor the echinocandins resistant Candida species when echinocandins has been used as empirical therapy.

The oretically, MICs to echinocandins against *C. parapsilosis* usually tend to be higher due to intrinsic resistance that should lead to less successful treatment by echinocandins. *C. parapsilosis* isolates still comprised echinocandins susceptible strains. In Spain, among 200 episodes of *C. parapsilosis* bloodstream infection, initial use of an echinocandin-based regimen had no impact on clinical failure.[12] Thus, echinocandins remains a preferably empiric choice regarding *C. parapsilosis* infection as one of the etiologic candidemia.

In this study, results were obtained from in vitro assay of antifungal activity against identified *Candida* spp. Practically, for each healthcare setting, selection of antifungal therapy has to be based on *Candida* species identification, antifungal susceptibility pattern, patients' severity of illness and underlying diseases, and co-administered medications including certain drugs prescribed in some patients' conditions.

Conclusion

Prevalence of *Candida* bloodstream species and the role of echinocandins as empirical therapy were investigated. Due to drug resistance of nonalbicans *Candida* spp., especially, C. glabrata, *C. tropicalis* and *C. parapsilosis,* fluconazole, an alternative choice for invasive candidiasis, should be used cautiously. Echinocandins remains the preferable choice for candidemia; however, the increase of echinocandins resistant *C. glabrata* isolates needs to be closely monitored.

Acknowledgments

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BIOCHEMICAL FINITE ELEMENT ANALYSIS OF THE LOCKED KIRSCHNER WIRE SYSTEM VERSUS VOLAR PLATE FIXATION OF DISTAL RADIUS FRACTURE

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Abstract
Background: Volar locking plate (VP) and Kirschner wire (K-wire) fixations of distal end radius fractures are the most frequently used techniques that produce similar long term clinical results. However, inadequate fixation strength of the K-wire may cause pin loosening or migration. Although these complications can be prevented by immobilization, joint stiffness and a prolonged recovery period can occur.
Objective: Herein, a technique that provided more stability, allowing immediate motion after fixation by linking the K-wires into a single system (locked K-wire system) was proposed.
Methods: We evaluated biomechanical responses of the locked K-wire system and a VP in extra-articular distal radius fracture models AO/OTAa type 23A2 and 23A3 using three-dimensional finite element analysis. All models were tested under axial, bending, and torsional loads.
Results: From the simulation results, the total displacement was greater in the dorsal wedge fracture than that from the simple fracture under all loads for both fixation systems. The locked K-wire system and the VP could withstand immediate physiologic load with maximum displacements of 1.15 mm and 1.39 mm, respectively.
Conclusion: Considering the immediate physiologic load resistance and the ability to preserve its position during the bone-healing period, the locked K-wire system might be used as an alternative to fix distal radius fractures.

Keywords: Finite element analysis, Distal radius fracture, Volar plate, K-wire, Locked K-wire, Biomechanical study

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Introduction

Distal radius fractures are one of the most common skeletal injuries; their incidence has been increasing worldwide. A shift in favor of surgical treatment has taken place in general. [1–3] The direct economic costs of distal radius fractures in the US are more than USD 480 million annually. [4] Several surgical options are available for distal radius fractures, and the cost of the treatment depends on the choice of fixation. [5] The two most common surgical techniques are Kirschner wire (K-wire) and volar locking plate (VP) fixations. [5,6] VP provides stronger fixation that facilitates early motion and early return to work which is still considered more invasive, time-consuming and delays wound healing[5–9]

K-wire fixation is a well-established procedure with many advantages including minimal invasion, rapid application and lower cost of treatment. However, one disadvantage includes the fixation strength, the most concerning drawback, leading to pin loosening or migration. Commonly surgeons resort to immobilization which may lead to stiffness and prolonged recovery. [7, 10, 11] To overcome this limitation, we linked all K-wires that were fixed to a fracture site in one system (locked K-wire system). No further immobilization was needed so patients could immediately perform early range of motion exercises. Although clinical studies comprise the optimum investigations of differences between surgical options, unfortunately, confounding variables are found that are difficult to identify and isolate. Cadaveric studies are limited by the shortage of specimens. Meanwhile, finite element (FE) analysis is commonly used in biomechanical studies because parameters can be adjusted in a more controllable manner. [12, 13] Thus, we used three-dimensional (3D) FE analysis to investigate the biomechanical responses of the VP and locked K-wire systems with two most common fracture patterns of the distal radius under three physiologic load conditions, i.e., bending, axial, and torsional load.

Methods

This study was conducted under Police General Hospital Ethics Committee No. 111/2562. Informed consent was obtained from the subjects enrolled in the study.

