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EDITORIAL STATEMENT

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Editorial Statement of Vajira Medical Journal: Journal of Urban Medicine

Anongnard Kason PhD, Lakhanawan Charoensuk PhD, Saiwasan Buathong PhD, Jitti Hanprasertpong MD

Editors,
Vajira Medical Journal: Journal of Urban Medicine

Vajira Medical Journal has been operating under the Faculty of Medicine Vajira Hospital of Navamindradhiraj University for 60 years. This journal publishes a wide range of academic works both within and outside the institute in Thailand. Recently, this journal was renamed from "Vajira Medical Journal" to **"Vajira Medical Journal: Journal of Urban Medicine (Vajira Med J)"**. The rebranding process not only sets the new name, but also gears for the scope of our journal. The identity of this journal focuses on basic or applied medical and health sciences research especially urban medicine field.

Regarding academic Thai ranking, the Vajira Med J is indexed in the journal database of the Thai-Journal Citation Index Centre: TCI for the first time in 2002. The Journal was certified as an academic journal (Tier 1) from 2012 until 2019. However, the journal has currently been classified as tier 2 by the TCI. From this issue with new image of the journal, we attempt to raise the level of this journal back to the tier 1 level and further to the international level. To ensure that high quality scientific works are contributed to the field of academic publication, the editors enforce a rigorous peer-review procedure along with strong ethical principles and standards. Moreover, we have such a strong commitment to this journal that we look forward to having the support of national/international authors and readers to join us in this great achievement in the future.

As Editors of the Vajira Medical Journal: Journal of Urban Medicine, we would like to take this opportunity to welcome all the authors and express our sincere desire to use this journal for communicating and sharing the ideas of readers and/or researchers in the medical (especially urban medicine) and health sciences.

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Original Article

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The Study of Pathological Findings in Medico-Legal Cases Positive for Urinary Methamphetamine in Thai Postmortem Cases

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ABSTRACT

OBJECTIVE: This study aims to study pathological findings in Thai postmortem cases who were positive for methamphetamine in urine and compare these findings to the control group which was negative for drugs of abuse.

METHODS: Retrospective study was conducted from autopsy reports and toxicological data of Thai postmortem cases between January 2018 and March 2020. The data were categorized into two groups including methamphetamine group and control group based on the detection of methamphetamine in urine. Sex, age and pathological findings were recorded in both groups. Chi-square test, Mann-Whitney U test and multiple comparisons with Games-Howell post-hoc test were performed where appropriate.

RESULTS: There were 85 methamphetamine cases with 170 in the negative control group. All study subjects were male. Average ages of these two groups were 46.71 and 45.38 years old. Heart weight in the methamphetamine group was significantly greater than in the control group ($p<0.05$). Histologically, the methamphetamine group showed significant myocardial hypertrophy and interstitial fibrosis compared with the control group ($p<0.01$). The presence of alveolar hemosiderin-laden macrophages in the methamphetamine group was significantly higher than in the control group ($p<0.001$). Coronary artery stenosis was considered adjusted with age. In the methamphetamine group, the stenosis of the left anterior descending artery (LAD) at greater than 50% was significantly detected in younger ages than in the control group ($p<0.05$).

CONCLUSION: Methamphetamine had an association with increased heart weight and LAD stenosis greater than 50% in younger age in Thai male cadavers.

KEYWORDS: coronary artery, heart, methamphetamine, Thai

INTRODUCTION

Methamphetamine is an amphetamine-type stimulant and the most prevalent drug found in Thailand. The United Nations Office on Drugs and Crime (UNODC) Report in 2019, listed Thailand in the top five countries where the highest amount of methamphetamine was seized[1]. Worasuwannarak et al. reported that methamphetamine was the most common drug detected in Thai medico-legal postmortem cases at 6.37% in 2018 and the trend was increasing compared to other drugs[2]. Thus, the impact of methamphetamine abuse on the physical and mental health of Thai people is also possibly increasing.

Methamphetamine has several negative effects on multiple organ systems, particularly the cardiovascular and central nervous systems.

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Previous studies detected cardiovascular system defects such as coronary atherosclerosis and cardiomegaly as a result of long-term methamphetamine abuse[3-6]. The prevalence of stroke in the young also increased in methamphetamine abusers[7-8]. However, these studies involved people from European countries, Australia and the United States of America (USA) and applying these findings to Thai people may be erroneous. Prasobsrikul et al. reported pathological findings in 61 Thai postmortem cases where methamphetamine was detected in biological samples submitted for toxicological analysis[9]. However, this study mainly focused on the analysis of blood methamphetamine concentrations and did not compare the pathological findings to a control Thai population group where methamphetamine was not detected.

To rectify this research lacuna, this study aims to compare pathological findings of Thai postmortem cases that were positive for only methamphetamine and amphetamine as its metabolite in urine to those that were negative for drugs of abuse to obtain data on the effect of methamphetamine abuse on the principal organ systems in the Thai population. Findings will be useful for interpretation of pathological findings in the Thai population and raise awareness when methamphetamine abuse is suspected in Thai medico-legal cases.

METHODS

A retrospective case control study was conducted from autopsy reports and toxicological data of Thai postmortem cases sent for medico-legal autopsy at the Department of Forensic Medicine, Faculty of Medicine Siriraj Hospital from 1st January 2018 to 31st March 2020. Inclusion criteria included Thai people who were 18 years old and over, for whom urine samples could be collected. Definite causes of death were identified by gross and microscopic findings for all the studied cases. The Thai postmortem cases were divided into two groups

1. Methamphetamine group: urine samples detected for only methamphetamine and amphetamine. Due to definition, there were only male subjects in the methamphetamine group.

2. Control group: urine samples were not positive for any drugs of abuse and medications as described below. The control group was recruited from Thai male subjects in the same period of the methamphetamine group for consistency with male subjects in the methamphetamine group.

The urine samples were analyzed by a liquid chromatography-tandem quadrupole Time-of-Flight mass spectrometry (LC-QTOF) for targeted drugs of abuse including methamphetamine, amphetamine, 3,4-methylenedioxy-methamphetamine (MDMA), 3,4-methylenedioxy-amphetamine (MDA), 3,4-methylenedioxy–N-ethyl-amphetamine (MDEA), methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), buprenorphine, fentanyl, tramadol, ketamine, diazepam, desmethyldiazepem (nordiazepam), oxazepam, temazepam, lorazepam, alprazolam, clonazepam, midazolam, chlordiazepoxide, phenazepam, amitriptyline, nortriptyline, fluoxetine, sertraline, chlorpromazine, haloperidol, and mitragynine. Urine samples were also analyzed by a gas chromatography mass spectrometry (GC-MS) for 6-acetylmorphine (6-AM), morphine, codeine, cocaine, benzoylecgonine, delta-9-tetrahydro-cannabinol (THC), and 11-nor-9-carboxy- delta-9-tetrahydrocannabinol (THC-COOH). Urine samples in the control group were negative for all drugs of abuse and medications as described above.

Exclusion criteria included decomposed bodies whose organ pathologies could not be evaluated, dead bodies who had underlying diseases that impacted organ pathologies like diabetes mellitus, hypertension and ischemic heart disease, dead bodies with drug intoxication, and dead bodies who had cardiac injuries that led to inaccurate evaluation of heart weights. Data including sex, age, height, weight, and cause of

death were recorded in each group. Body mass index (BMI) was calculated from height and weight. Pathological findings in each group were documented including:

1. Heart: heart weight, left ventricular thickness, degree of coronary artery stenosis for each coronary vessel (left anterior descending artery (LAD), right coronary artery (RCA) and left circumflex artery (LCX)), presence of microscopic myocardial hypertrophy and presence of interstitial myocardial fibrosis.

Degree of coronary artery was stratified into 4 categories by histological findings: no stenosis, mild stenosis (<50%), moderate stenosis (50-75%) and severe stenosis (≥75%).

2. Brain: presence of atherosclerosis of either anterior or posterior circulation of circle of Willis including intracranial internal carotid arteries, middle cerebral arteries, basilar artery and vertebral arteries, and presence of areas of cerebral infarction or intracerebral hemorrhage.

3. Lungs: presence of pathological signs of pulmonary hypertension including proliferation of medial layer of pulmonary vessels with obliterated lumen or plexogenic pulmonary arteriopathy, and presence of alveolar hemosiderin-laden macrophage (heart-failure cell).

4. Liver: presence of triaditis (accumulation of chronic inflammatory cells at portal triad) Analysis of methamphetamine in urine.

Urinary methamphetamine and amphetamine concentrations were quantified by a gas chromatography nitrogen phosphorus detector (GC-NPD). Urine samples were extracted by liquid-liquid extraction protocol. Briefly, 50 µL of 25 µg/mL phentermine (internal standard) was pipetted into a test tube and 1 mL of urine was added. 50 µL of 25 µg/mL sodium hydroxide was pipetted into the test tube for basic pH adjustment. Then, 5 mL of dichloromethane was pipetted into the test tube. The test tube was shaken for 15 minutes and then centrifuged at 4,000 rpm for 10 minutes. The lower layer was taken and 50 µL of 25% hydrochloric acid in methanol was added. This solution was evaporated for dryness using a nitrogen evaporator at room temperature. Then, 50 µL of methanol was used for re-constitution and 2 µL was injected into the GC-NPD.

Method validation was performed in accordance with SWGTOX 2013 guidelines[10]. Selectivity and interference studies were performed to ascertain no interference peaks occurring at retention times of amphetamine, phentermine and methamphetamine at 4, 5 and 6 minutes, respectively. Limit of detection (LOD) and lower limit of quantitation (LLOQ) were determined by spiking gradually decreasing concentrations of amphetamine and methamphetamine working solutions into blank postmortem urine. Amphetamine and methamphetamine at 150 ng/mL and 250 ng/mL produced peaks with a signal-to-noise ratio (S/N) greater than 3 times and 10 times, respectively. Thus, 150 ng/mL and 250 ng/mL were set as LOD and LLOQ for both amphetamine and methamphetamine, respectively.

A calibration model was performed using six amphetamine and methamphetamine calibrators ranging from 250 to 10,000 ng/mL (250, 500, 1,000, 2,500, 5,000 and 10,000 ng/mL). Calibration curves were generated using Agilent Software® Version 6.20 from back-calculated concentrations for each calibrator. Curve weighting factors 1/x were used to obtain the best linear regression fit that achieved r^2 ≥ 0.99 and accuracy of each calibrator within ±15% (for LLOQ within ±20%). Three spiked QC samples at 750, 1,500 and 7,500 ng/mL of amphetamine and methamphetamine were analyzed to determine accuracy and precision. Accuracy and intra-day and inter-day precision for each QC were within acceptable criteria at ±15% accuracy and ±15% coefficient of variation (%CV). There was no carry over following the injection of spiked blank urine samples with amphetamine and methamphetamine at 50,000 ng/mL. Extract stability of three QC samples

was evaluated for auto-sampler stability and stability in the fridge (4 °C). Amphetamine and methamphetamine were stable in the extract samples for both in the auto-sampler and in the fridge (4 °C) after 72 hours and 5 days, respectively.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS for Window version 21. Descriptive statistics were analyzed for mean, median, range and standard deviation. Continuous data were tested using the Kolmogorov-Smirnov test and Levene's test for equality of variance. Age and BMI were both normally distributed; therefore, the independent sample t-test was used to compare age and BMI between the methamphetamine and the control groups. Heart weight data were not normally distributed, and the Mann-Whitney U test was employed for data comparison. Multiple comparisons were assessed using the Games-Howell post-hoc test to analyze the degree of coronary artery stenosis between age groups. Other binary data were analyzed using non-parametric contingency table Chi-square test. Statistical significance was set at p-value <0.05.

This research project was approved by the Institute Review Board of the Faculty of Medicine, Siriraj Hospital, Mahidol University (COA No. Si 414/2020 and Research Project No.356/2563 (IRB4)).

RESULTS

A total of 85 cases were positive for methamphetamine in urine and 170 control cases were negative for drugs of abuse. All the subjects were male. The age and BMI profiles of these two groups were shown in Table 1. These profiles were not significantly different. The comparison of causes of death between these two groups was shown in Table 2. The figure of traffic accident in the methamphetamine group were significantly less than the control group whereas the figure of hanging in the methamphetamine group were significantly greater than the control group (p<0.001). However, there was no statistical significance for the number of other causes of death between these two groups.

Table 1 Age and BMI profiles of the methamphetamine and the control groups

Parameters	Methamphetamine group		Control group		P-value
	Mean ± SD	Range	Mean ± SD	Range	
Age (years)	36.56 ± 9.62	22-65	37.60 ± 10.94	20-65	>0.05
BMI (kg/m^2)	23.12 ± 3.76	17.44-31.31	23.07 ± 3.15	17.27-33.06	>0.05

Abbreviations: kg, kilogram; m, meter; SD, standard deviation

Table 2 Comparison of causes of death between the methamphetamine and the control groups

Cause of death	Methamphetamine group	Control group	P-value
Traffic accident	16/85 (18.82%)	88/170 (51.76%)	<0.01
Hanging	30/85 (35.29%)	20/170 (11.76%)	<0.01
Coronary artery disease/acute myocardial infarction	19/85 (22.35%)	28/170 (16.47%)	>0.05
Intracerebral hemorrhage	5/85 (5.88%)	8/170 (4.71%)	>0.05
Electrocution	6/85 (7.06%)	5/170 (2.94%)	>0.05
Ruptured aortic dissection	2/85 (2.35%)	5/170 (2.94%)	>0.05
Pneumonia	3/85 (3.53%)	6/170 (3.53%)	>0.05
Drowning	2/85 (2.35%)	6/170 (3.53%)	>0.05
Gunshot wound to the head	2/85 (2.35%)	4/170 (2.35%)	>0.05

The top three causes of death in these two groups were hanging, traffic accident, and coronary artery disease/acute myocardial infarction. Hanging recorded a higher percentage in the methamphetamine group (30/85, 35.29%) compared with the control group (20/150, 11.77%) whereas traffic accident was predominant in the control group (88/170, 51.76%) compared with the methamphetamine group (16/85, 18.82%). Coronary artery disease/acute myocardial infarction and cerebrovascular disease comprised 22.35% (19/85) and 5.88% (5/85), whereas ruptured aortic dissection presented only 2.35% (2/85) among all causes of death in the methamphetamine group.

Heart weight in the methamphetamine group was significantly higher than in the control group as shown in Table 3 (p=0.043). However, a comparison of left ventricular thickness values between these two groups showed no statistical significance.

For microscopic findings, myocardial hypertrophy and interstitial fibrosis were significantly higher in the methamphetamine group than in the control group (p<0.001 and p=0.007) as shown in Table 4.

When degree of coronary artery stenosis was considered, there were 16.5% (14/85), 11.8% (10/85) and 10.6% (9/85) of moderate stenosis for LAD, RCA and LCX and there were 14.1% (12/85), 9.4% (8/85) and 1.1% (1/85) of severe stenosis for LAD, RCA and LCX, respectively. When the number of coronary artery stenosis was considered, severe single vessel disease, double vessel disease and triple vessel disease comprised 11.8% (10/85), 4.7% (4/85) and 1.1% (1/85), respectively. Thus, there were 17.6% (15/85) for overall severe coronary artery stenosis.

Table 3 Comparison of gross cardiac parameters between the methamphetamine and the control groups

Cardiac parameters	Methamphetamine group		Control group		P-value
	Mean ± SD	Range	Mean ± SD	Range	
Heart weight (g)	356.59 ± 103.63	200-680	326.53 ± 62.50	220-670	0.043
Left ventricular thickness (cm)	1.34 ± 0.18	1.0-1.9	1.32 ± 0.16	1.1-2.0	>0.05

Abbreviations: cm, centimeter; g, gram; SD, standard deviation

Table 4 Comparison of histologic cardiac parameters between the methamphetamine and the control groups

Cardiac parameters		Methamphetamine group	Control group	P-value
Myocardial hypertrophy	Presence	40	42	<0.001
	Absence	45	128	
Interstitial fibrosis	Presence	24	24	0.007
	Absence	61	146	

Degree of stenosis at greater than 50% in each coronary vessel was used to compare results between these two groups. Multiple comparisons were assessed using the Games-Howell post-hoc test to analyze the degree of coronary artery stenosis between age groups, The LAD with degree of stenosis greater than 50% was detected at a younger age in the methamphetamine group and significantly higher than in the control group (p=0.041) as shown in Table 5. However, no significant difference was found between the degree of stenosis and age group for the right coronary artery (RCA) and left circumflex artery (LCX) between these two groups (p>0.05).

When other autopsy parameters were analyzed, the presence of hemosiderin-laden macrophages (heart-failure cells) in lungs was the only parameter that presented at a significantly higher rate in the methamphetamine group than

in the control group as shown in Table 6. Our results did not detect microscopic signs of pulmonary hypertension in any cases in the methamphetamine group.