Finite element modeling

Computed tomography (CT) was used to scan the right radius bone of a healthy 60-year-old Thai man in a neutral position. Images were taken in the transverse plane at series of 80 scans at 1 mm intervals. The contours of the cancellous and cortical bone were extracted from the set of CT images and imported into Mimics 10.01 (Materialize, Leuven, Belgium) to create three-dimensional radius geometry. To simplify calculations, all soft tissues were excluded. These data were then imported into PowerSHAPE 2016 (Delcam Plc, Birmingham, UK) to create a computer-aided design (CAD) model suitable for meshing. Afterward, a CAD file was used to mesh an FE model in an FE package (ANSYS, V 15.0, Ansys Inc., Canonsburg, PA, USA) to generate the solid bone model. The summary of model creation is shown in **Figure 1**.
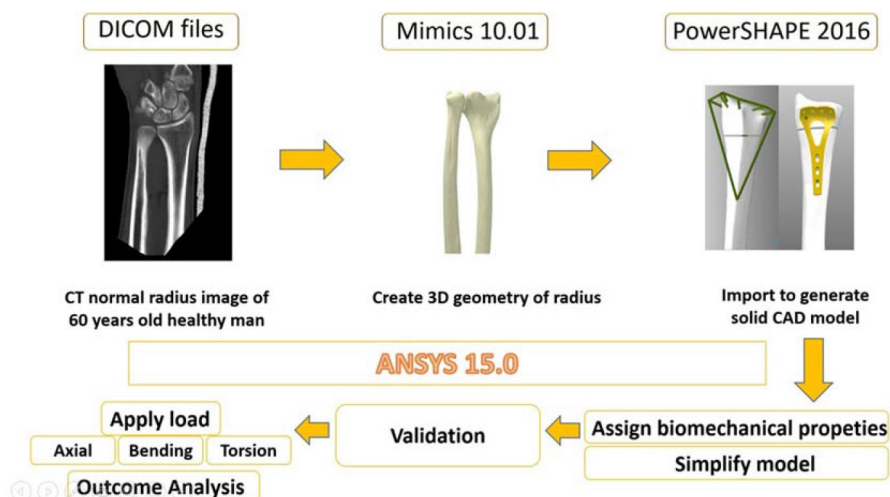

Figure 1. Approach of FE analysis

To simulate the distal radius fracture, the fracture pattern was assumed to be one of two types, namely, metaphyseal or dorsal wedge fractures, according to the 23-A2 classification of the AO surgery reference (**Figure 2**). [14] First, an undisplaced fracture with impaction but no abnormal palmar or dorsal tilt was made with a fracture gap of 1 mm, 25 mm proximal from the distal end of the radius using an idealized planar cut (**Figure 2a**). Then a simple extra-articular with dorsal tilt (Colles fracture) was made with a cut having a 35° wedge toward the dorsal site, 25 mm proximal from the distal end of the radius using an idealized planar cut (**Figure 2b**). Two models were built to compare different fixation techniques, including VP and locked K-wire systems. In the VP model, the plate was created using Titanium Variable Angle LCP Two-Column Volar Distal Radius Plate (2.4, six holes, a width of 22 mm, a length of 54 mm, six head holes, three shaft holes, right, DePuy Synthes, USA) as a template. Thread details of the locking screws were excluded from our model. The screws were bonded with the bone to simulate conditions occurring after osteo-integration. All screws were bonded with the plate to simulate thread clenching with the plate.

For the locked K-wire system, K-wires were created using a stainless-steel K-wire with a diameter of 1.6 mm as a template. Each K-wire was modeled with linear-elastic, 8-noded brick-shaped elements. The locked K-wire system was composed of seven K-wires. The first two K-wires started at the radial styloid tip and passed through the fracture site to the opposite cortex. Three other K-wires were introduced from the dorsal cortex of the lunate fossa and passed through the fracture site to the volar cortex. One K-wire passed parallel just below the articular surface in the coronal plane. The other one was fixed at 10 cm proximal to the articular surface. All protruding parts of the K-wires were assembled in a single unit using the last K-wire as the core (**Figure 3**).