When urinary methamphetamine and amphetamine concentrations were considered, the median concentration of methamphetamine was 4,403.76 ng/mL (range: 365.40-17,6158.18 ng/mL) whereas the median concentration of amphetamine was 547.64 ng/mL (range: <150-16,653.82 ng/mL). When urinary amphetamine concentrations greater than 250 ng/mL were considered, the median concentrations of methamphetamine and amphetamine were 5,062.34 ng/mL (range: 919.44-17,6158.18 ng/mL) and 671.98 ng/mL (range: 250.13-16,653.82 ng/mL), respectively. The mean and median amphetamine/methamphetamine percentage ratios were 16.57% and 13.86% (range: 3.79%-55.66%), respectively.

Table 5 Comparison of degree of coronary artery stenosis against age between the methamphetamine and the control groups

Coronary	Degree of stenosis	Age (years old)				P-value
		Methamphetamine group		Control group		
		Mean ± SD	Range	Mean ± SD	Range	
LAD	<50%	35.56 ± 9.13	22-61	33.81 ± 9.41	20-61	>0.05
	≥50%	38.85 ± 10.48	25-65	45.53 ± 9.63	24-65	0.041
RCA	<50%	34.81 ± 8.66	22-61	35.22 ± 9.72	20-61	>0.05
	≥50%	43.11 ± 10.42	25-65	48.29 ± 9.75	25-65	>0.05
LCX	<50%	35.23 ± 9.19	22-65	36.03 ± 10.37	20-65	>0.05
	≥50%	46.60 ± 6.57	35-56	48.18 ± 8.72	32-65	>0.05

Abbreviations: LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; SD, standard deviation

Table 6 Association of other autopsy parameters between the methamphetamine and the control groups

Other associated paramete		Methamphetamine group	Control group	P-value
Atherosclerosis of circle of Willis	Presence	14	22	>0.05
	Absence	71	148	
Presence of intracerebral hemorrhage	Presence	5	8	>0.05
	Absence	80	162	
Presence of cerebral infarction	Presence	3	4	>0.05
	Absence	82	166	
Hemosiderin-laden macrophage in lungs	Presence	31	35	0.006
	Absence	54	135	
Triaditis in liver	Presence	27	55	>0.05
	Absence	58	115	

DISCUSSION

Methamphetamine was associated with negative effects on the cardiovascular system in the Thai population. Severe coronary artery stenosis (≥75%) comprised 17.6% and severe single vessel disease was the most common form in this study. LAD was the most common affected vessel both in moderate and severe stenosis. The incidence of severe coronary artery stenosis could be varied among literatures. Karch et al. stated that severe coronary atherosclerosis was found at 5.8% in all methamphetamine abusers[3]. However, Darke et al. indicated that severe coronary atherosclerosis (>75% occlusion) was found at 19.0% in methamphetamine-related cases[5]. The left main coronary artery and/or LAD were the most common vessels involved in coronary atherosclerosis in the methamphetamine group[5].

Our results showed that degree of LAD stenosis greater than 50% was detected in younger ages in the methamphetamine group than in the control group. This result supported that methamphetamine was associated with the increasing rate of coronary atherosclerosis. In addition, the methamphetamine group presented with higher heart weight than the control group. Microscopic findings showed that the methamphetamine group had a greater degree of interstitial myocardial fibrosis and myocardial hypertrophy than the control group. Previous studies showed that methamphetamine was associated with cardiotoxic effects and produced increased heart weight[3-6]. These findings were consistent with previous studies and supported that methamphetamine had an impact on cardiac function[3-6,9,11-12]. Increased catecholamine release, increased reactive oxygen species, cellular organelle modification and promotion of inflammatory pathway were the other mechanisms identified for cardiac infrastructure alteration[11-12]. For atherogenicity, a previous study suggested that methamphetamine increased atherogenic cytokines and reactive oxygen species and promoted inflammatory T cells and macrophages[13]. This response enhanced atherogenicity and increased the rate of coronary atherosclerosis[13]. Our finding supported that methamphetamine was associated with coronary atherosclerosis in the younger age group, especially for LAD.

Other autopsy findings showed that increased alveolar hemosiderin-laden macrophages (heart-failure cells) were strongly associated with methamphetamine use when compared with the control group. A review publication stated that the stimulant like cocaine was associated with an increasing number of hemosiderin-laden macrophages in broncho-alveolar lavage compared to smokers and non-smokers and this finding suggested the association with chronic subclinical alveolar hemorrhage[14]. However, no evidence existed for the association between the presence of increased alveolar hemosiderin-laden macrophages and methamphetamine use. Our findings should be further studied for the cause of increased alveolar hemosiderin-laden macrophages in methamphetamine users. Atherosclerosis of the circle of Willis and triaditis recorded no association with the methamphetamine group. Previous studies indicated that intracranial atherosclerosis was strongly associated with increased age, hypertension and diabetes mellitus[15,16]. A review study suggested that methamphetamine-associated cerebrovascular disease was possibly associated with cerebral arteritis or vasospasm[17]. A previous study identified triaditis at 6.0% in the methamphetamine group but no statistical difference was recored between the methamphetamine group and the control group3. Our result concurred with this previous study, suggesting that triaditis might be related to other mechanisms such as viral infection, parasitic infestation, immune-mediated mechanism and alcohol. Unfortunately this study detected no histologic findings of pulmonary hypertension in the methamphetamine group. Subject gender was possibly associated with this finding because a previous study showed that female sex was associated with the presence of pulmonary arterial hypertension in documented methamphetamine abusers[18]. As all the study subjects were male, this might not show the effect of methamphetamine use on pulmonary vessels. Thus, further research should be conducted on Thai female methamphetamine abusers to prove the incidence of pulmonary arterial hypertension.

Our results showed that urinary methamphetamine and amphetamine concentration ranges in Thai people were relatively large. When compared with a previous study, urinary methamphetamine and amphetamine concentration ranges in methamphetamine-related deaths were 143-90,340 ng/mL and 36-39,300 ng/mL while median urinary methamphetamine and amphetamine concentrations were 5,300 ng/mL

and 1,400 ng/mL, respectively[19]. Our results showed a higher concentration range in methamphetamine and a lower concentration range in amphetamine compared with this study, possibly because of different purity, dosage, time and frequency of methamphetamine use by the subjects before death. Al-Asmari also found that the median amphetamine/methamphetamine percentage ratio in urine was 25%[19]. However, Kim et al. reported that mean amphetamine/methamphetamine percentage ratio in urine from volunteers under controlled oral methamphetamine administration ranged from 13.4 ± 6.5% to 22.7 ± 16.1%[20]. When compared with two studies on Thai people, Kaewpunya and Kaewmun found that mean urinary methamphetamine and amphetamine percentage ratios in Thai living people were 22-41% and 20-33%, respectively[21-22]. Our ratio results were lower than the ratios in these two previous studies on Thai people. This finding could be attributed to the difference between the time interval of methamphetamine use in our study and these two studies because the previous study suggested that urinary methamphetamine and a mphetamine percentage ratio varied over time after methamphetamine use[20].

This study had some limitations. First, all subjects were Thai males. These led to limitations when generalizing the findings to Thai females. Second, histories of methamphetamine abuse in the methamphetamine group including the duration and frequency of abuse, route of administration and forms of drugs used were not available. Therefore, association between these variables and cardiac parameters and degrees of coronary stenosis could not be assessed. Finally, only a small number of subjects presenting with degrees of coronary stensis for RCA and LCX at greater than 50% possibly led to reduced statistical significance for multiple comparisons for RCA and LCX. Thus, our findings should be viewed with caution and further studies should be conducted to expand and confirm our results.

CONCLUSION

Methamphetamine had an association with some pathological findings in Thai male subjects. Increased heart weight, myocardial hypertrophy and interstitial fibrosis were significantly found in methamphetamine positive cases. Methamphetamine positive cases with LAD stenosis greater than 50% also presented at a younger age than in the control group.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT

None

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Rate and Predictors of Postoperative Respiratory Complications Following Adenotonsillectomy in Children with Obstructive Sleep Apnea

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ABSTRACT

OBJECTIVE: This study aimed to determine the rate and risk factors of postoperative respiratory complications in children with obstructive sleep apnea (OSA) who underwent adenotonsillectomy.

METHODS: A retrospective study was conducted on the date of children with OSA who underwent adenotonsillectomy between April 2013 and July 2021. Data on demographics, medical history, tonsil grading, polysomnography parameters, and postoperative respiratory complications including cough, position, airway intervention, and desaturation were collected. Chi-square test or Fisher's exact test was performed to evaluate risk factors.

RESULTS: Seventy-one children with OSA who underwent adenotonsillectomy were included in this study. The overall rate of postoperative respiratory complications was 32/71 (45.1%) and that of minor respiratory complications was 37/52 (71.2%), including desaturation, supplement oxygen, reposition, and cough. Statistically significant association with postoperative respiratory complications was observed for obese versus non-obese ($p < 0.001$), severe apnea–hypopnea index (AHI) ($p = 0.001$), and severe lowest oxygen saturation ($p = 0.001$).

CONCLUSION: Despite the high rate of minor respiratory complications, postoperative respiratory complications are frequent after adenotonsillectomy among children with OSA. Obese versus non-obese and severity of AHI and lowest oxygen saturation are associated with postoperative respiratory complications following adenotonsillectomy.

KEYWORDS: adenotonsillectomy, obstructive sleep apnea, respiratory complication

INTRODUCTION

Obstructive sleep apnea (OSA) is a breathing sleep disorder that can affect up to 4% of children and is characterized by recurrent upper airway obstruction association intermittent nocturnal hypoxia and sleep disruption. Adenotonsillectomy (A&T) is the first line of treatment for children with OSA[1-2]. The rate of A&T postoperative respiratory complications can vary between 5.8% and 26.8% among children with OSA[3-4]. These postoperative respiratory events include cough, oxygen desaturation, laryngospasm, pneumonia, pulmonary edema, need for supplemental oxygen, apnea requiring ventilator support, and intensive care unit admission[5-6]. Under the age of 3 years, failure to thrive, obesity, and comorbidities, such as asthma, cardiac disease, neurological disease, and craniofacial syndrome, have been identified

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as high risk factors for postoperative respiratory complications following A&T in children[7-8]. Different polysomnography (PSG) criteria have been established; for example, the American Academy of Otolaryngology Head and Neck Surgery (AAO–HNS) and American Society of Anesthesiologist (ASA) have recommended overnight monitoring for children less than 3 years and those with severe OSA having apnea–hypopnea index (AHI) ≥ 10/hr and lowest oxygen saturation (LSAT) < 80%. Meanwhile, the American Academy of Pediatrics (AAP) recommended monitoring and overnight postoperative hospitalization for children with AHI ≥ 24/hr, LSAT < 80%, and PCO_2 > 60 mmHg[2, 9-10]. AAO–HNS has recommended PSG prior to A&T for children aged < 2 years or those with OSA and comorbidities. Meanwhile, AAP has recommended PSG prior to A&T for all children with OSA[2]. In this study, we aimed to evaluate the rate of postoperative respiratory complications and identify the factors associated with postoperative respiratory complications after A&T among children with OSA.

METHODS

This retrospective chart review was conducted for children aged 2 to 18 years who were diagnosed with OSA according to PSG (AHI > 1/hr) and underwent A&T between April 01, 2013 and July 31, 2021 at Vajra Hospital, Navamindrathiraj University. The study was approved by the Institutional Review Board of the Faculty of Medicine Vajira Hospital (012/2565). Children with only overnight pulse oximetry for the diagnosis of OSA and AHI < 1/hr on PSG were excluded. The criteria used for OSA diagnosis were as follows: AHI > 1/hr, further delineating the severity as mild OSA (AHI > 1–5/hr), moderate OSA (AHI > 5–10/hr), or severe OSA (AHI > 10/hr). LSAT was classified as normal (≥ 92%), mild (86%–91%), moderate (76%–85%), or severe (≤ 75%)[11].

Data were collected from the medical records and PSG results and included age, gender, weight, height, tonsil size, comorbidity condition, total AHI, mean oxyhemoglobin saturation, lowest oxyhemoglobin saturation, and respiratory complications either intraoperatively or postoperatively. Postoperative respiratory complications were divided into major respiratory complications: Intubation, apnea, pneumonia confirmed by chest X-ray, bronchospasm/laryngospasm (documented audible wheezing or use of bronchodilator and audible stridor, respectively), and minor respiratory complications (desaturation as oxygen saturation less than 95%, oxygen supplemental documented mask with bag or oxygen canular from recovery room to ward until discharge from hospital, and cough recorded by use medication or reposition).

The patients were grouped as obese or non-obese according to their weight status. Obese was defined as a median of weight-for-height > median +2 SD, including overweight and obesity. Non-obese was defined as a median of weight-for-height ≤+2 SD and ≥−2 SD[12]. Tonsils were graded from 0 to 4 by Brodsky. Medical comorbidities were categorized into respiratory conditions (e.g., asthma and allergic rhinitis), cardiovascular disease (e.g., hypertension and congenital heart disease), neurologic conditions (e.g., epilepsy and attention hyperactivity), metabolic conditions (e.g., diabetes mellitus and dyslipidemia), and miscellaneous.

PSG (Embla, USA) included electroencephalography, electro-oculography, submental and anterior tibialis electromyography, electrocardiography, oronasal airflow, thoracoabdominal movement, positions, snoring, and oxygen saturation. Sleep study was attended by a trained sleep technician. Sleep staging and respiratory scoring were interpreted by a sleep physician using the criteria defined by the American Academy of Sleep[13]. AHI was defined as the combined number of apneas and hypopneas recorded per hour of sleep. Apnea was defined as the decrease in peak signal excursions by more than 90% of the pre-event

baseline for at least two breaths. Hypopnea was defined as the decrease in peak signal excursions by more than 30% of the pre-event baseline for at least two breaths and associated with more than 3% oxygen desaturation or an electroencephalography arousal.

Descriptive statistics were described as frequencies and percentages for categorical variables and mean±standard deviation for continuous variables. The prevalence of intraoperative or postoperative respiratory complications was determined by percentage. Risk factors of respiratory complications were examined with chi-square test or Fisher's exact test to analyze the variables associated with postoperative respiratory complications following A&T in a significant level set at $p < 0.05$. All statistical analyses were performed using SPSS version 28.0 (IBM Corporation, Armonk, NY).

RESULTS

Seventy-one children with OSA (47 males and 24 females) with a mean age of 6.9 years who underwent adenotonsillectomy were included in this study. The mean of body weight and hight were 37.5±24.2 kg and 124.8±19.4 cm, respectively. Obesity was observed in 36 patients (50.7%). The comorbidity conditions were categorized into respiratory conditions (26, 36.6%), cardiovascular conditions (11, 15.5%), neurologic conditions (3, 4.2%), and metabolic conditions (6, 8.5%). The mean preoperative AHI was 13.8 events/hr. and the mean oxygen saturation was 96.6%. Thirty-two children had postoperative respiratory complications (45.1%). The overall rate of postoperative respiratory complications following A&T was 45.1%. The baseline data are summarized in Table 1.

We identified 52 respiratory complications during intraoperative or postoperative periods. Many of the children had at least one postoperative respiratory complication. Among them, 15 children had major postoperative respiratory complications (28.8%), and 37 children had minor postoperative respiratory complications (71.2%). The most common postoperative respiratory complications were as follows: Supplemental oxygen (23.1%) and

Table 1 Characteristics of the entire cohort

Characteristics	All patients (n = 71)
Gender, n (%)	
Male	47 (66.2%)
Female	24 (33.8%)
Weight status, n (%)	
Obese	36 (50.7%)
Non-obese	35 (49.3%)
Tonsil size, n (%)	
1	3 (4.2%)
2	9 (12.7%)
3	44 (62.0%)
4	15 (21.1%)
Medical comorbidities, n (%)	
Respiratory	26 (36.6%)
Cardiovascular	11 (15.5%)
Neurologic	3 (4.2%)
Metabolic	6 (8.5%)
Miscellaneous	2 (2.8%)
Polysomnographic variables, mean (SD)	
AHI (events/hr)	13.8 (12.7)
Mean oxygen saturation (%)	96.6 (1.7)
Lowest oxygen saturation (%)	81.9 (10.5)
Number patients of respiratory complication	32 (45.1%)

Abbreviations: AHI, apnea-hypopnea index; SD, standard deviation

Table 2 Prevalence of postoperative respiratory complication following adenotonsillectomy

Complication	n = 52 (%)
Major complication	15 (28.8)
Intubation	4 (7.7)
Pneumonia	1 (1.9)
Apnea	1 (1.9)
Bronchospasm/Laryngospasm	9 (17.3)
Minor complication	37 (71.2)
Desaturation	6 (11.5)
Supplement oxygen	12 (23.1)
Reposition	10 (19.2)
Cough	9 (17.3)

reposition (19.2%). The postoperative respiratory complications are shown in Table 2.