a
b

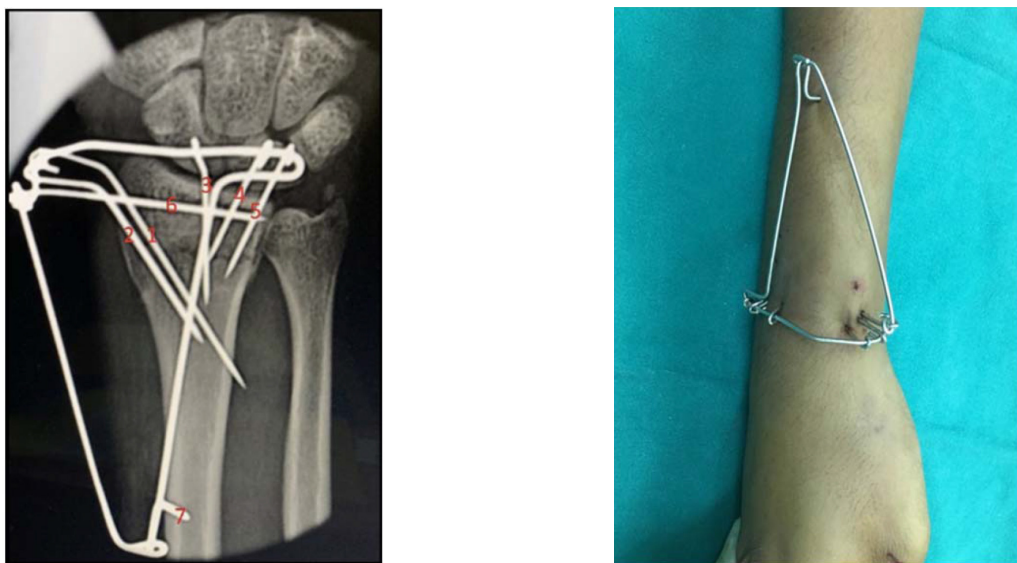**Figure 2.** Radius model: (a) simple fracture (23A2); (b) dorsal wedge fracture (23A3)

Figure 3. Locked K-wire system consisting of seven pins

Convergence test and model validation

For model verification, a convergence test was used to guarantee that our numerical model reached the converged results and that no further mesh refinement was necessary. The radius FE models were meshed with 1-, 2-, and 3-mm element sizes using quadratic tetrahedral elements (Solid 92) in ANSYS. The cancellous and cortical bones were considered isotropic, linear, and elastic, with elastic moduli of 1.3 GPa and 17 GPa, respectively. Poisson's ratio was set to 0.3. [13, 15] A surface-to-surface gluing contact parameter was inserted at the interface of the cortical bone and cancellous bone, to prevent movement between the meshes of these regions at the interface. The elastic modulus and Poisson's ratio of the titanium plates and screws were 110 GPa and 0.3, respectively. [16]

The proximal end of the model was fixed, and an axial force (compression force) of 100 N was applied at the center of the distal end radius. The maximum displacement, maximum strain, and maximum von Mises stress value at the fracture gap were evaluated for convergence in all models. The tolerance level was set within 5%.

To validate our FE model, the converged results from the model were compared with the experimental results from the fresh cadaveric study and prior FE of distal radius studies. [8, 17]

Finite element analysis

To avoid numerical differences arising due to FE meshing, all models were derived from the same solid model with a single meshed pattern. The resulting FE model was meshed using a 2-mm element size after the convergence test. The element number totaled 58682, 59929, 62588, and 64027 for dorsal wedge fracture with VP, simple fracture with VP, dorsal wedge fracture with locked K-wire, and simple fracture with K-wire, respectively. For VP models, the plate was placed volarly just proximal to the watershed line. A minimal gap between the plate and the bony surface was left to represent the limitation of an actual bone surface. Screws were projected perpendicular to the plate through the bone. Six screws were placed to the head and

three were filled in the shaft of the plate (the locking features were removed from the slots). The surface-to-surface gluing contact was inserted at the volar plate-screw and screw-bone. As for the interaction of the K-wire system, the frictional values between K-wire and cortical and cancellous bone were 0.5 and 0.3, respectively. [18, 19] The K-wires were glued to each other.

Biomechanical responses from the VP and the locked K-wire system were investigated under the simulation of the magnitudes and directions of physiologic loads during active wrist joint movement of daily activities. Bending and torsional loads of 1 Nm and an axial load of 100 N, under the boundary condition and the material properties used in the convergence test, were applied at the end of the distal radius. [8, 13, 20] Four FE models, two fracture patterns and two fixation methods, were simulated under three load conditions. To study the load transmission pattern and loosening potential of the fixation, the von Mises stress values, and maximum displacements of the distal radius were recorded.

Results

To avoid geometry distortions, the FE model was meshed using an element size of 2 mm. As for the convergence assessment, the differences in the maximum von Mises stress, displacements, and strain values were less than 5% in our models. For model validation, we compared with the fresh cadaveric distal radius experimental results of the compressive stiffness of 379 ± 146 Nmm^{-1} [17] and from the finite element study of the distal radius of 494 Nmm^{-1} [18], while our result was 478 Nmm^{-1}, indicating that the radius FE model was reliable for further analysis.

The maximum displacements of all models were documented to evaluate the responses of immediate motions after the operation. The dorsal wedge pattern fracture exhibited a larger displacement than the simple fracture regardless of fixation technique. The VP had a larger displacement than the locked K-wire system under the bending force but smaller displacement under axial and torsional forces for both fracture patterns. The maximum displacements of the

locked K-wire system and the VP found in the dorsal wedge pattern were 1.15 mm (torsional force) and 1.39 mm (bending force), respectively (**Figure 4**).

The stress distribution was similarly concentrated around the fracture gap area in all simulated models (**Figure 5**). Regardless of the fracture pattern, the maximum von Mises stress of the VP (σ-VP Max) was the highest under the bending load and the lowest under the compression load. The maximum von Mises stress of the locked K-wire system (σ-LKW Max) was the highest under the torsional load and the lowest under compression load. The locked K-wire system revealed lower stress than the VP only under the bending force (**Figure 6**).

Discussion

In a related study, a similar method of linking K-wires was used, but a metal clamp was used as a linkage in the setting of a hand fracture. Based on the mechanical analysis, that system had significantly greater resistance to flexion and traction loads than a normal K-wire fixation.[21] However, the clamp was not easily available. The simulation results showed that both constructs can withstand immediate postoperative functional loads. The displacement, stiffness and stress values of the VP were similar to those of related studies. The moment force was higher under bending and torsional loads; thus, creating significantly higher displacement and stress values compared with those under axial load. [19, 23]
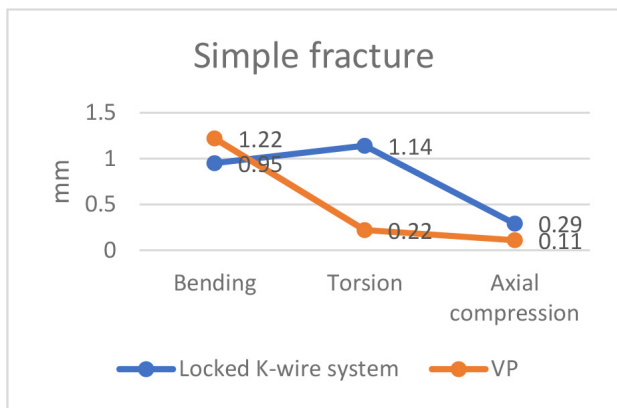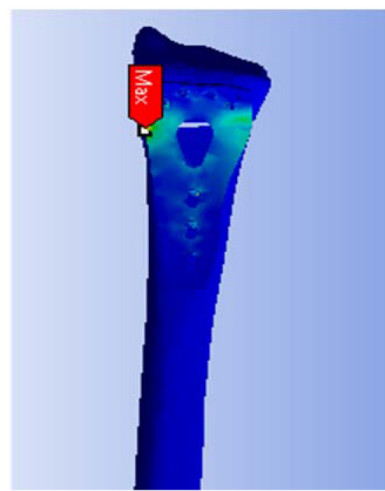

a
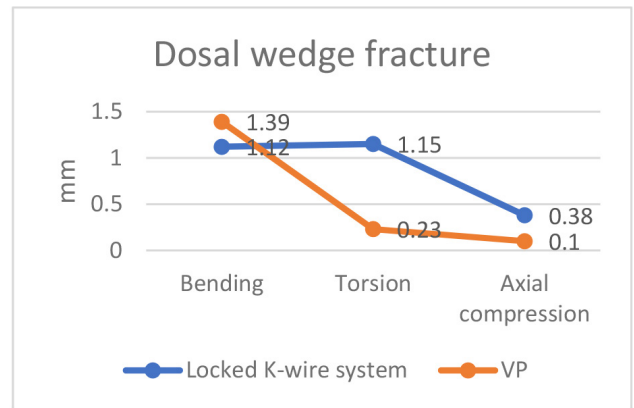
b

Figure 4. Displacement at the fracture site for all simulated models: (a) simple fracture model; (b) dorsal wedge fracture