No statistically significant associations with postoperative respiratory complications were found for gender, comorbidity condition, and tonsil grading. The parameters that were significantly associated with postoperative respiratory complications were weight status, AHI severity, and LSAT. We found high rates of severe AHI and LSAT in children with postoperative respiratory complications (table 3).

Table 3 Association of parameters and postoperative respiratory complications

Factors	Complication n = 32 (%)	No complication n = 39 (%)	P-value
Gender		n = 39 (%)	0.802
Male	22 (46.8)	25 (53.2)	
Female	10 (41.7)	14 (58.3)	
Comorbid disease			0.240
Yes	21 (51.2)	20 (48.8)	
No	11 (36.7)	19 (63.3)	
Weight classified			<0.001
Obese	25 (35.2)	11 (15.5)	
Non-obese	7 (9.9)	28 (39.4)	
Tonsil grading			0.133
1	0 (0.0)	3 (4.2)	
2	4 (5.6)	5 (7.0)	
3	18 (25.4)	26 (36.6)	
4	10 (14.1)	5 (7.0)	
Severity of AHI			0.001
Mild	5 (20.8)	19 (79.2)	
Moderate	5 (33.3)	10 (66.7)	
Severe	22 (68.8)	10 (31.3)	
Severity of lowest oxygen saturation			0.001
Normal	2 (13.3)	13 (86.7)	
Mild	5 (33.3)	10 (66.7)	
Moderate	9 (42.9)	12 (57.1)	
Severe	16 (80.0)	4 (20.0)	

Abbreviations: AHI, apnea-hypopnea index

DISCUSSION

Our study shows a 45.1% overall rate of postoperative respiratory complications in children with OSA following A&T. The rates of major and minor postoperative respiratory complications were 28.8% and 71.2%, respectively. This finding is similar to the study by Rossi et al., who reported 46.4% (65/140) total postoperative respiratory complications[14]. By contrast, Caetta et al. reported a low rate (2.7%) of postoperative respiratory complications in children with OSA after A&T[15]. Another study found that the postoperative respiratory complication rate was 5.8%–26.8%[9]. Fung et al. found that the rates of major and minor complications in obese children were 20.4% and 73.5%, respectively, and those in non-obese children were 4.1% and 24.5%, respectively[16]. Hill et al. found that the rates of major and minor postoperative complications among children with severe OSA were 4.8% and 19.3%, respectively[17]. This difference may be due to the use of different criteria to describe major and minor postoperative complications.

Known risk factors for postoperative respiratory complications among children with OSA after A&T include young age (aged <3 years)

and medical comorbidities such as cardiac disease, craniofacial disorder, genetic disease, and neurological disease[2,4,7,9,18]. Previous studies showed that obesity/overweight or under weight was associated with postoperative respiratory complication[19-21]. Other researchers reported that obesity was not a risk factor of respiratory complications[18,22]. In the current work, an association with respiratory complications was observed for weight status (obese and non-obese) but not for gender, tonsil size, and medical comorbidity.

PSG parameters may be a risk factor for postoperative respiratory complications. An association with postoperative respiratory complications was observed for the severity of AHI and LSAT. Similar to our study, Jarysak et al. found that AHI and LSAT were risk factors of respiratory complications[19]. In contrast to the current findings, Konstantinopoulou et al. revealed that LSAT was not a predictive factor of adverse respiratory events[23].

Some guidelines have been established regarding postoperative care following A&T in children with OSA. AAO–HNS has recommended overnight monitoring for children less than 3 years and those with severe OSA including AHI ≥ 10 /hr and oxygen saturation nadir < 80%; meanwhile, healthy children with suspected OSA do not require preoperative PSG.[9] AAP has recommended monitoring and overnight postoperative hospitalization for children with AHI ≥ 24/hr, LSAT < 80%, or PCO_2 > 60 mmHg[2]. PSG is the gold standard for diagnosis OSA; nevertheless, it is expensive, has a long waiting list, and lacks PCO_2 measurements. An overnight pulse oximetry, which is used as a screening tool for OSA severity prior to A&T, should be used for healthy children suspected with OSA[24].

This study was limited by its retrospective design and single institution data collection. Bias might have aroused in selecting children with comorbidity condition for sleep study according to AAO–HNS guidelines. Despite the small sample size, this study reached statistically significant difference. Future studies with large population and multivariate analysis will show great difference.

CONCLUSION

The rate of postoperative respiratory complications among children with OSA after A&T is 45.1%. The majority of these respiratory complications are minor. Our study demonstrated the association of obese, AHI and LSAT severity with postoperative respiratory complications. Further studies should focus on postoperative respiratory complications and the use of overnight pulse oximetry among healthy children suspected with OSA requiring A&T.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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None

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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A Study of Hand Dermatitis and Associated Factors During The COVID-19 Pandemic

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ABSTRACT

OBJECTIVE: This study was conducted to determine the associated factors of hand dermatitis during a COVID-19 pandemic versus a non-COVID pandemic year by comparing the frequency of outpatient clinic visits.

METHODS: This retrospective study used data from the dermatology department from January 2019 to December 2020. As an epidemiological assessment of increased dermatologic clinic visits of hand dermatitis patients, the Poisson mean difference model with generalized estimating equation regression was used.

RESULTS: The study comprised a total of 16,506 outpatient dermatological clinic visits, including 793 hand dermatitis visits. After controlling the confounders such as demographic data, occupation, and corticosteroid use, hand dermatitis visits increased by 30% during the pandemic period compared to the pre-pandemic period. The average age of patients was 55.2 ± 16.4 years. Females mainly composed 70.6% and 62.8% of the subjects during the pandemic and pre-pandemic periods, respectively (P = 0.022). Patients reported significantly less hand cream usage (P = 0.013) and foot dermatitis diagnosed (P = 0.009) during the pandemic period than during the pre-pandemic period. Furthermore, patients were prescribed topical corticosteroids with low to moderate potency more frequently during the pandemic period (P = 0.019), whereas the use of topical corticosteroids with moderate to high potency and systemic corticosteroids did not differ between the two time periods.

CONCLUSION: The COVID -19 pandemic had an impact on hand dermatitis in increasing outpatient dermatologic clinic visits. Emollient use is an important preventive factor in hand dermatitis. More hand cream use might help prevent hand dermatitis during COVID-19 pandemic and other infectious pandemics in the future.

KEYWORDS: associated factors, COVID-19 pandemic, hand dermatitis, hand eczema

INTRODUCTION

Hand dermatitis is a subtype of skin inflammation that affects only the hands and/or wrists. This condition is regarded as one of the most significant dermatologic health issues worldwide with lifetime prevalence of 14.5% in the general population[1]. Hand dermatitis is often burdensome and has a substantial effect on patients' quality of life and a financial burden on society. Hand dermatitis risk factors, both endogenous and exogenous, have been thoroughly investigated. Atopic dermatitis history, exposure to irritants and wet work are risk factors. Health care workers (HCWs), mechanical industry workers, cleaners, hairdressers, farmers, florists and food handlers are

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examples of wet work occupations as their hands are frequently exposed to water[2]. Furthermore, lifestyle factors including smoking, alcohol consumption, stress and body mass index (BMI) might have an influence on hand dermatitis[3].

The coronavirus disease 2019 (COVID-19) pandemic has resounding global health implications, especially in the dermatologic field due to the hand hygiene recommendations implemented during this time. While the health guidelines recommended increase hand washing and frequent use of hand sanitizer have been integral in preventing the spread of infectious disease, it may have potentially adverse consequences on dermatologic issues such as irritant contact dermatitis and chronic paronychia. In a previous study examining the prevalence of irritant hand dermatitis among German HCWs due to increased hygiene measures, there was a significant increase in the incidence of signs of irritant hand dermatitis despite using emollient as a preventive measure[4]. Risk factors of hand dermatitis include frequent handwashing more than 10 to 20 times per day, wearing latex gloves, and previous hand dermatitis history[5]. While other studies focused on HCW groups, the current study will include a large study population including both the HCWs and non-HCWs and the changes in their hand hygiene habits.

The objective of this study is to determine the associated factors of hand dermatitis during a COVID-19 year versus a non-COVID year by comparing the visit frequency of patients. The results will explore methods to prevent hand dermatitis while performing the necessary hand hygiene during the infectious pandemic.

METHODS

This retrospective study examined hand dermatitis visits between January 2019 and December 2020 to compare the frequency of visits and associated factors pre-pandemic versus during the COVID-19 pandemic. This study was collected from the outpatient unit of the dermatology department data records at Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. To have a concrete time period for data collection, the COVID-19 pandemic period was defined to be between January 2020 to December 2020 since this time period accounts for multiple epidemics within Thailand. The pre-pandemic period was defined to be between January 2019 to December 2019. The International Classification of Diseases, tenth revision (ICD-10) codes: L20, L23, L24, L25 and L30 codes were extracted from electronic medical records[6]. All patients were diagnosed and managed by dermatologists who were board-certified. In this study, topical corticosteroids with low to moderate potency were classified as topical corticosteroids class V to VII, while topical corticosteroids with moderate to high potency were classified as topical corticosteroids class I-IV[7]. All data was de-identified to maintain privacy and security of patient records. Inclusion criteria were patients diagnosed with hand dermatitis who were 15 years and older. Exclusion criteria were patients who required inpatient care and patients with incomplete medical records.

STATISTICAL ANALYSIS

The main results were a comparison of the visit frequency of hand dermatitis patients at the outpatient unit of dermatology clinic at Vajira Hospital during the pandemic and pre-pandemic period. Categorical data were displayed as frequency and percentage and were compared using the Chi-square test. For normally distributed continuous data, the mean and standard deviation were used and were compared using the independent t-test. For non-normally distributed continuous data, the median and interquartile range were described and were compared using the Mann-Whitney U-test. Based on the correct distribution of count data, we estimated the impact of the pandemic period on hand dermatitis visits. If the visit data was unbalanced, we assumed zero visit frequency for the pre-pandemic period visit frequency or pandemic period visit frequency if a patient did not visit the department in order to equalize both arms of analysis based on the baseline of the first visit in each period. Poisson mean difference with generalized estimating equation regression was used. With explanatory modeling strategy, the confounders were adjusted. STATA version 13.0 software (Stata Corporation, College Station, TX, USA) was used for all analysis. A p-value of 0.05 or less was defined as statistical significance.

Table 1 A comparison of demographic characteristics of patients with hand dermatitis visited the outpatient dermatology clinic at Vajira Hospital, Navamindradhiraj University, between the COVID-19 pandemic and pre-pandemic periods

	Hand dermatitis visits			
Variables	**Total (n=793) n, (%)**	**Pandemic Period (n=449) n, (%)**	**Pre-pandemic Period (n=344) n, (%)**	**P-value**
Female*	533 (67.2)	317 (70.6)	216 (62.8)	0.022
Age (years) (Mean±SD)	55.2 ± 16.4	55.2 ± 16.9	55.3 ±15.8	0.928
Live in Bangkok	653 (82.4)	373 (83.1)	280 (81.4)	0.573
Marital status				
Single	381 (48.7)	223 (50.2)	158 (46.6)	0.348
Married	356 (45.5)	190 (42.8)	166 (49.0)	0.096
Divorced	46 (5.9)	31 (7.0)	15 (4.4)	0.167
Career related to hand wash	102 (16.9)	56 (17.1)	46 (16.7)	1.000
Career unrelated to hand wash	501 (83.1)	272 (82.9)	229 (83.3)	1.000
Exposed to water history	87 (11.0)	37 (8.2)	50 (14.5)	0.006
Body mass index (kg/m2) (Mean±SD)	24.5 ±4.4	24.5 ±4.4	24.4 ±4.4	0.923
Tobacco use				
Occasionally use	7 (0.9)	2 (0.5)	5 (1.5)	0.249
Active smoker	44 (5.6)	20 (4.5)	24 (7.1)	0.158
Alcohol use				
Occasionally use*	38 (4.9)	13 (3.0)	25 (7.4)	0.007
Active alcohol user	26 (3.3)	17 (3.8)	9 (2.7)	0.424
Hand cream use*	725 (92.6)	401 (90.5)	324 (95.3)	0.013
Foot dermatitis*	142 (18.1)	66 (14.9)	76 (22.4)	0.009
Topical corticosteroids use				
High to moderate potency	618 (80.2)	342 (78.4)	276 (82.4)	0.202
Low to moderate potency*	128 (16.6)	85 (19.5)	43 (12.9)	0.019
Oral prednisolone use				
0-0.5 mg/kg/day	210 (26.5)	124 (27.6)	86 (25.0)	0.418
0.5-1.0 mg/kg/day	5 (0.6)	2 (0.5)	3 (0.9)	0.658
Oral prednisolone duration				
> 14 days	99 (12.5)	59 (13.1)	40 (11.6)	0.588
Mean arterial blood pressure (mmHg) (Mean±SD)	93.5 ± 11.9	94.2 ± 11.7	91.7 ± 12.2	0.060
Fasting plasma glucose (mg/dl) (Mean±SD)	108.8 ± 27.9	109.3 ± 29.3	108.3 ± 26.3	0.754
Triglyceride (mg/dl) (Median, IQR)	104 (75,136)	99 (70,137)	105 (82, 136)	0.146
Total cholesterol* (mg/dl) (Mean±SD)	189 ± 41	184 ± 40	195 ± 41	0.020
HDL (mg/dl) (Mean±SD)	59.7 ± 17.1	60.7 ± 17.8	58.4 ± 16.2	0.245
LDL (mg/dl) (Mean±SD)	112.4 ± 31.9	112.3 ±31.8	112 ± 32.0	0.921
HbA1c (%) (Median, IQR)	6.0 (5.6,6.8)	5.9 (5.5,6.7)	6.1 (5.7,6.8)	0.151
eGFR (ml/min/1.73m2) (Mean±SD)	84.3 ± 23.5	86.0 ± 22.5	82.9 ± 24.2	0.201
Vitamin D level (ng/ml) (Median, IQR)	27.5 (19.2,31.9)	29 (19.8,31.9)	19.6 (17.0,36.1)	0.115

Abbreviations: SD, standard deviation; IQR, interquartile range; m, meter; mg, milligram; kg, kilogram; ng, nanogram; dl, deciliter; ml, milliliter; mmHg, millimeters of mercury; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobinA1c; eGFR, estimate glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). * P < 0.05 significant difference

RESULTS

The overall number of dermatology clinic visits was 8,424 during the COVID-19 pandemic period and 8,082 during the pre-pandemic period, according to data collected from January 1, 2019 to December 31, 2020. The number of hand dermatitis visits during the COVID-19 pandemic was 449 (5.3%). While the number of hand dermatitis visits during the year preceding the pandemic in 2019 was 344 (4.3%). The patients' average age was 55.2 ± 16.4 years. During the pandemic and pre-pandemic periods, females were predominant in two periods, 70.6% and 62.8%, respectively (P = 0.022). The majority of the patients resided in Bangkok, the capital of Thailand. The clinical characteristics of patients were shown in Table 1.

The most common occupations in this study were office workers (32.3%), followed by cleaners (14.1%) as shown in Table 2. However, there was no difference in patient occupation between the two time periods. As compared to the pre-pandemic period, individual behavior of water exposure significantly decreased during the pandemic period (P = 0.006).

During the pandemic period, the hand dermatitis patients who were social alcohol drinkers visited clinics less often than pre-pandemic period. While the contradictory result was found in active alcohol users. The hand dermatitis patients who used hand cream and who were diagnosed with foot dermatitis were reported to decrease significantly during the pandemic period (P = 0.013 and P = 0.009, respectively). Additionally, the hand dermatitis patients who were prescribed topical corticosteroids with low to moderate potency visited the clinic more frequently in pandemic period than pre-pandemic period (P = 0.019). The usage of topical corticosteroids with moderate to high potency and systemic corticosteroids did not differ between the two periods. The patients with higher blood cholesterol level visited the clinic less during pandemic time. All other blood investigations were non-significant associated with hand dermatitis visits.