a

b

Figure 5. Stress distribution and σMax: (a) locked K-wire system; (b) VP system.
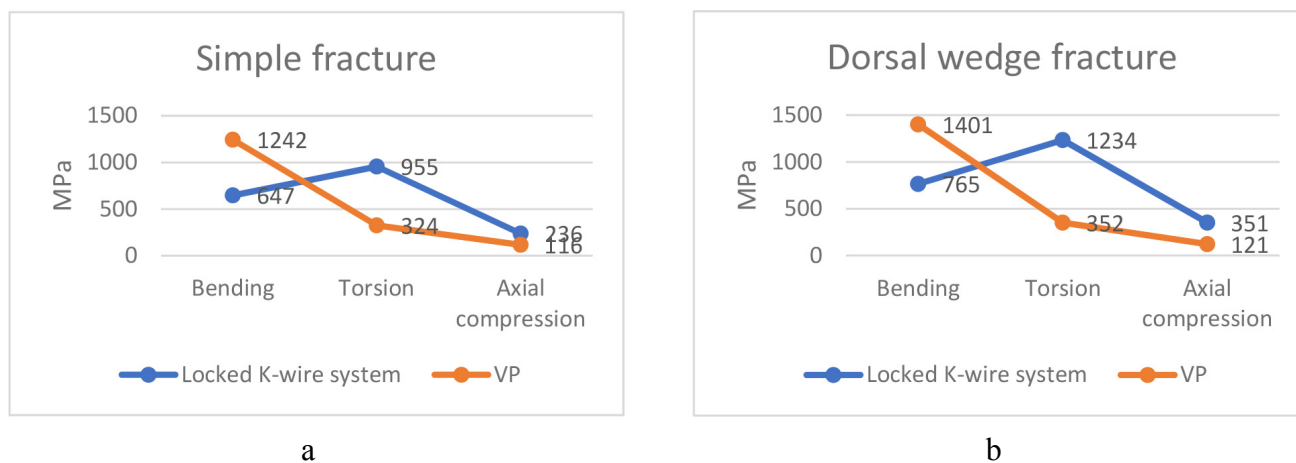
a
b

Figure 6. Maximum von Mises stress values for all simulated models: (a) simple fracture model; (b) dorsal wedge fracture.

The VP was a stable fixation for the dorsal wedge fracture that had slightly higher displacement and stress values compared with the simple fracture. [19]

The locked K-wire system had smaller displacement under the bending load conditions. This phenomenon is explained by the structure of the locked K-wires system, which is mainly constructed in the dorsal-volar position, and the increased moment arm, so the resistance to the bending force was enhanced. The largest displacement of the locked K-wire, caused by the torsional force (1.14 mm in the simple fracture and 1.15 mm in the dorsal wedge fracture), was within acceptable limits (**Figure 4**).

When comparing the two systems, the locked K-wire system had smaller displacement and σ-Max than those of the VP system under the bending load conditions. The bending force is considered the most crucial because it tends to separate the fragments, preventing fracture healing. [16, 13, 24] Thus, the locked K-wire system could be considered to exhibit excellent fixation properties.

The highest stress distribution for all the models was localized around the fracture gap, similar to a related study, which could be explained by the load-bearing property of the fixation principle. [19]

Therefore, we used the same principle to design the locked K-wire system without any special instruments. Three reasons for constructing the locked K-wire system included 1) reducing articular surface, 2) supporting radial height, inclination, and dorsovolar tilt, and 3) providing distraction force to resist compressive force.

Hence, we used a construct of seven K-wires. The first and second K-wires were used to maintain the radial inclination and height. The next three K-wires were used to perform fine reduction and support the axial load from the articular surface. The sixth K-wire was used to support the articular surface, while the seventh wire was used as a lever to generate a distraction force by locking the extrusion parts of the other K-wires onto itself (**Figure 3**). The linkage technique of K-wires also played an essential role in the strength of the construct. The protruded first six K-wires were made into a small loop in the sagittal plane for the last K-wire to pass through. Thus, better resistance to the dorsovolar bending force of wrist flexion and extension, considered the most important deforming force, was achieved. Then, all the loops were tightened such that the K-wires could not be individually moved, and an ideal single-unit system could be achieved, similar to locking plates.

This study was also designed to compare the biomechanical responses of VP and locked K-wire systems during axial, bending, and torsional loads comprising physiological loadings in daily life activities. [12, 22] The radius model in our study was simulated from a normal bone even though the distal radius fracture was more common in an osteoporotic population. The reason was the variety of the severities of osteoporosis, which consequently changes the elastic modulus and Poisson's ratio. With lower stiffness (from osteoporosis), the biomechanical responses would show a similar tendency; and hence, the results could be applied to osteoporosis cases. [13]

In the clinical setting, once K-wires are linked in the locked K-wire system, we need to tighten every linkage so that it would be nearly impossible to remove a wire individually. The locking facilitates the use of the system and encourages early motion exercises.[7] Even though the locked K-wire system might not be superior to the VP system in every aspect, it remains sufficiently strong to withstand the physiologic force with the additional advantage of the ability to maintain bony alignment until bone union. The locked K-wire system is considered to be a good alternative for distal radius fracture fixation.