As Kernel density illustration reveals, the frequency of hand dermatitis visits in both periods was right-skewness data (figure 1). According to the right skewness, Poisson mean difference

Table 2 Occupations of hand dermatitis patients visited the outpatient dermatology clinic at Vajira Hospital, Navamindradhiraj University, between the COVID-19 pandemic and pre-pandemic periods

		Hand Dermatitis visits		
Occupations	**Total (n=793) n, (%)**	**Pandemic Period (n=449) n, (%)**	**Pre-pandemic Period (n=344) n, (%)**	**P-value**
Occupations related to wet work activities	102 (16.9)	56 (17.1)	46 (16.7)	1.000
Cleaner	85 (14.1)	44 (13.4)	41 (14.9)	0.639
Farmer	5 (0.8)	4 (1.2)	1 (0.4)	0.383
Health care worker	5 (0.8)	5 (1.5)	0 (0.0)	0.066
Hairdresser	4 (0.7)	2 (0.6)	2 (0.7)	1.000
Florist	1 (0.4)	0 (0.0)	1 (0.4)	0.456
Chef	2 (0.3)	1 (0.3)	1 (0.4)	1.000
Occupations unrelated to wet work activities	501 (83.1)	272 (82.9)	229 (83.3)	1.000
Office worker	195 (32.3)	112 (34.2)	83 (30.2)	0.336
Student	34 (5.6)	24 (7.3)	10 (3.6)	0.053
Merchant	29 (4.8)	12 (3.4)	17 (6.2)	0.182
Police	3 (0.5)	3 (0.9)	0 (0.0)	0.225
Other	240 (39.8)	121 (36.9)	119 (43.3)	0.113

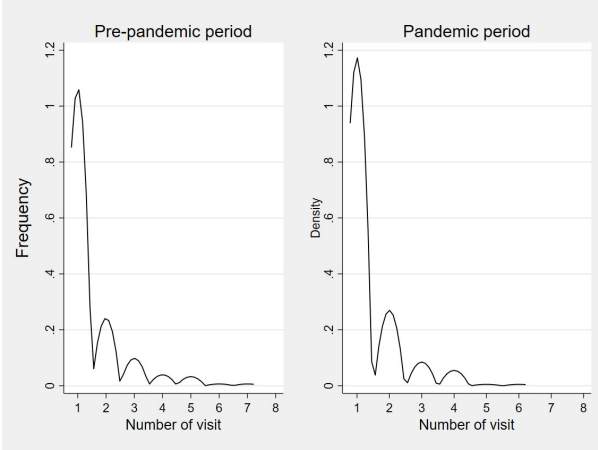

Figure 1 Kernel density plot of number of hand dermatitis visits during pre-pandemic and pandemic periods

model with generalized estimating equation was used for multivariate analysis.

Hand dermatitis visits significantly increased by 30% of the Poisson mean difference during the pandemic period compared to the previous period after adjusting for the demographic factors including age, gender, body mass index, living in Bangkok, marital status, occupation, hand cream use, present with foot dermatitis, tobacco use, alcohol consumption and corticosteroid use (table 3).

The margins plots revealed the mean of the number of hand dermatitis visits and the pandemic event and visualized the change of mean between the periods (figure 2).

Table 3 The Poisson mean difference with generalized estimating equation results: effect modifications of the demographic factors on the mean difference of hand dermatitis visits between pandemic and pre-pandemic periods

	Adjusted Poisson mean difference*	S.E.	95% Confidence interval		P-value
			Lower	Upper	
Pandemic period	0.30	0.11	0.09	0.50	0.005

*Adjusted with gender, age, body mass index, live in Bangkok, marital status, health care job, exposure to water job, hand cream use, present with foot dermatitis, low to moderate potency topical corticosteroids, moderate to high potency topical corticosteroid, tobacco use, alcohol use.
Abbreviations: S.E., standard error

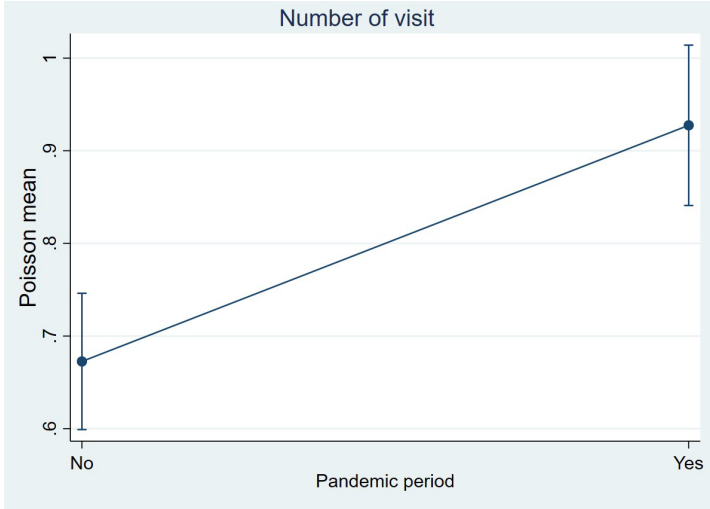

Figure 2 Plots of Poisson mean versus period for the pandemic effect when comparing the number of hand dermatitis visits

DISCUSSION

The number of outpatient dermatologic visits for patients diagnosed with hand dermatitis increased by 30% during the COVID-19 pandemic compared to pre-pandemic period based on the electronic medical databases collected at Vajira Hospital, Bangkok, Thailand. The findings of this study revealed that approximately two-thirds of patients with hand dermatitis were females which was similar to the findings of previous study[1]. According to another published study, the disease had a greater impact on females, as there were reported a lower quality of life even at the same disease severity as males, as well as more aggravating factors and sick leave[8]. The reason of this finding might because of the more awareness of personal health care in females than males, including hand hygiene[9].

Water exposure habit is a known risk factor to hand dermatitis. In this study, individual behavior of water exposure was significantly decreased, while hand dermatitis visits were increased during the pandemic period. This could imply that people probably used alcohol sanitizer as dry hand rub for infectious control but unaware that alcohol is one of most common irritant contact dermatitis causes. For infectious control strategies, most people pay more attention to the sanitation of their hands over feet. That could be the reason for less foot dermatitis in pandemic time. The patients also reported less frequent used of hand cream during the pandemic period. As an important preventive measure for hand dermatitis, emollient or moisturizer has an important role in moist the affected area, immediate barrier repair, decrease transepidermal water loss and irritation[10]. Patients should be educated to choose a lipid-rich moisturizer free of perfumes and preservatives with the lowest allergen potential[11]. These findings implied that inadequately educated hand dermatitis prevention can cause public health problems. Individuals should be encouraged to use hand emollients after washing their hands with water or with alcohol sanitizers especially during infectious pandemic.

Lifestyle factors such as smoking and drinking had an impact on hand dermatitis[12]. In this study, people who were social drinkers had lesser hand dermatitis, while active users found more hand dermatitis diagnosed in the pandemic period. As people are staying indoor, the social drinkers are not socializing with their friends and not participating in outdoor activities. On the other hand, the active alcohol user may be using alcohol to cope with their stress during the pandemic period, which might affect the immune-mediate and increased hand dermatitis. These findings were different from a systematic review and meta-analysis study that showed no association of alcohol and hand dermatitis[3]. Tobacco use of ≥8 cigarettes per day or ≥15 pack-years was found to be related to hand dermatitis[12]. However, smoking did not differ between the two periods in this study. Other lifestyle factors, such as obesity, have been linked to hand dermatitis in previous studies. Hand dermatitis was more common in obese patients with BMI ≥ 30 kg/m^2 [12]. However, BMI did not differ between the two time periods in the current study. Topical corticosteroids were the first-line treatment in management of hand dermatitis due to their effectiveness in the short term, however long-term use poses adverse effects of inhibiting epidermal barrier repair and causing skin atrophy[13]. The consideration of using topical corticosteroids potency was determined by the affected sites and the severity of diseases. In this study, patients with hand dermatitis who were prescribed with low to moderate potency topical corticosteroids visited the dermatologic clinic more frequently during the pandemic, while there was no change in patients who were prescribed moderate to high potency topical corticosteroids visits.

Nature of hand dermatitis affected the palmar side more than the dorsal side due to almost all activities used the volar side of the hand such as writing, typing, washing, painting and cooking[14]. Moreover, the volar side is the thickest epidermis in the body[15]. Therefore, moderate to high topical corticosteroids are more suitable than low to moderate topical corticosteroids in the treatment of hand dermatitis. Total cholesterol was the only blood test that showed a lower level in patients with hand dermatitis who visited during the pandemic period compared to the pre-pandemic period, but this finding needed to be confirmed.

The strengths of this study include all diagnoses and management of hand dermatitis

made by board-certified dermatologists. The study's limitations included the warm and humid temperature of Bangkok, Thailand, where the data was collected. This may not represent the incidence of hand dermatitis in other climate zones. Second, because the study was carried out as a retrospective study, some important details such as the number of cigarettes smoked, the frequency of daily water exposure, and the number of alcohol consumption could not be determined. Further studies are needed to address more specific in larger research sites to reflect hand dermatitis in the real world.

CONCLUSION

The COVID-19 pandemic had an impact on hand dermatitis that required dermatologic consultation. It is imperative to put more education in the preventive strategies against hand dermatitis during infectious pandemic periods in order to reduce unnecesary dermatologic clinic visits, especially to encourage the use of hand emollients.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest regarding the publication of this article.

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DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Antibody Response after ChAdOx1 nCoV-19 Vaccination in Patients with Type 2 Diabetes at Vajira Hospital

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ABSTRACT

OBJECTIVE: A question exists as to whether people with diabetes can respond effectively to the COVID-19 vaccine. This study aimed to evaluate antibody response after COVID-19 vaccination in patients with type 2 diabetes.

METHODS: This was a cross-sectional analytical study. Two hundred and twelve type 2 diabetes patients were enrolled after receiving a second dose of the ChAdOx1nCoV-19vaccine 3 months previously. Demographic data, medical history, and blood drawn were collected. Antibodies against receptor binding domain (anti-RBD) was investigated in the laboratory department. Other factors that could affect anti-RBD level, i.e. age, gender, BMI, glycemic control, duration of diabetes, and comorbidity, were collected and analyzed.

RESULTS: Among 212 patients with type 2 diabetes 3 months after receiving a second dose of the ChAdOx1nCoV-19 vaccine, the anti-RBD level mean was 989.56 U/ml. Patients with type 2 diabetes, with or without cardiovascular disease as a comorbidity, had median anti-RBD levels equal to 258 U/ml and 442 U/ml, respectively. The median of anti-RBD levels between groups had statistically significant differences (p-value = 0.021). Age, gender, BMI, duration of diabetes, glycemic control, and other comorbidities showed no statistically significant differences in the median anti-RBD levels.

CONCLUSION: Only patients with type 2 diabetes with cardiovascular disease as a comorbidity showed statistically significant differences in Anti-SARS-CoV-2 response 3 months after receiving a second dose of the ChAdOx1nCoV-19 vaccine. Therefore, patients with diabetes and cardiovascular disease require earlier revaccination to ensure protection against COVID-19 infection.

KEYWORDS: antibodies, chAdOx1 nCoV-19, COVID-19, COVID-19 vaccine, diabetes mellitus type 2

INTRODUCTION

The COVID-19 pandemic has existed in Thailand since early 2020. Previous reports from international sources, including Thailand, have suggested that older adults (over 60 years old) and patients with comorbidities, especially non-communicable diseases (NCDs) such as diabetes mellitus, obesity, hypertension, and heart disease, are in high-risk groups for increased severity of COVID-19 and mortality rates[1]. The most common comorbidities are hypertension, followed by diabetes mellitus and chronic obstructive respiratory disease[2]. COVID-19 patients with comorbidities, such as diabetes mellitus, are more

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likely to develop an increased severity and progression of the disease[3]. It was found that patients with diabetes were linked to higher severity for the effects of COVID-19, such as intensive care unit (ICU) admission, the need for invasive mechanical ventilation, and death[4-5]. Although diabetes mellitus has been associated with an increased risk for COVID-19 complications and severe symptoms, there is inadequate data to indicate whether people with diabetes are more likely to get COVID-19 compared to the general population[6-7].

Recombinant viral vector vaccine (COVID-19 Vaccine AstraZeneca, ChAdOx1 nCoV-19) produces a viral vector vaccine using a genetically engineered virus that cannot cause disease, but encodes coronavirus proteins to safely generate an immune response. Recombinant viral vector vaccine is approved for people aged 18 years or older as well as patients in high-risk groups, such as those with diabetes. ChAdOx1 nCoV-19 vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered 12-16 weeks after the first dose.

A previous study by Ramasamy et al. found that the factors affecting levels of antibody response in the general population were associated with older age. It was believed that, as people got older, their immune systems would deteriorate and decline[8]. Therefore, the decline of the immune function probably affected the levels of antibody response. According to a recent study by Ali et al. concerning the levels of anti-SARS-CoV-2 IgG and neutralizing antibodies in patients with type 2 diabetes after receiving the BNT162b2 mRNA COVID-19 vaccine compared with people without type 2 diabetes, the results showed that both groups had significantly high levels of antibody response to the vaccine (high titer). However, the results also showed that patients with type 2 diabetes had lower levels of anti-SARS-CoV-2 IgG and neutralizing antibodies than those without type 2 diabetes. Additionally, type 2 diabetes might impact the humoral immune response to the BNT162b2 mRNA vaccine[9].

There is insufficient data on the antibody response of the COVID-19 vaccine in people with diabetes who received the ChAdOx1 nCoV-19 vaccine, which was considered the initial main vaccine in Thailand. Therefore, this study aimed to evaluate the COVID-19 vaccine response in patients with type 2 diabetes who underwent treatment at Vajira Hospital after receiving a second dose of the ChAdOx1 nCoV-19 vaccine for 3 months.

METHODS

The target population comprised patients with type 2 diabetes listed in the medical records or ICD-10 system Codes E110-E119 as reviewed by physicians and those who underwent treatment at the Diabetes Clinic, Division of Endocrinology and Metabolism, Faculty of Medicine Vajira Hospital, Navamindradhiraj University. The participants were patients with type 2 diabetes who received a second dose of the ChAdOx1 nCoV-19 vaccine during a period of 3 months (from September 2021 to January 2022). However, patients infected with COVID-19 before receiving the vaccine and those with pregnancy were excluded.

The quantity of antibodies against the SARS-CoV-2 virus was analyzed using Elecsys Anti-SARS-CoV-2 based on electrochemiluminescence immunoassay "ECLIA," which was a Double-antigen sandwich. The content of the serum used was 12 microliters of serum per time per person. An analysis was performed using Cobas e801 immunoassay analyzers at the laboratory of the Department of Central Laboratory and Blood Bank, Faculty of Medicine Vajira Hospital, in accordance with the manual in the Anti-SARS-CoV-2 test kit. Spike protein was the main antigenic component responsible for inducing the host immune response. Spike protein was the target region of the SARS-CoV-2 virus; this part was used for developing the vaccines available today. After receiving vaccines, the immune

system produced Anti-RBD, which favored the detection of high-affinity antibodies, including IgG.

Nowadays, data from research papers shows that not only can IgG be a neutralizing antibody, but IgM and IgA also have a chance to become neutralizing antibodies. Therefore, manufacturers focused on detecting all high-affinity antibodies, which were suitable for seeking immune response after COVID-19 vaccination.

The results were interpreted based on antibody levels and reported as positive when antibody levels were greater than or equal to 0.80 U/ml., but reported as negative when antibody levels were less than 0.80 U/ml.

This research project was approved by the Institutional Review Board, Faculty of Medicine Vajira Hospital, Navamindradhiraj University (COA No. 170/2564).

STATISTICAL DATA ANALYSIS

Quantitative variables, namely age, height, weight, BMI, duration of diabetes, laboratory test results, HbA1c levels, and antibody level against spike protein receptor binding domain (anti-RBD), were presented in the form of mean and standard deviation or median and IQR, depending on data distribution. T-test independence was used in the analysis with statistical significance when p-value was less than 0.05. Regarding the qualitative variables, namely gender, comorbidity, data about the COVID-19 infection after receiving a COVID-19 vaccine, and side effects after a COVID-19 vaccination, were presented in the form of percentages. Chi-squared test was used to measure the statistical relationships, while SPSS version 21.0 was used for data analysis.

RESULTS

The study included 212 patients with type 2 diabetes who received the ChAdOx1 nCoV-19 vaccine 3 months prior (from September 2021 to January 2022). Most of the participants were women (63.7%). The mean age was 63.27 ± 12.32 years, and most participants were under 70 years old (67.5%). The mean BMI was 26.94 ± 5.30 kg/m^2, and most participants were obese (62.3%). The participants had a median duration of diabetes at 12.5 years [IQR 6 – 20 U/ml], and nearly two-thirds of participants had had diabetes for longer than or equal to 10 years (67.5%). The participants had a median of HbA1c level equal to 7.6 [IQR 6.7 - 8.7 U/ml], and most of them had HbA1c levels higher than or equal to 7.0 (67.9%). The most common comorbidities found were dyslipidemia (81.1%), followed by hypertension (78.8%) and cardiovascular disease (10.4%). (table 1)

Table 1 Baseline characteristics of patients with type 2 diabetes (n = 212)

Characteristics	n	(%)
Gender		
Male	77	(36.3)
Female	135	(63.7)
Age (years), Mean ± SD	63.27 ± 12.32	
<70	143	(67.5)
≥70	69	(32.5)
BMI (kg/m^2), Mean ± SD	26.94 ± 5.30	
<23.0	51	(24.0)
23.0-24.9	29	(13.7)
≥25.0	132	(62.3)
Duration of type 2 diabetes (years), Median [IQR]	12.5	(6 - 20)
<10	69	(32.5)
≥10	143	(67.5)
HbA1c (%), Median [IQR]	7.6	(6.7 - 8.7)
<7.0	68	(32.1)
≥7.0	144	(67.9)

Table 1 Baseline characteristics of patients with type 2 diabetes (n = 212) (continued)

Characteristics	n	(%)
Comorbidity		
Cardiovascular disease	22	(10.4)
Respiratory disease	2	(0.9)
Other comorbidity		
Hypertension	167	(78.8)
Dyslipidemia	172	(81.1)
Chronic kidney disease/ESRD	20	(9.4)
Hypothyroid	17	(8.0)
Old CVA	9	(4.2)
Cancer	3	(1.4)
Thalassemia	1	(0.5)

Data are presented as number (%), mean ± standard deviation or median (interquartile range)
Abbreviations: BMI, body-mass index; HbA1c, glycated hemoglobin; ESRD, end stage renal disease; CVA, cerebrovascular accident

Regarding the antibody level against receptor binding domain (anti-RBD) 3 months after receiving the second dose of the ChAdOx1 nCoV-19 vaccine, it was found that the participants had an antibody level on the average of 989.56 U/ml. The median was 412 U/ml [IQR 196 – 991 U/ml]. (table 2)

According to the analysis, the factors affecting anti-RBD levels in patients with type 2 diabetes were gender, age, BMI, duration of diabetes, HbA1c levels, and comorbidities. The results of the study showed that male and female participants had no statistically significant differences in the median of anti-RBD levels (p-value = 0.427). The median of anti-RBD levels between groups of patients showed no statistically significant differences, specifically among patients with type 2 diabetes aged below 70 years and patients aged 70 years and above; patients with type 2 diabetes having BMI below 23.0 kg/m^2, 23.0-24.9 kg/m^2, and above or equal to 25.0 kg/m^2; patients with type 2 diabetes having diabetes less than 10 years and longer than or equal to 10 years; patients with type 2 diabetes having HbA1c levels below 7.0% and above or equal to 7.0%. The median of anti-RBD levels for patients with type 2 diabetes, with and without cardiovascular disease as a comorbidity, were 258 U/ml [IQR 128 – 438 U/ml] and 442 U/ml [IQR 203 – 1150 U/ml], respectively. The median of anti-RBD levels between groups exhibited statistically significant differences (p-value = 0.021). The median of anti-RBD levels between groups of patients with type 2 diabetes, with and without other comorbidities such as respiratory disease, hypertension, dyslipidemia, chronic kidney disease/ESRD, hypothyroid, old CVA, cancer, and thalassemia, presented no statistically significant differences (p-value = 0.505). (table 3)

Table 2 Antibody level against receptor binding domain (anti-RBD) after COVID-19 vaccination in patients with type 2 diabetes (n = 212)

Antibody level against receptor binding domain (anti-RBD)	U/ml
Mean	989.56
Median	412
SD	1570.37
Minimum	40
Maximum	9645
IQR	196 - 991

Table 3 Factors affecting antibody level against receptor binding domain (anti-RBD)

Characteristics	N	Anti-SARS-CoV-2 Response		P-value
		Median U/ml	[IQR]	
Gender				
Male	77	379	(145 - 1210)	0.427
Female	135	429	(221 - 942)	
Age (years)				
<70	143	464	(220 - 1454)	0.150
≥70	69	368	(130 - 684)	
BMI (kg/m^2)				
<23.0	51	325	(152 - 707)	0.116
23.0-24.9	29	399	(125 - 1051)	
≥25.0	132	462	(208 - 1441)	
Duration of type 2 diabetes (years)				
<10	69	368	(177 - 966)	0.494
≥10	143	429	(204 - 1087)	
HbA1c (%)				
<7.0	68	413	(213 - 908)	0.811
≥7.0	144	406	(188 - 1105)	
Comorbidity				
Cardiovascular disease				
No	190	442	(203 - 1150)	0.021
Yes	22	258	(128 - 438)	
Other comorbidity				
No	204	260	(127 - 1518)	0.505
Yes	8	413	(201 - 988)	

P-value corresponds to the Mann-Whitney U test or the Kruskal-Wallis test
BMI, body-mass index; HbA1c, Glycated hemoglobin; ESRD, End stage renal disease

According to the study results, 29.7% of patients with type 2 diabetes had side effects after receiving the ChAdOx1 nCoV-19 vaccine. In addition, the most common side effect was muscle pain (15.6%). (figure 1)

Regarding the COVID-19 infection rate of patients with diabetes in the third month after receiving the second dose of the ChAdOx1 nCoV-19 vaccine, the results indicated that none of the patients infected with COVID-19 had it in the third month after receiving the ChAdOx1 nCoV-19 vaccine; the COVID-19 infection rate of patients with diabetes in the third month after receiving the ChAdOx1 nCoV-19 vaccine was 0.0%. (figure 1)

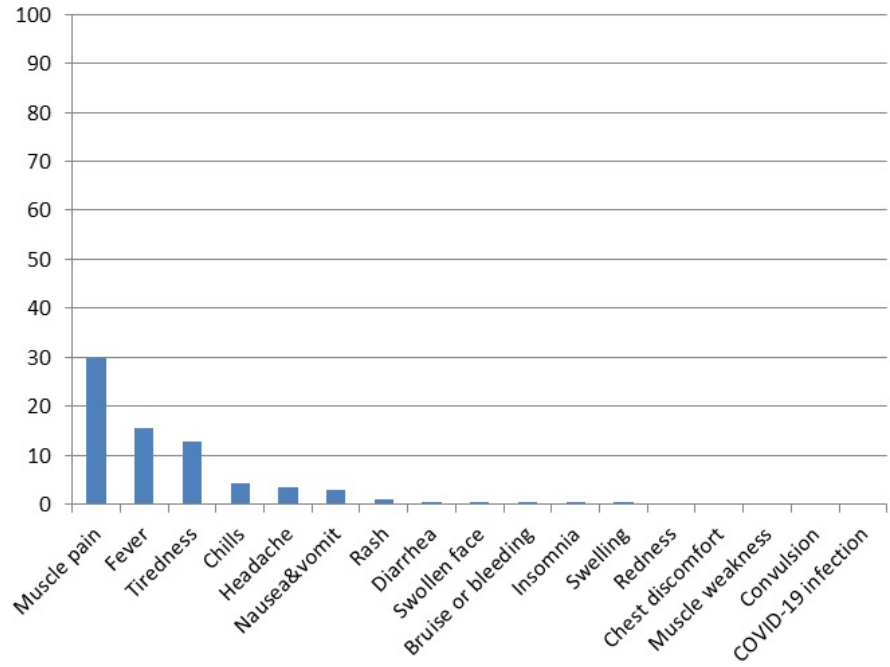

Figure 1

DISCUSSION

There have been many questions and concerns about the effects of vaccination on patients with diabetes. Clinical evidence seems limited only to the immune response after COVID-19 vaccination. Based on this study, analysis of the results of antibody levels against spike protein receptor binding domain (anti-RBD) and factors affecting anti-RBD 3 months after receiving the ChAdOx1 nCoV-19 vaccine in patients with type 2 diabetes were gender, age, BMI, duration of diabetes, HbA1c levels, and other comorbidities. The median of anti-RBD levels between subgroups revealed no statistically significant differences except for cardiovascular disease, in which the median of anti-RBD levels between groups had statistically significant differences. In patients with diabetes, age, gender, BMI, duration of diabetes, HbA1c levels, and other comorbidities had no effect on the anti-RBD level 3 months after receiving a second dose of the ChAdOx1 nCoV-19 vaccine. The results for age, gender, BMI, and hypertension were consistent with the results from the previous cohort study[9]. The previous cohort study indicated that type 2 diabetes had antibody titers (SARSCoV-2-specific IgG and neutralizing antibody responses, following two doses of Pfizer-BioNTech BNT162b2 mRNA vaccine) that were significantly lower than non-diabetics. In contrast, age, gender, BMI, and hypertension did not significantly affect antibody titers. The results of glycemic control (HbA1c levels) were in contrast with an observational study (CAVEAT study) since the observational study reported a lower antibody response to COVID-19 vaccination in people with type 2 diabetes having an HbA1c above 7.0%, compared with normoglycemic individuals and type 2 diabetes patients with good glycemic control[10]. However, the results of this observational study should be interpreted in the context of certain limitations. This was a single-health system study and the participants included in the study received several different vaccines (mRNA-BNT162b2 and mRNA-1273 vaccine, ChAdOx1 nCoV-19 vaccine).

The median of anti-RBD levels in patients with type 2 diabetes, with and without cardiovascular disease as a comorbidity, showed statistically significant differences. Cardiovascular disease might affect the anti-RBD level in patients with diabetes after receiving a second

dose of the ChAdOx1 nCoV-19. These results were consistent with a previous prospective study related to the RBD-IgG level after receiving the BNT162b2 mRNA COVID-19 vaccine in patients with cardiovascular disease (CVD)[11]. The study found that patients with CVD may have a poor humoral response to the BNT162b2 mRNA COVID-19 vaccine. The mechanisms that emphasized the association between CVD and a poor humoral response to the BNT162b2 mRNA COVID-19 vaccine remain unclear. It is possible that the medications used could be associated with a lower humoral response in patients with CVD. Further investigations are required to clarify this issue. However, the results of this prospective study should be interpreted in the context of certain limitations, such as the small sample size, a single-center study approach, and the paucity of long-term data.

In this regard, data from future research studies conducted in Thailand are required. Currently, there is insufficient medical information on the topic, including the use of antibody level testing against spike protein receptor binding domain (anti-RBD), to confirm that antibody detection can prevent COVID-19 infection or serve as a protective antibody. Moreover, further studies are required to clarify how antibody titers potentially affect COVID-19 morbidity.

Regarding the side effects and COVID-19 infection rates of patients with diabetes after receiving the ChAdOx1 nCoV-19 vaccine, the study found that the most common side effect was injection site pain, which was consistent with the current data. On the other hand, no serious side effects from COVID-19 vaccination were detected[12].

Research participants were selected from patients with type 2 diabetes who had undergone treatment at the Endocrinology and Metabolism Clinic, Vajira Hospital and received two doses of the ChAdOx1 nCoV-19 vaccine for 3 months. Data from the database of the E-phis could not be used to represent all patients with diabetes in Thailand. Therefore, the lack of data concerning the non-diabetes population who received two doses of the ChAdOx1 nCoV-19 vaccine for comparing the vaccine response should be addressed. Due to the current situation and the limited quantity of vaccines in Thailand, policies related to exclusively providing the ChAdOx1 nCoV-19 vaccine to high-risk patients with comorbidities such as diabetes were formulated. In contrast, the general population without diabetes has been approved for inactivated COVID-19 vaccination. Moreover, multiple types of COVID-19 vaccines were imported and developed in Thailand during the middle of 2021, contributing to heterologous schedules combining multiple vaccine platforms (e.g. vaccinating a vectored vaccine followed by an mRNA vaccine). In data collection, therefore, there was a small number of participants receiving two doses of the ChAdOx1 nCoV-19 vaccine.

CONCLUSION

Patients with type 2 diabetes and cardiovascular disease as a comorbidity had statistically significant differences in Anti-SARS-CoV-2 responses after receiving a second dose of the ChAdOx1nCoV-19 vaccine for 3 months. Age, gender, BMI, duration of diabetes, HbA1c levels, and other comorbidities had no effect on the Anti-SARS-CoV-2 response. Accordingly, patients with type 2 diabetes and cardiovascular disease are at a high risk for a poor prognosis with COVID-19. Thus, they should be a prioritized group to be vaccinated with a vaccination booster.

CONFLICTS OF INTEREST

The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Prevalence of Thiamine Deficiency in Cirrhotic Patients

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ABSTRACT

OBJECTIVE: This study aimed to evaluate the prevalence of thiamine deficiency in outpatient cirrhosis and compare thiamine deficiency between alcoholic cirrhosis and non-alcoholic cirrhosis, whether there are any factors or clinical outcomes associated with thiamine deficiency, and short-term follow-up after vitamin B1 replacement.

METHODS: This cross-sectional study included patients who were diagnosed with cirrhosis at the Gastrointestinal and Hepatology Division of Vajira Hospital in outpatient settings. All patient data characteristics were collected and also baseline laboratory and erythrocyte transketolase activity (ETKA), which is a standard test for the diagnosis of thiamine deficiency. Patients who were diagnosed with thiamine deficiency were identified as ETKA ≥ 1.25. Thiamine deficiency patients were tested for clinical outcomes; ophthalmoplegia, nystagmus, ataxia, and Adult ADHD self-report scale v.1.1 and all of them underwent replacement with vitamin B1 for 3 months.

RESULTS: From January 2020 to December 2020, 121 eligible cirrhotic patients were enrolled. Alcoholic cirrhosis comprised 41/121 (33.9%), and non-alcoholic cirrhosis amounted to 80/121 (66.1%). The comparison of prevalence in alcoholic and non-alcoholic cases was 14.6% vs. 11.2% (P=0.59). Neither the severity of disease nor baseline nutritional status was related to thiamine deficiency. The prevalence of hepatocellular carcinoma (HCC) was higher in the thiamine deficiency group compared to the others (46.7% vs. 12.3%; p=0.003). In univariate analysis, HCC was the only factor related to thiamine deficiency. Almost all thiamine deficiency status cases did not have either neurologic abnormality or any attention deficit.

CONCLUSION: Thiamine deficiency was found in end-stage liver disease, irrespective of cirrhotic etiology. HCC was considered an associated factor of the thiamine deficiency. The occurrence of HCC may be emphasized as a proxy for the condition of thiamine deficiency.

KEYWORDS: alcoholic cirrhosis, non-alcoholic cirrhosis, thiamine deficiency

INTRODUCTION

Thiamine or vitamin B1 is an essential co-enzyme in multiple metabolism pathways, especially glucose metabolism, and is a factor for producing neurotransmitters[1]. Clinical presentation in thiamine deficiency is varied depending on the stage, ranging from asymptomatic, through nonspecific symptoms such as fatigue, memory disturbance, sleep-wake disturbance, anorexia, abdominal pain, and constipation. It can present with cardiac beriberi, lactic acidosis, bradycardia, edema, Wernicke-Korsakoff syndrome, delirium,

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ventricular thickening, and brain edema in the end terminal stage[1,2,6,16]. The diagnosis of thiamine deficiency in this study is confirmed when erythrocyte transketolase activity (ETKA) is equal to or more than 1.25[7-8].

The most common cause of thiamine deficiency in Thailand is chronic alcoholism, though other causes include the consumption of raw food that contains thiaminase[6], renal replacement therapy in end-stage renal disease (ESRD) patients, acute illness, hyperthyroidism, pregnancy, and lactation[1]. Around 40% of thiamine is found in tissue, with the remainder being accumulated in the heart, liver, kidney, and brain, respectively. Therefore, chronic liver disease patients were associated with thiamine deficiency[15]. In a previous study, the incidence was 80% in alcoholism. Until now, there has been no known defined mechanism for thiamine deficiency. Probable hypotheses encompass multiple factors: poor intake, decreased accumulation in the hepatocyte, and decreased absorption of thiamine in the gastrointestinal tract from ethanol toxicity[1,4-5]. In addition to thiamine deficiency, deficiencies in other minerals, including vitamins A and D are associated with negative effects on the prognosis of liver cirrhosis[3].

In this study, we compared thiamine deficiency status in alcoholic cirrhosis and non-alcoholic cirrhosis, and evaluated the clinical manifestation of thiamine deficiency in patients while examining other factors associated with thiamine deficiency. Moreover, patients who were diagnosed with thiamine deficiency underwent thiamine replacement for three months due to previous data showing improving liver enzymes, increase survival, and prevention of cirrhotic complications after thiamine replacement[4-5].

METHODS

This was a cross-sectional, analytical, single center study. Ethical approval by Faculty of Medicine Vajira Hospital Navamindradhiraj University COA 018/2563. Patients were recruited from the outpatient department of the Gastrointestinal and Hepatology Division, Department of Medicine, Navamindradhiraj University, between February 2020 and December 2020. The trial was approved by the institutional ethics review committee. The patients provided informed consent before enrolling.

Cirrhotic patients were screened for the following criteria of eligibility: age 15-80 years, diagnosed with cirrhosis by ultrasound, computer tomography scan (CT), transient elastography above 13 kPa, magnetic resonance imaging (MRI), or by liver biopsy[9-14]. Key exclusion criteria included patients who were diagnosed with thiamine deficiency or use of thiamine replacement therapy before enrolling, acute illness in 2 weeks, pregnant women, hyperthyroidism, ESRD and on renal replacement therapy, or gastrointestinal tract surgery with anastomosis.