Nonetheless, this study encountered limitations of the simplification of numerical convergence considerations. These included the load conditions, which may not represent the realistic tendon force on the wrist joint, implant, and model simplification including bone material properties, screw geometry, and the strength of the linkage between K-wires. These may vary practically depending on the patient and the surgeon's experience which may possibly influence the response accuracy.

Conclusion

Even though the VP system is considered to be the fixation of choice with superior biomechanical properties for distal radius fracture, with appealing biomechanical responses, cost-effectiveness, and the advantage in preventing wire migration, the locked K-wire system proved to be an alternative fixation technique in treating distal radius fractures. One of the main drawbacks of the proposed approach was that some parameters had to be simplified using finite element analysis, which may not truly represent the strength of the fixation. Therefore, in a future study, an actual prototype of the locked K-wire system should be applied to a cadaver to evaluate the biomechanical properties precisely.

Acknowledgment

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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ESOPHAGEAL IMPACTION OF FERTILIZED DUCK EGG ALBUMEN (HARDENED BALUT WHITE) IN A TERTIARY GOVERNMENT HOSPITAL IN THE PHILIPPINES: A CASE SERIES

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Abstract
Background: This study described the clinical profile of patients who developed esophageal impaction after ingesting the hardened white portion (albumen) of a fertilized duck egg (colloquially termed *balut*).
Methods: A review of patients with foreign body impaction of hardened *balut* egg white was performed. These patients were admitted in the emergency room from November 2013 to November 2018. Clinical features analyzed included age, sex, clinical signs and symptoms, imaging performed, operative findings and complications.
Results: In all, 18 patients were included in the review. Seventeen were male with a majority in the 20- to 40-year-old age range. Dysphagia and neck tenderness were the most commonly presented symptoms and physical examination finding, respectively. Twelve cases were successfully extracted via rigid esophagoscopy under general anesthesia, while one case was resolved through spontaneous ejection. The most common site of impaction was at the cervical esophagus. One third of patients undergoing extraction had minor noncircumferential esophageal abrasions.
Conclusion: Ingestion of the entire hardened *balut* white can lead to esophageal impaction, necessitating admission and operative management. Young males are commonly affected. Due to its intrinsic characteristics as a foreign body, its removal can prove challenging. Push technique and extraction (both via piecemeal and wholly) were found to be effective, and when performed correctly, minimized complications. Nevertheless, this condition may be prevented with health education.

Keywords: Esophageal impaction**,** Hardened white portion (albumen), Fertilized duck egg

Introduction

Esophageal foreign body impaction is one of the more common reasons for consults and referrals directed to an otorhinolaryngologist in the emergency room necessitating urgent operative management. Among adults, the most commonly ingested foreign body leading to impaction is food [1,2] containing food bolus, meat chunks or bones.[3–5]

Eating boiled fertilized duck egg (*balut*) is a shared practice in Asian culture. In the Philippines, *balut* is usually sold by local street vendors and eaten as a stand-alone snack. Traditionally, males believe it bestowed aphrodisiac properties when ingested, is deeply nourishing and an energy-giving source for females. [6,7] The cooked *balut* egg consists of four parts, the liquid (soup), the egg yolk, the chick embryo, and the hardened egg white (albumen) (**Figure 1**). All parts of the balut are eaten and consumers usually save the chick embryo for last. The hardened white is ingested as a matter of preference. Some first chew it into pieces then swallow. Others do not attempt to eat this part due to its tough consistency, while others consume the hardened *balut* white whole. Unfortunately, due to the albumen's peculiar shape and firmness, it has been known to cause esophageal impaction. Limited literature is available describing this phenomenon. A case

report of three patients was noted to provide some description regarding its removal.[8] Vietnam, Cambodia, Thailand and China share this particular food culture, but language barriers precluded the authors from performing thorough literature reviews in their respective local publications.

This study aimed to describe the clinical profile and characteristics of patients developing esophageal impaction after wholly ingesting the hardened white part (albumen) of a fertilized duck egg (*balut*), and to review its presentation, management, and outcomes among patients admitted at a tertiary university hospital in the Philippines from November 2013 to November 2018.

Methods

A review of medical records was conducted for all patients who attended for foreign body impaction of hardened *balut* white (HBW) from November 2013 to November 2018. Data collected included age, sex, clinical symptoms, physical examination findings, imaging performed, management or method of extraction performed, including esophageal level at which impaction was found, complications, and number of hospital days. Total patients were enumerated given the small size of the patient population.