The medical records of each cirrhotic patient were reviewed. The patients who had fulfilled the aforementioned enrollment criteria were selected. Blood tests were performed at the baseline: liver function test, coagulogram, renal function test, sodium, and ETKA. Other data were collected from medical records including gender, age, body weight, height, body mass index, etiology of cirrhosis, alcohol consumption, method for diagnosis of cirrhosis, Child Turcotte Pugh score (CTP), Model for End Stage Liver Disease (MELD) score, and comorbid diseases. Patients were also evaluated for nutritional status and malnutrition by the Royal Free Hospital-Nutritional Prioritizing tool (RFH-NPT)[18-19]. Society of Parenteral and Enteral Nutrition of Thailand (SPENT) nutritional screening tool, and followed by Nutrition Alert Form (NAF)[20] if the score from SPENT was equal to or greater than 2.

The patients who were diagnosed with thiamine deficiency by ETKA equal to or greater than 1.25 were physically examined for nystagmus, ophthalmoplegia, and ataxia to evaluate Wernicke-Korsakoff syndrome, and were tested for adult attention deficit hyperactivity disorder (ADHD) using the Adult ADHD Self

Report Scale (ASRS) screen version 1.1 to diagnose attention deficit if the score was higher than 4[16]. These patients received vitamin B1-6-12 (Patar3B) which contained 100 mg thiamine twice daily for three months, followed up with ETKA, neurological signs, and ASRS V1.1 at 3 months, including side effects of thiamine replacement.

The primary outcome is the comparison for the prevalence of thiamine deficiency between alcoholic cirrhosis and non-alcoholic cirrhosis. The secondary assessment included the following: (1) factors influencing thiamine deficiency other than the etiology of cirrhosis; (2) clinical manifestation of thiamine deficiency patients in neurologic signs and symptoms and attention deficit; (3) improvement of thiamine deficiency after replacement for 3 months.

Based on the previous trial by Rossouw[7], it was estimated that there was 70.6% thiamine deficiency in alcoholic cirrhosis and 42.8% in non-alcoholic cirrhosis. The number of patients needed to evaluate the prevalence in this study was calculated to be at least 200 with a significance level of 0.05 (one-tailed). All patients enrolled in the study were analyzed. Categorical variability was presented as proportion or frequency, while continuous variables were presented as mean with standard deviation or median (interquartile range). P-values correspond to the independent t-test or Mann-Whitney U and Chi-square tests. Logistic regression was also used to evaluate the association between thiamine deficiency and baseline demographic data. All tests were two-tailed and P<0.05 was considered to indicate statistical significance.

RESULTS

A total of 121 cirrhotic patients were enrolled in this study, with the mean age of 58 ± 10.5 years, of whom 88 (73%) were male. Alcoholic etiology was found in 41 patients (33.9%). Non-alcoholic cirrhosis in this study included chronic hepatitis B (CHB), chronic hepatitis C (CHC), non-alcoholic steatohepatitis (NASH), cardiac cirrhosis, cryptogenic cirrhosis, and autoimmune hepatitis (AIH). The most common cause of cirrhosis was CHC (31.4%), followed by CHB (19%). The median duration of cirrhosis was 20.9 months. Due to the outpatient setting, the severity of cirrhosis was mostly mild. Most cases were in child A (81.8%) and the mean MELD score was 9.78±3.85. Only one patient could not undergo evaluation of severity due to concurrent warfarin consumption, while 20 of 121 cases (16.5%) had hepatocellular carcinoma (HCC) at the time of enrollment. In terms of nutritional status, most of the patients had a low risk of malnutrition when assessed by RFH-NTP (86 from 121, 71%). The baseline parameters are summarized in Table 1.

Table 1 The baseline parameters of 121 cirrhotic patients

Baseline parameter	
Gender N (%)	
Male	88 (73)
Age (Mean ± SD)	58.03 ± 10.5
Etiology N (%)	
Alcoholic cirrhosis	41 (33.9)
CHC	38 (31.4)
CHB	23 (19)
NASH	14 (11.6)
CHB and CHC	2 (1.6)
Cardiac cirrhosis	1 (0.8)
Cryptogenic cirrhosis	1 (0.8)
AIH	1 (0.8)
Child-Pugh score (N)	
A	99
B	15
C	6
MELD score (Mean ± SD)	9.78 ± 3.85
RFH-NPT	
Low risk	86 (71.1)
Moderate risk	19 (15.7)
High risk	16 (13.2)

Abbreviations: CHC, chronic hepatitis C; CHB, chronic hepatitis B; NASH, non-alcoholic steatohepatitis; AIH, autoimmune hepatitis; RFH-NPT, Royal Free Hospital-Nutritional Prioritizing tool

Of 121 cirrhotic patients, thiamine deficiency in this study affected 15 patients, and the prevalence was 12.4% (figure 1). There was no different in the prevalence of thiamine deficiency between alcoholic vs. non-alcoholic etiology (14.6% vs. 11.3%; p=0.59) (figure 2). Moreover, more than half (60%) of the thiamine deficiencies were within non-alcoholic cirrhosis. In a non-alcoholic setting, mostly CHC 5 (33.3%) patients, followed by CHB 4 (26.7%) (table 2).

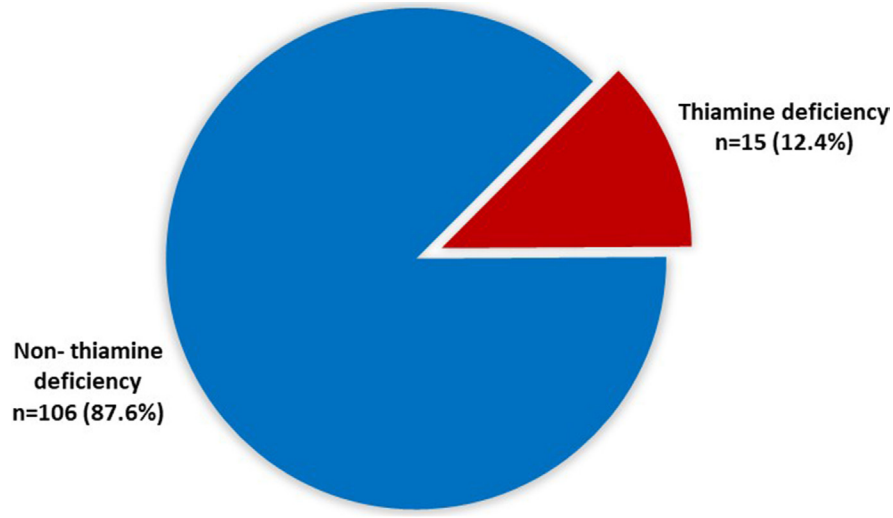

Figure 1 Prevalence of thiamine deficiency

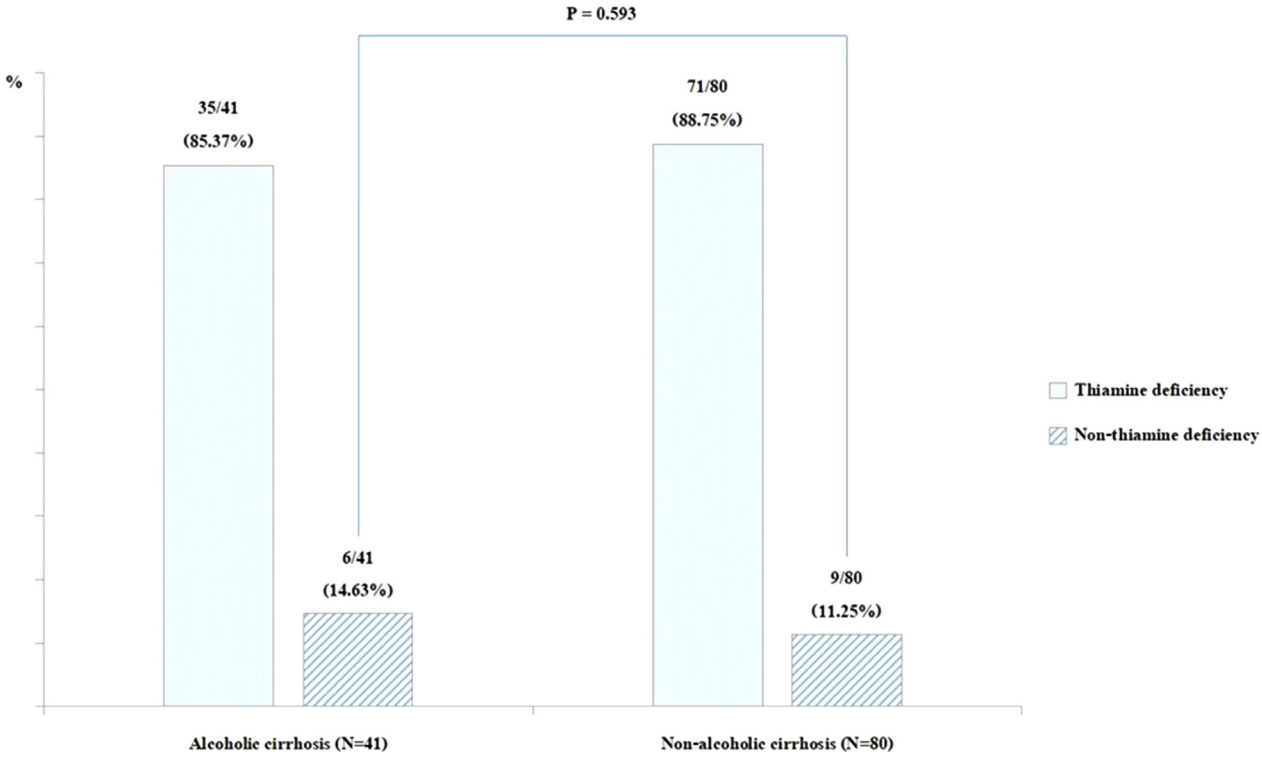

Figure 2 Comparison of the prevalence of thiamine deficiency in alcoholic and non-alcoholic cirrhosis

Table 2 Comparison of the demographic data and ETKA level between the thiamine deficiency group and the non-thiamine deficiency group, along with subgroup analysis

	Thiamine deficiency (n=15)	Non thiamine deficiency (n=106)	P-value
Gender			
Male	12 (80%)	76 (71.7%)	0.758
Female	3 (20%)	30 (28.3%)	0.758
Age (years)#	57.07 ± 6.72	58.17 ± 10.89	0.701
<50	2 (13.3%)	27 (25.5%)	0.518
≥50	13 (86.7%)	79 (74.5%)	0.518
Body weight (kg) #	71.87 ± 14.94	66.92 ± 14.4	0.218
Height (cm) #	167.43 ± 10.09	163.42 ± 9.88	0.157
BMI (kg/m^2) #	25.93 ± 4.67	25.1 ± 4.76	0.528
Etiology of cirrhosis			
Alcoholic cirrhosis	6 (40%)	35 (33%)	0.593
Non-alcoholic cirrhosis	9 (60%)	71 (67%)	0.593
Non-alcoholic cause			
CHC	5 (33.3%)	33 (31.1%)	0.864
CHB	4 (26.7%)	19 (7.9%)	0.419
CHB, CHC	0 (0%)	2 (1.9%)	1.000
AIH	0 (0%)	1 (0.9%)	1.000
Cardiac cirrhosis	0 (0%)	1 (0.9%)	1.000
cryptogenic	0 (0%)	1 (0.9%)	1.000
NASH	0 (0%)	14 (13.2%)	0.212
Amount of alcohol (gm/d)#	116.83 ± 81.65	137 ± 97.01	0.634
No	9 (60%)	71 (67%)	0.575
<50 gm/d	1 (6.7%)	6 (5.7%)	1.000
50-100 gm/d	3 (20%)	13 (12.3%)	0.418
100-200 gm/d	1 (6.7%)	11 (10.4%)	1.000
>200 gm/d	1 (6.7%)	5 (4.7%)	0.556
Drinking duration (months) #	140 ± 61.97	258.86 ± 132.87	0.039*
Cessation alcohol (months) #	63.83 ± 97.75	46.54 ± 89.67	0.669
<3 months	2 (13.3%)	17 (16%)	1.000
3-6 months	0 (0%)	1 (0.9%)	1.000
>6 months	4 (26.7%)	17 (16%)	0.293
Transient elastography (kPa) #	36.86 ± 20.34	28.9 ± 15.67	0.295
Duration of diagnosis cirrhosis #	40.86 ± 92.92	18.24 ± 21.04	0.380
Child-Pugh score			
A	12 (80%)	87 (82.1%)	0.735
B	3 (20%)	12 (11.3%)	0.397
C	0 (0%)	6 (5.7%)	1
Child-Pugh score#	5.67 ± 0.98	5.86 ± 1.46	0.625
MELD score#	8.5 ± 1.99	9.95 ± 4.01	0.486
Comorbidity			
Diabetic mellitus	5 (33.3%)	23 (21.7%)	0.334
Hypertension	4 (26.7%)	29 (27.4%)	1
HIV infection	0 (0%)	5 (4.7%)	1
HCC	7 (46.7%)	13 (12.3%)	0.003*

Table 2 Comparison of the demographic data and ETKA level between the thiamine deficiency group and the non-thiamine deficiency group, along with subgroup analysis (continued)

	Thiamine deficiency (n=15)	Non thiamine deficiency (n=106)	P-value
SPENT nutrition tool			
0	4 (26.7%)	39 (36.8%)	0.570
1	11 (73.3%)	63 (59.4%)	0.401
2	0 (0%)	4 (3.8%)	1.000
NAF	N/A	8.25 ± 4.92	N/A
NAF level			
1	0 (0%)	2 (1.9%)	1.000
3	0 (0%)	2 (1.9%)	1.000
RFH-NPT			
low risk	11 (73.3%)	75 (70.8%)	1.000
moderate risk	2 (13.3%)	17 (16%)	1.000
high risk	2 (13.3%)	14 (13.2%)	1.000
ETKA level at diagnosis#	1.43 ± 0.21	1.03 ± 0.11	<0.001*

Abbreviations: N/A, not available; CHC, chronic hepatitis C; CHB, chronic hepatitis B; NASH, non-alcoholic steatohepatitis; AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; NAF, nutrition alert form; RFH-NPT, Royal Free Hospital-Nutritional Prioritizing tool; ETKA, erythrocyte transketolase activity
* Indicates P < 0.05
# Values are reported as mean ± SD

Neither the amount of alcohol nor the abstinence time before ETKA was different in mean thiamine levels (116.8 ± 81.6 gm/day vs. 137 ± 97 gm/day; P=0.63 in amount of alcohol, 63.8 ± 97.8 months vs. 46.5 ± 89.7 months; P=0.67 in abstinence duration). However, drinking duration was shorter in thiamine deficiency (140 ± 61.97 months vs. 258.86 ± 132.87 months; P=0.039). In the thiamine deficiency group, 12 patients (80%) were CTP A, 3 (20%) were CTP B cirrhosis, and there was no CTP C in this group. The mean MELD score was 8.5 ± 1.99 (table 2).

In the part of nutritional status, 4 from 15 (26.7%) had a score of 0, 11 from 15 (73.3%) had a score of 1 from the SPENT nutrition screening tool, so in cases where the score was less than 2, nobody in this group was evaluated for NAF level. And most of the patients (11, 73.3%) were classified in the low-risk group for malnutrition by RFH-NTP. In the thiamine deficiency group, the mean of ETKA was 1.43 ± 0.21 at diagnosis (table 2).

Of the 15 patients with thiamine deficiency from ETKA diagnosis, 12 patients underwent complete neurological examination and performed the ASRS V1.1 test at the baseline before thiamine replacement, but the remaining 3 patients (20%) were lost at follow up and did not have thiamine replacement. At baseline neurologic signs, one patient had peripheral nystagmus, and another patient had an abnormal ASRS test. After 3 months of thiamine supplementation, a persistent abnormal ASRS test but the disappearance of peripheral nystagmus could be seen. During follow up, a total of 5 (4.1%) patients did not survive: 1 from 15 (6.7%) in the thiamine deficiency group died from the advanced stage of HCC after 2 months of diagnosis, and of the remaining 4 from 106 (3.8%) in the non-thiamine deficiency group, 2 patients died from liver-related causes (1 ruptured HCC, 1 severe alcoholic hepatitis), and the others died from sepsis; Figure 3 No statistically significant variance was found in deaths between the 2 groups; P = 0.598.

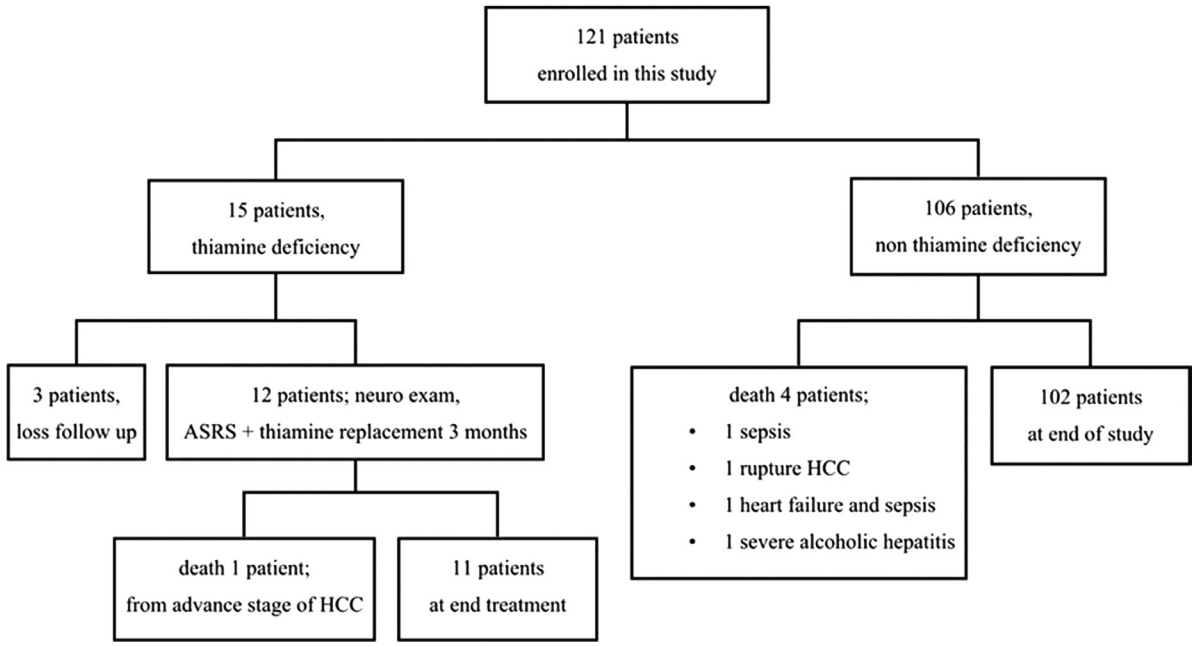

Figure 3 Patient flow chart, follow up diagram

Among the 2 groups who were diagnosed with thiamine deficiency and non-thiamine deficiency, there was no difference in terms of baseline age, etiology, and severity of liver disease: male gender, age, alcoholic cirrhosis, non-alcoholic cirrhosis, CHB cirrhosis, CHC cirrhosis, liver stiffness, CTP score, MELD score, and comparable in nutritional status when evaluated by SPENT and RFH-NPT tests (table 2). For logistic regression, HCC patients were 4.42 times (95% CI 1.18, 10.08) significantly greater in the thiamine deficiency group (46.7% vs. 12.3%; P=0.003) (table 3). Most of the HCC patients were in the intermediate stage based on the Barcelona Clinic Liver Cancer (BCLC) criteria. Moreover, we found nearly one-third of HCC cases had thiamine deficiency, mostly CHB 4 patients, CHC 2 patients, followed by 1 patient in alcoholic cirrhosis.

Table 3 Logistic regression analysis to evaluate factors associated with thiamine deficiency

	Univariate	
	OR (95%CI)	P-value
Etiology of cirrhosis		
Alcoholic cirrhosis	1.35 (0.4, 4.6)	0.593
Non-alcoholic cirrhosis	0.74 (0.2, 2.7)	0.593
Child-Pugh score		
A	0.89 (0.3, 2.9)	0.735
B	1.77 (0.6, 5.5)	0.397
C	N/A	1
Hepatocellular carcinoma	4.42 (1.8, 10.8)	0.003*
RFH-NPT		
Low risk	1.12 (0.4, 3.3)	1.000
Mod risk	0.83 (0.2, 3.4)	1.000
High risk	1.01 (0.3, 4.1)	1.000

Abbreviations: N/A, not available; NAF, nutrition alert form; RFH-NPT, Royal Free Hospital-Nutritional Prioritizing tool

Mean ETK activity at the baseline was 1.43 ± 0.21 in the thiamine deficiency group. After 3 months of 200 mg/day of thiamine replacement in 11 patients, the mean ETKA decreased to a level of 1.04 ± 0.15. Significant improvement of mean ETKA was -0.41 ± 0.26; P < 0.001. ETKA improvement did not depend on the etiology and severity of disease. In only 1 from 11 patients did ETKA not return to normalization.

DISCUSSION

In this study, we report data from a prospective cohort on thiamine deficiency status in cirrhotic patients. As thiamine status is not easy to evaluate and unavailable in general hospitals, data concerning the exact prevalence of thiamine deficiency in cirrhosis are scarce. In this study, we observed that thiamine deficiency was found to be 12.4% in stable cirrhotic patients, while 80% were CTP A. This is similar to the trial of Bandidwattanawong in 2019, for which the prevalence of thiamine deficiency was 13.2% in cirrhosis with complications, although half of enrolled patients (52.6%) were CTP B[21]. These data may imply that the severity of disease was not correlated to the thiamine level. Consistent with the trial of Stephane Levy in 2002[17], thiamine deficiency was 21.6% in alcoholic and CHC cirrhosis, classified to CTP A 21%, B 47%, and C 31%. Because thiamine deficiency is related to multiple factors, such as food type, medication, and acute infection which can occur in any stage of the disease, the severity of disease alone cannot predict thiamine status. And in this study might be under estimate of prevalence thiamine deficiency in cirrhosis because most case in Child pugh A. So, we need more data and sample size to analyze association between thiamine deficiency and severity of cirrhosis.

Prevalence of thiamine deficiency was varied, in comparison to the trial of Rossouw in 1978[7]. The prevalence in our study was lower, as 14.6% (6/41) had thiamine deficiency status in the current study compared to 70.6% in the Rossouw trial in alcoholic cirrhosis, and 11.3% (9/80) vs. 42.8% from the Rossouw trial in the non-alcoholic cirrhosis setting. Since the previous study enrolled severely ill-patients, in each case there were at least two of the following features: hepatic encephalopathy, jaundice, ascites, low albumin, and coagulopathy, which may result in predisposition to a higher prevalence of thiamine deficiency. Focusing on etiology, the current study found no difference in thiamine status in alcoholic and non-alcoholic etiology (P=0.59), consistent with the Stephane Levy trial, and no difference in frequency of thiamine deficiency was found between alcoholic and chronic hepatitis C cirrhosis (25% vs. 19%; P=0.09)[17]. And because sample size in this study are less than calculation that might not show significant different of both groups.

Neither the amount of alcohol consumption nor the abstinence time was different in mean thiamine levels. However, the duration of consumption was longer in the non-thiamine deficiency group in this study. This may be due to unreliable alcoholic habitual information from patients or binge drinking of alcohol rather than regular consumption in the thiamine deficiency group. Therefore, gamma glutamyl-transferase (GGT) is possibly helpful in determining alcoholic status at the time of enrollment.

Wernicke's encephalopathy is often mentioned in thiamine deficiency. The triad of nystagmus, ophthalmoplegia, and mental status change was found in only 16% of patients[22]. In this study, only one (8.3%) had peripheral nystagmus and another one had attention deficit. Due to the small sample size of the thiamine deficiency group, and no confirmatory test by imaging, neurological abnormality is not significant in this study.

In the current study, hepatocellular carcinoma (HCC) is the only associated factor of thiamine deficiency status (OR 4.42,1.81-10.8). There is no prevalence of thiamine deficiency in HCC in previous studies, but among patients with all cancers, a high rate of thiamine deficiency was observed. Thiamine deficiency was found in 55.3%

of cancer patients for which hepatopancreatobiliary was 7.4% in the Isenberg-Grzeda trial 2017[23]. In our study, HCC may be a predisposing factor of thiamine deficiency due to loss of appetite, receiving transarterial chemoembolization (TACE) in most cases, and increasing metabolic demands which is the mechanism of relative thiamine deficiency[23].

Our study has the strength of a cross-sectional study, together with detailed demographic baseline characteristics, etiology of cirrhosis, and HCC data. Data from the real-life cohort represent a spectrum of patients wider than randomized controlled trials. This result applies to routine clinical practice. Nonetheless, our study has some limitations. First, the sample size of cirrhotic patients was less than the 200 calculated to be enrolled at first due to the limited duration of the study and the COVID-19 outbreak, causing fewer patients to present at the outpatient department. Second, the current trial was studied in a single center, so it cannot be used to validate data for other centers. Third, this is a single-arm study with no placebo arm for comparing the efficacy of thiamine replacement therapy. Fourth, we did not record compliance with thiamine replacement or document food types that may be associated with the improvement of ETKA. And the last one, HCC usually arises from cirrhosis and prone to be more nutritional deficiency, so we cannot definitely summarize that HCC is only one factor of thiamine deficiency.

In future studies, outcomes after thiamine replacement such as improvement of CTP, MELD score, or cirrhotic complications are needed. Following cessation of thiamine replacement is interesting, whether or not there is a return to deficiency status.

CONCLUSION

All etiologies of cirrhosis are associated with thiamine deficiency, not only alcoholic cirrhosis. Hepatocellular carcinoma also associated with thiamine deficiency, but not in end stage liver disease, child B and C. The possible cause of this association is still doubtful, because it did not show in advanced liver disease, especially child C. Empirical replacement of thiamine in cirrhosis and HCC may be beneficial. Consistent with European Association for the Study of the Liver (EASL) clinical practice guidelines on nutrition in chronic liver disease (2019), supplementary oral multivitamins are recommended in decompensated cirrhosis because of the cost effectiveness and lack of serious side effects[24] .

CONFLICT OF INTEREST

The authors report no relevant conflicts of interest for this article.

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DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Remote Ischemic Preconditioning to Prevent Contrast-Associated Kidney Injury in Elective Coronary Angiogram: A Randomized Controlled Trial

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ABSTRACT

OBJECTIVE: Remote ischemic preconditioning (RIPC) is a new strategy to prevent organ injury from oxidative stress and ischemic reperfusion injury, particularly for the kidney, heart, and brain. Contrast-associated acute kidney injury (CA-AKI) is a complication of coronary angiography (CAG). Based on previous studies, whether RIPC prevents CA-AKI post-CAG remains unclear. Therefore, this study aims to compare the efficacy of standard (std) management and standard management with RIPC to prevent CA-AKI post-CAG.

METHODS: This study was an open-label 1:1 randomized controlled trial. The elective CAG patients with an estimated glomerular filtration rate of 15–45 mL/min/1.73 m^2 were enrolled. For the RIPC group, patients performed RIPC starting from inflating manual cuff pressure to 200 mmHg for 5 min on an extremity and then deflating 5 min alternate to four times before coronary angiogram at least 1 hr. All patients had received the usual standard management of pre-CAG. The AKI outcomes were evaluated at 48 hrs and 1 week post-CAG. The adverse events were also assessed.

RESULTS: A total of 27 patients (RIPC group = 14, std group = 13) were enrolled in this study. Baseline characteristics were comparable between both groups except for male gender was higher in the RIPC group (std group 7 [53.85%] and RIPC group 11 [78.57%]), in part of the amount of contrast media volume and procedure duration was higher in the std group (mean contrast volume are 140 [120] mL in the std group and 40.00 [31.25] mL in the RIPC group). No AKI event was observed in the RIPC group. By contrast, AKI in the std group at 48 hrs included two (15.4%) participants and one (7.7%) participant at 1 week. Serious adverse events were not observed in both groups.

CONCLUSION: RIPC may be implemented as a systematic strategy to prevent CA-AKI post-CAG. Some researchers tend to improve CA-AKI. Further studies in a larger number of participants may verify the benefit of RIPC and provide definite conclusion.

KEYWORDS: acute kidney injury, contrast media, coronary angiogram, remote ischemic preconditioning

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INTRODUCTION

Contrast-associated acute kidney injury (CA-AKI) is the third most common cause of hospital-acquired acute kidney injury (AKI) caused by the frequent use of contrast media for diagnostic tools and most intervention procedures[1]. Diagnosis of CA-AKI is indicated by the increase of serum creatinine level after exposure to contrast media and exclusion of another causes[2]. The incidence of CA-AKI varies in several studies, accounting for 9.1%–31.9%[3-4].

The mechanism of CA-AKI is not well proven but perhaps from direct toxic to renal cellular and renal hemodynamic modification as intrarenal vasoconstriction[5]. Contrast media produce oxygenated free radicals and proinflammatory cytokines, which cause AKI and acute tubular necrosis[6-7]. However, using contrast media may affect high-risk patients, particularly those with chronic kidney disease (CKD), and a higher Mehran's risk score, which evaluates the risk of CA-AKI[8-9].

A previous large recent clinical trial has shown no benefit of N-acetylcysteine in CA-AKI[10]. In addition, a strategy to prevent CA-AKI remains unknown. Since 1993, remote ischemic preconditioning (RIPC) was studied to prevent myocardial ischemia after coronary artery bypass surgery and percutaneous coronary artery intervention[11]. The principle of RIPC is making repeated transient nonlethal ischemia and reperfusion to produce various mediators for physiological adaptation to tissue hypoperfusion[5,7]. The signal of transduction in RIPC cascades through the phosphoinositide 3-kinase/Akt (Protein kinase B)/endothelial nitric oxide synthase/cyclic guanosine monophosphate/PKG (Protein kinase G) pathway, thereby leading to the opening of the ATP-dependent mitochondrial potassium (K_{ATP}) channel. The activated mitochondrial K_{ATP} channels can limit the opening of mitochondrial permeability transition pores, thereby causing a marked improvement in cell survival[12]. Some studies suggest that CA-AKI may be due to anti-inflammatory or antioxidant effects, including decreased extracellular levels of noxious metabolites, by activating tumor necrosis factor receptor and promoting the production of manganese superoxide dismutase, a potent antioxidant and protector against reactive oxygen species[13-14]. Moreover, RIPC decreases the generation of free radicals such as xanthine oxidase activity[11].

Based on previous studies, numerous studies have shown the benefit of RIPC in preventing CA-AKI[3,5,11]. However, the data from the AKI high-risk group are scarce. Hence, the efficacy of RIPC for the prevention of AKI in patients who underwent elective CAG was explored in this study.

METHODS

This study was an open-label 1:1 randomized controlled trial conducted at a university hospital located in Bangkok, Thailand. The first date of enrollment was May 2020. This study was early terminated in January 2021 because of the following factors: (1) low rate of enrollment caused by the Coronavirus disease 2019 (COVID-19) pandemic and (2) low incidence of CA-AKI.

The inclusion criteria were as follows: at least 18 years of age, scheduled for an elective coronary angiogram, and the estimated glomerular filtration rate (eGFR) was stable at 15–45 mL/min/1.73 m^2 for at least 3 months. eGFR was calculated by CKD-EPI equation, expressed as a single equation: GFR = 141 * min (Scr/κ,1)$^{\alpha}$ * max (Scr/κ, 1)$^{-1.209}$ * 0.993^{Age} * 1.018 (if female) * 1.159 (if black).

However, given the small number of enrolled participants than expected, the inclusion criteria were amended by adding adjusting criteria to (1) eGFR <60 mL/min/1.73 m^2 and age >60 years old or (2) diabetes mellitus in June 2020. The critical exclusion criteria were as follows: AKI, congestive heart failure or acute myocardial infarction, active infection, history of recent nephrotoxic drug in the previous 3 months, and limb-amputated patients. The full inclusion and exclusion criteria were published in the

Thai clinical trial registry (TCTR20200526009). After enrollment, participants were randomly allocated to receive standard management or standard management with RIPC by using a block-of-four technique. The standard management group received isotonic intravenous hydration before the intervention and continued current medication. Blood pressure level was controlled to below 160/90 mmHg. We also controlled blood sugar at 80–140 mg/dL. Furthermore, they were checked, and the use of nephrotoxic drugs was discontinued. In RIPC, the procedure was performed by an investigator. The RIPC procedure[5] starts from inflating standard manual cuff pressure to 200 mmHg for 5 min on the left arm of the participant and then deflating 5 min alternate to four times before the coronary angiogram for at least 1 h (figure 1). All participants also received standard management to prevent CA-AKI.

The primary outcome was AKI, defined as an increase in serum creatinine level by ≥0.3 mg/dL within 48 hrs or an increase in serum creatinine level to ≥1.5 times baseline, which is known or presumed to have occurred within the last 7 days in accordance with the KDIGO guidelines[2]. Secondary outcomes were as follows: (1) the incidence of acute hemodialysis and (2) death. Serious adverse events and any adverse events were observed for 7 days. Specific adverse events included ischemic limb, presence of petechiae, and hematoma present at the extremity of patients who performed RIPC.