Figure 1. Parts of a *balut:* (A) duck egg just removed from its shell. (B) hardened albumen (C) from left to right: chick embryo, yolk sac, hardened albumen

Data were encoded and analyzed using Stata 14 Software and presented in frequencies and percentages. The case series was approved by the hospital Health Research Ethics Committee.

Results

Demographics

Between November 2013 and November 2018, 1,367 consults were recorded for esophageal impaction in our institution. Three hundred sixty-five patients (26.7%) suffered from food-related impaction. Eighteen patients were identified as presenting esophageal impaction from HBW, which totaled 5% of food impactions. **Table 1** shows a summary of their clinical information. Seventeen were male. The ages ranged from 17 to 50 years old with more than two thirds of the patients (13/18) between 21 and 40 years.

Clinical signs and symptoms, and physical examination findings

The most commonly presented symptoms included dysphagia (12/18 or 66.7%), globus sensation (7/18 or 38.9%), increased salivation and drooling (6/18 or 33.3%), and neck pain (6/18 or 33.3%). Other elicited symptoms are detailed in **Table 1**.

Three of the 18 patients (16.7%) presented neck tenderness on palpation of the anterior neck, while the rest showed unremarkable physical examination. No associated erythema, or other signs of inflammation were observed. None of the patients presented a visible foreign body in the oropharynx, hypopharynx, and laryngeal inlet on flexible nasopharyngolaryngoscopy.

Imaging

Radiographs of the chest and neck soft tissue were ordered but only one revealed a retro-pharyngeal lucency. Two patients underwent modified barium swallow demonstrating filling defects. One was at the level of the 7th cervical vertebra, and the other at an area between the 1st and 2nd thoracic vertebra.

Treatment

Fourteen of the 18 patients (77.8%) completed the course of management, while four either went home against medical advice or absconded. One patient spontaneously ejected the HBW while the rest underwent rigid esophagoscopy under general anesthesia for extraction. The HBW was directly visualized in twelve cases, where eight

Table 1. Demographic and clinical profiles of patients presenting esophageal impaction after ingesting a hardened white portion (albumen) of a fertilized duck egg

Clinical Profile	Frequency (%) n=18
Age (years)	
0 to 10	0
11 to 20	2 (11.1)
21 to 30	8 (44.4)
31 to 40	5 (27.8)
41 to 50	3 (16.7)
51 and above	0
Sex	
Male	17 (94.4)
Female	1 (5.6)

Table 1. Demographic and clinical profiles of patients presenting esophageal impaction after ingesting a hardened white portion (albumen) of a fertilized duck egg (ext.)

Clinical Profile	Frequency (%) n=18
Symptoms	
Dysphagia	12 (66.7)
Globus sensation	7 (38.9)
Increased salivation	6 (33.3)
Neck pain	6 (33.3)
Vomiting	5 (27.8)
Odynophagia	5 (27.8)
Difficulty of breathing	3 (16.7)
Chest pain	2 (11.1)
Dysphonia	1 (5.6)
Treatment provided	
Rigid esophagoscopy with push technique	7 (38.9)
Rigid esophagoscopy with en bloc extraction	4 (22.2)
Rigid esophagoscopy with piecemeal extraction	1 (5.6)
Rigid esophagoscopy without extraction (no foreign body seen)	1 (5.6)
Spontaneous ejection and observation	1 (5.6)
No treatment (absconded or home against medical advice)	4 (22.2)
Esophageal level of foreign body	
Cervical esophagus[a]	8
Upper thoracic esophagus[b]	4
Middle thoracic esophagus[c]	0
Lower thoracic esophagus[d]	0

[a] 15 to 19 cm from upper central incisors; [b] 20 to 24 cm from upper central incisors; [c] 25 to 29 cm from upper central incisors; [d] 30 to 39 cm from upper central incisors [9]

were found at the cervical esophagus (15 to 19 cm from the upper central incisors) and four were found at the upper thoracic esophagus (20 to 24 cm from upper central incisors). In one case, no foreign body was noted on two passes of the esophagoscope reaching to the level of the lower esophageal sphincter, despite the patient's symptoms. The most common method of resolution was using push technique, which was provided among more than one third of patients (7/18 or 38.9%).

Complications

Four of the 12 patients undergoing esophagoscopy with extraction had minor esophageal noncircumferential abrasions on second pass esophagoscopy. None of the four showed profuse bleeding or necessitated a nasogastric tube insertion, but they were maintained on soft diet for one week. No major complications were noted. All patients were discharged within 1 to 2 days postoperatively.