STATISTICAL ANALYSIS

Er *et al*.[14] reported that CA-AKI occurred in 40% of the patients in the control group but only 12% of the patients in the RIPC group (P = 0.002). We calculated the sample, and the result was compared between the two populations[15] with a confidence level 0.95, power 0.8, and dropout rate of 10%. The sample size was 40 patients for each group.

All continuous data were tested for normal distribution by using the Shapiro–Wilk test. We reported the mean ± standard deviation for normal distribution data and median (interquartile range) for otherwise. We compared the mean and median between the two groups by T-test and Mann–Whitney U test, respectively. Categorical data were presented in number and percentage by comparing using Chi-square test or Fisher's exact test depending on appropriateness. We performed modified intention-to-treat analysis for patients who follow-up after CAG at 48 hrs. Laboratory results for participants who lost follow-up on the 7th day after enrollment were obtained and analyzed using last observation carried forward. Statistical analysis was performed by Python version 3.7.10 (library-package: Pandas, 1.1.5; Numpy, 1.19.5; and Statsmodels, 0.11.1). A p-value of <0.05 was a threshold of statistical significance.

This study was approved by the research ethics committee of the Vajira Hospital, COA 150/2562. The trial was performed under the principles of the Declaration of Helsinki[17]. In addition, this trial was registered at the Thai Clinical Trials Registry (TCTR20200526009).

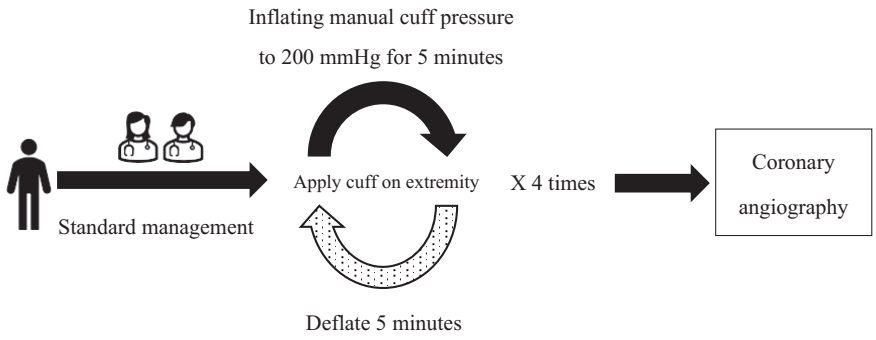

Figure 1 RIPC procedure

RESULTS

From June 2020 to January 2021, a total of 141 patients underwent screening (figure 2). Twenty-seven patients were randomly allocated to the standard management group (std group) with 13 patients and the RIPC group with 14 patients.

Baseline characteristics were primarily balanced between the two groups (table 1). The average age was 68 years old. The most common comorbidities were hypertension (85.1%), coronary artery disease (66.7%), and dyslipidemia (63.0%). Many participants in the std group had dyslipidemia and lower body weight. Current medications and laboratory baseline between the two groups were similar. However, in the CAG procedure, the amount of contrast media and procedure duration were significantly higher in the std group (mean contrast volume is 140.00 [120.00] mL in the std group and 40.00 [31.25] mL in the RIPC group).

The primary outcome was AKI at 48 hrs, which did not occur in the RIPC group. However, two (15.4%) events occurred in the std group (table 2). Both participants had AKIN stage 1. After CAG for 1 week, only one AKI event occurred in the std group. The serum creatinine level was not statistically different between the two groups at 48 hrs and the end of the study. However, eGFR at 48 hrs and the end of the study were higher in the RIPC group. No incidence of initiated hemodialysis or death occurred during the study.

Serious adverse events such as an ischemic limb, presence of petechiae, and presence of hematoma at the affected extremity were not observed during the study period.

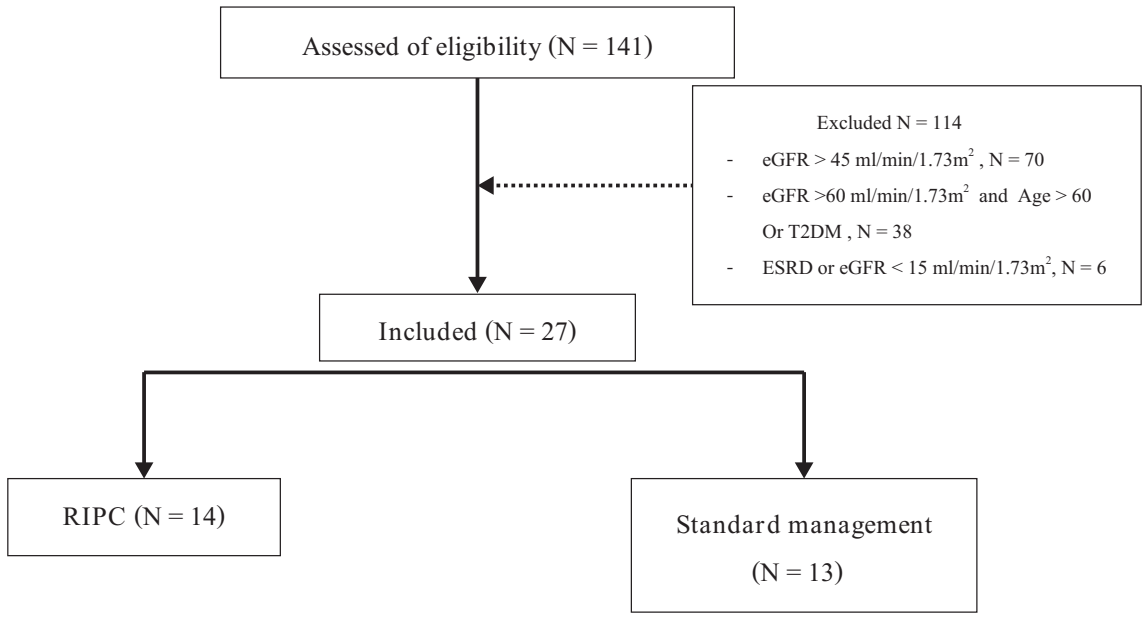

Figure 2 Consort flow diagram of randomization

Abbreviations: CAG, coronary Angiogram; N, number of participants; RIPC, remote ischemic preconditioning

Table 1 Baseline characteristics of participants*

characteristics	Total	Std-group	RIPC	P-value
N	27	13	14	
Age, years	68.67 (±6.99)	69.54 (±7.48)	67.86 (±6.41)	0.551
Male; N (%)	18 (66.67%)	7 (53.85%)	11 (78.57%)	0.173
Hypertension; N (%)	23 (85.10%)	11 (84.61%)	12 (85.71%)	0.935
Dyslipidemia; N (%)	17 (62.96%)	11 (84.61%)	6 (42.86%)	0.025
DM; N (%)	5 (18.50%)	2 (15.38%)	3 (21.43%)	0.686
CAD; N (%)	18 (66.67%)	10 (76.92%)	8 (57.14%)	0.276
Bodyweight, Kg	60.00 (12.35)	60.00 (7.00)	65.15 (12.65)	0.011
BMI, Kg/M^2	23.01 (3.56)	22.22 (2.79)	24.21 (2.95)	0.108
LVEF,%	42.60 (19.00)	45.50 (20.00)	42.20 (19.50)	0.279
Drugs, N (%)				
ASA	23 (85.10%)	11 (84.61%)	12 (85.71%)	0.936
Other antiplatelet	21 (77.78%)	12 (92.31%)	9 (64.29%)	0.080
Atorvastatin	20 (74.07%)	8 (61.54%)	12 (85.71%)	0.152
Other statin	4 (14.80%)	3 (23.07%)	1 (7.14%)	0.244
fibrate/ezetimibe	5 (18.51%)	2 (15.38%)	3 (21.43%)	0.686
B-blocker	22 (81.48%)	11 (84.61%)	11 (78.57%)	0.686
ACEI/ARB	20 (74.07%)	8 (61.54%)	12 (85.71%)	0.152
Diuretics	18 (66.67%)	8 (61.54%)	10 (71.43%)	0.586
DM drugs (oral)	6 (22.22%)	3 (23.07%)	3 (21.43%)	0.918
Insulin	1 (3.70%)	0 (0.00%)	1 (7.14%)	0.691
Lab				
Hemoglobin, g/dl	12.26 ± 1.64	11.68 ± 1.03	12.79 ± 1.90	0.085
FBS, mg/dl	119.77 ± 27.47	112.38 ± 28.69	117.15 ± 25.92	0.644
HbA1C,%	6.93 ± 1.11	6.94 ± 1.07	6.92 ± 1.17	0.975
Baseline serum creatinine, mg/dl	1.43 ± 0.29	1.45 ± 0.28	1.41 ± 0.29	0.744
Baseline eGFR, ml/min/1.73m^2	45.00 (15.50)	44.00 (13.00)	51.00 (14.25)	0.054
CAG details				
Contrast volume, ml	60.00 (110.00)	140.00 (120.00)	40.00 (31.25)	0.007
Mehran risk score	5.00 (6.00)	6.00 (7.00)	4.50 (4.50)	0.080
Total CAG times, minute	53.00 (61.50)	78.00 (63.00)	48.00 (44.50)	0.024
Intravenous fluid, L	1 (0)	1 (0)	1 (0)	0.144

*Plus-minus value is mean ± SD, number with parenthesis are median with interquartile range
Abbreviations: ASA, Aspirin; ACEI/ARB, Angiotensin-Converting-enzyme inhibitors/Angiotensin II receptor blocker; DM, Diabetes Mellitus; BMI, Body Mass index; CAD, Coronary artery disease; CAG, Coronary angiogram; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; g/dl, gram/deciliter; HbA1C, Glycosylated hemoglobin A1C; IQR, Interquartile range Kg, Kilogram; L, Liters; LVEF, Left ventricular ejection fraction; ml, Milliliters; mg/dL, milligrams/deciliter; sd, Standard deviation

Table 2 Primary outcome of CA-AKI in std-group and RIPC group*

Outcomes	Total	Std-group	RIPC	P-value
AKI at 48 hrs, N (%)	2 (7.40%)	2 (15.38%)	0 (0%)	NA
AKI at 1 week, N (%)	1 (3.70%)	1 (7.69%)	0 (0%)	NA
Scr at 48 hrs, mg/dL	1.29 (0.33)	1.29 (0.28)	1.27 (0.35)	0.256
Scr at 1 week, mg/dL	1.34 (0.38)	1.41 (0.56)	1.34 (0.31)	0.148
eGFR at 48 hrs, mg/dL	51.11 ± 12.09	46.69 ± 11.96	55.21 ± 10.68	0.072
eGFR at 1 week, mg/dL	48.44 ± 11.62	43.31 ± 12.02	53.21 ± 8.87	0.027

*Plus-minus value is mean ± SD, number with parenthesis are median with interquartile range
Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; hr, hours; IQR, Interquartile range; mg/dL, milligrams/deciliter; NA, not applicable; Scr, serum creatinine; sd, standard deviation

Table 3 Secondary outcome

Secondary Outcome	Std-group, Incidence	RIPC-group, Incidence
Initiate hemodialysis	0	0
Death	0	0
Adverse event	0	0

DISCUSSION

This study showed no CA-AKI events in the RIPC group. By contrast, a few CA-AKI incidences occurred in the std group at 48 hrs and 1 week. Given the low incidence and small number of participants during the COVID-19 era, statistical analysis was not performed to detect the differences between the two groups. Therefore, the std group had baseline characteristics in the timing of the procedure and amount of contrast more than the RIPC group, which may lead to more CA-AKI events.

A previous systematic review reveals different results in each study, with no definite conclusion[5]. Most studies include patients who proceed in elective schedules with low-to-moderate risk of CA-AKI, which may lead to nonsignificant results of CA-AKI events between the RIPC and standard management[7,13]. However, the study in the CAG emergency setting showed that RIPC may significantly protect CA-AKI in patients with low-to-moderate Mehran's score[16]. Unstable hemodynamic status in acute myocardial infarction can increase CA-AKI risk, which differs from the elective setting in our study. Furthermore, another study used a biological marker, namely, urinary excretion of liver-type fatty acid-binding protein, which reflects tubulointerstitial damage and may early detect CA-AKI than serum creatinine[7]. Compared with our study, using serum creatinine to detect CA-AKI may not detect subclinical tubular injury.

The limitation of the study was the small number of participants, which led to low incidence and the inability to obtain statistical significance. Thus, whether the intervention is effective remains unknown, and it can only be interpreted as a pilot study. Furthermore, most participants had low-to-moderate risk of CA-AKI based on Mehran's risk score.

CONCLUSION

RIPC may be safe to implement in a systematic strategy for the prevention of CA-AKI post-CAG. Therefore, some researchers tend to improve CA-AKI. Further studies using a large number of participants may verify the benefit and provide definite conclusion.

CONFLICT OF INTEREST

None

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ ethical restrictions.

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Erratum to: Results of Posteromedial Capsule and Superficial Medial Collateral Ligament Release on Gap and Alignment in Total Knee Arthroplasty for Varus Knee Deformity by Computer-Assisted Surgery Measurement

Chaiyakit P, Onklin I, Ampunpong W. Results of posteromedial capsule and superficial medial collateral ligament release on gap and alignment in total knee arthroplasty for varus knee deformity by computer-assisted surgery measurement. Vajira Med J 2022;66(6):389-96.

In the manuscript, the authors notice major faults on their figures which are Figure 4a, 4b and 5 on page 394. The mistakes may lead to misunderstanding. The authors regret the error.

This erratum corrects the following Figures are shown below.

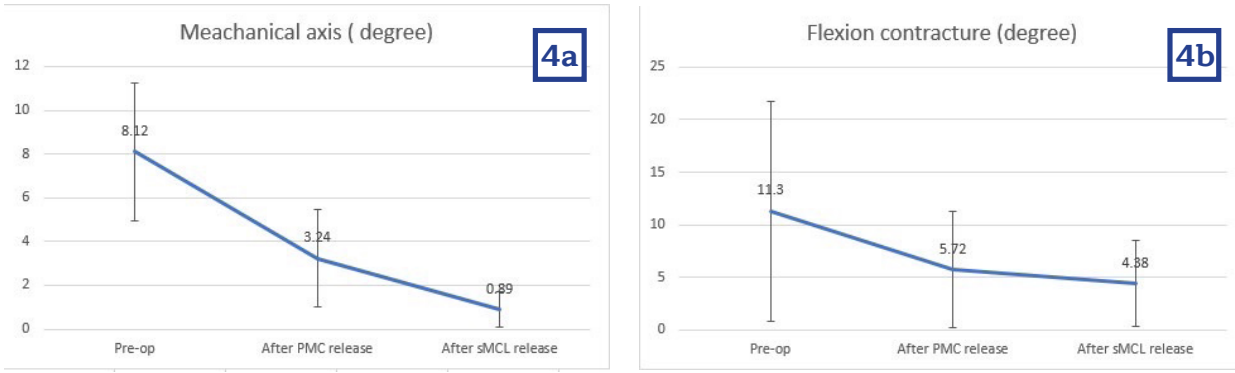

Figure 4a Hip-Knee-Ankle (HKA), Axis-X represents HKA and FC preoperative, after PMC and after sMCL release

Figure 4b Flexion contracture (FC) correction, Axis-Y shows HKA and FC (Degree), Positive HKA angle isdefined as varus alignment

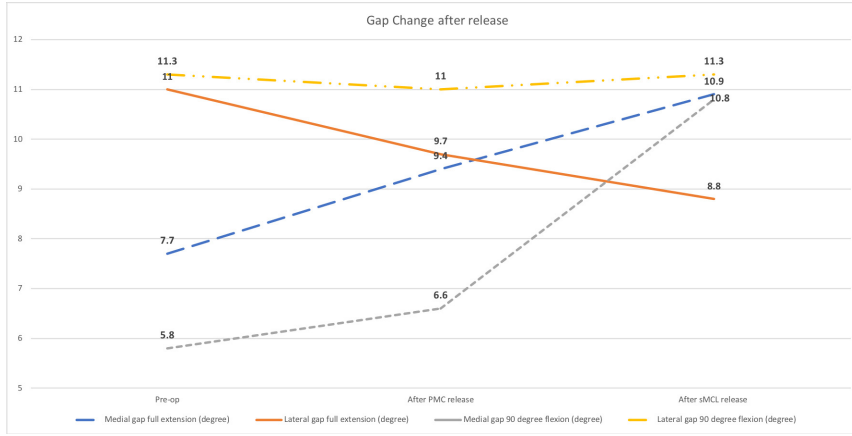

Figure 5 Medial and lateral gaps (mm.) changes at full extension and 90 degree flexion Axis-X represents Medial and lateral gaps preoperative, after PMC and after sMCL release Axis-Y shows Medial and lateral gaps (mm.)

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