Discussion

Foreign body ingestion is one of the more common cases for which emergent intervention by an otorhinolaryngologist is called upon. Among adults, food is the most common cause of esophageal impaction.[1–4] The nature of foreign bodies ingested may vary by region or country based on cultural nuances. This study described the clinical profile and management course of 18 patients who experienced esophageal impaction after ingesting the hardened white (albumen) of a fertilized duck egg (*balut*). Young males were the most commonly afflicted, which was consistent in the case report by Gonzales and Gonzales.[8] In their report, they stated that their patients may have had a history of alcohol intoxication. This was unsurprising as *balut* is a snack commonly accompanying intake of alcoholic beverages during street drinking sessions. [6,7]

Signs and symptoms of impaction for this particular foreign body does not appear to differ from other causes of food impaction with dysphagia and neck tenderness being the most common.[4,5] Wu, et al. (2011) reported that nearly all 326 patients included in their study reported dysphagia or foreign body sensation, while our study reported two thirds of patients having dysphagia and more than one third experiencing globus sensation. Results of imaging studies were also consistent with the related literature where plain radiographs were usually negative ranging from 60 to 85% of the time.[1,4,5] These estimates from related literature might even constitute an underestimation as they included radio-opaque foreign bodies such as coins and wires. The European Society of Gastrointestinal Endoscopy (ESGE) recommends against radiographic evaluation for nonbony food impaction. Barium swallow is also not recommended due to risk of aspiration in addition to serving as hindrance to endoscopic evaluation. [10] The role of imaging also occurs much less frequently in the setting of an obviously symptomatic patient.

The most common site of impaction of the HBW was at the cervical esophagus, followed by the upper thoracic esophagus, similar to other studies on esophageal foreign bodies, where 34 to 89% can be found in the proximal or cervical esophagus.[1,4,5] In one case, no foreign body was noted on esophagoscopy. This may be due to the spontaneous passage of the foreign body along the gastrointestinal tract before the procedure.

Removal of the HBW can be challenging, given its intrinsic properties. It has a smooth curved surfaces that may be difficult to securely grasp using standard forceps. On occasion, some areas of the HBW turn soft and friable, impeding attempts to remove the foreign body wholly. The cases that were managed operatively elucidated impaction removal in three distinct ways-rigid esophagoscopy using push technique, piecemeal extraction, and enbloc extraction of the entire hardened *balut* white. The push technique, or what we call in our institution as *aided ingestion*, where impacted food contents are gently guided past the lower esophageal sphincter into the stomach, is the primary method to treat food bolus impaction with a success rate of 90% [10] low quality evidence. In the study by Wu, et al. (2011), this technique was used among only 5.5% of patients, while in our review, more than one third of the 18 patients were successfully managed using this technique without complications. A major difference was the age of the studied population—the average age of the patients in Wu's study was 50 years old, while our cohort were all below 50 years old. The older population in Wu's study was associated with a higher prevalence in gastrointestinal tract abnormality with almost 65% of patients with food bolus impactions found to have esophageal stricture or carcinoma. The study by Vizcarrondo et al. (1983) showed a similar trend where 72% of food-related impactions subjects were older than 60. Available literature advises against blindly pushing impacted food bolus into the stomach among patients with pre-existing dysphagia or esophageal disease, as they have an increased risk for perforation [10-13], which was fortunately not the case in our cohort consisting mostly of young healthy males. Nevertheless, even when assessing the esophagus beyond the impacted food is impossible, as was the case in our institution due to some limitation in equipment, food boluses may be safely pushed into the stomach by breaking the bolus into smaller pieces.[10]

Piecemeal or enbloc extraction continues to constitute options for managing HWB especially in cases where significant resistance is encountered. However, enbloc retrieval is personally preferred by the authors as it ensures that no large chunk remains in the esophagus. Second pass esophagoscopy was performed at the end for all methods to ensure that no residual foreign body was left behind.

Although limited in sample size, this study illustrated the hardened *balut* white's unique qualities as a foreign body, as well as its implication in managing esophageal impaction. Several techniques may be employed, such as the push technique and extraction, whether via piecemeal or enbloc, which were all found effective. Regardless of technique used, all patients were without major complications in the immediate postoperative period and upon discharge from the hospital. Nevertheless, esophageal impaction from HBW is a preventable condition and steps should be taken to educate the younger male population regarding this.

Conclusion

Ingestion of the entire hardened *balut* white can lead to esophageal impaction, necessitating admission and operative management. Young males were commonly affected unlike the demographic profile seen in related studies, where patients 50 years and above were more commonly affected by food-related impaction. Due to its intrinsic characteristics as a foreign body, its removal can prove challenging. Push technique and extraction (both via piecemeal and wholly) were found to be effective techniques, and when performed correctly, minimized complications. Nevertheless, this condition may be prevented with health education.

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