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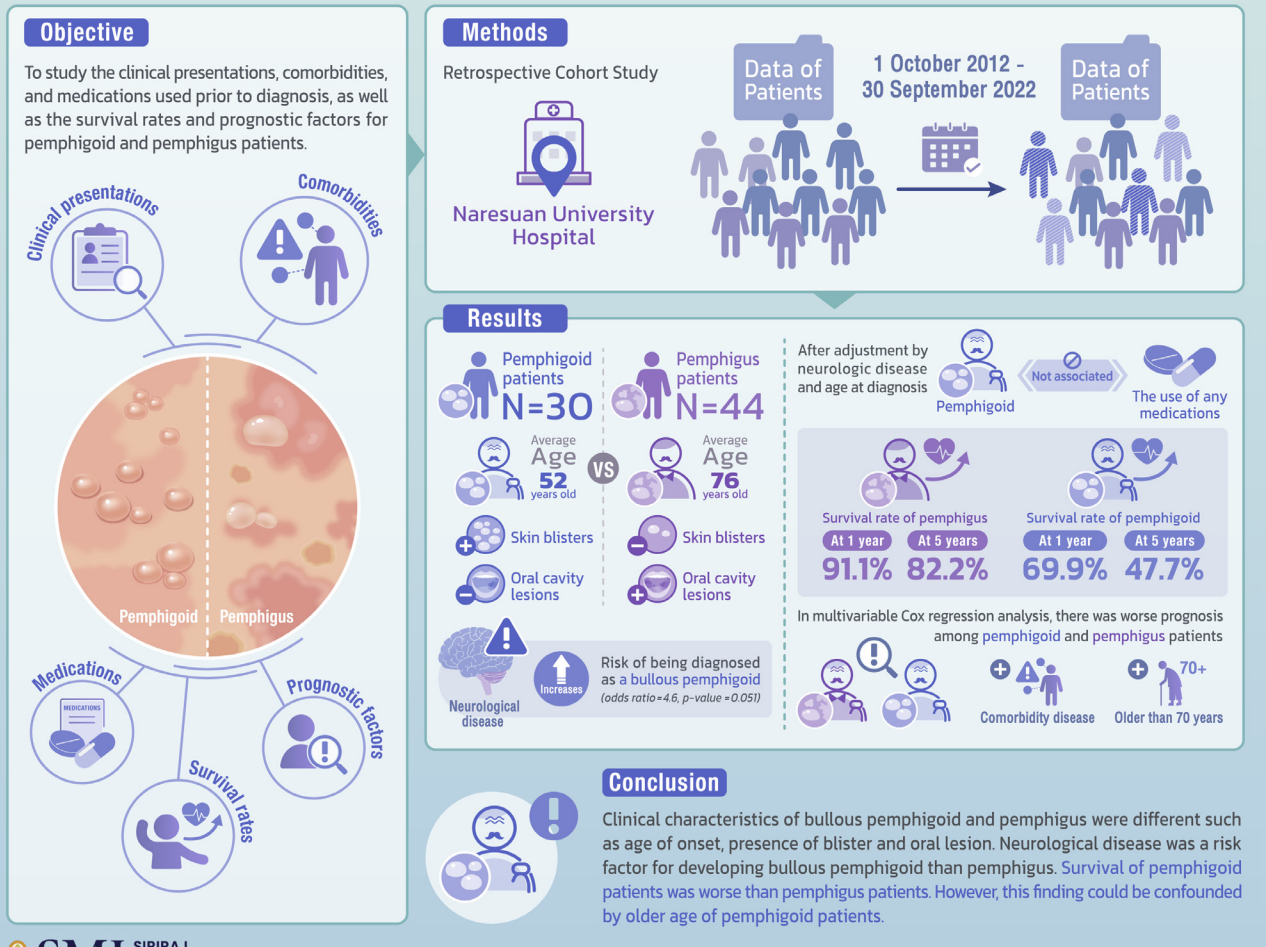

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Vitamin D Deficiency as a Factor Associated with Cognitive Impairment in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: Vitamin D as an essential nutrient is increasingly being studied and reported to have roles in diabetes and cognitive function through its antioxidant, anti-inflammatory, and neuroprotective functions. This study aimed to investigate vitamin D deficiency as a factor associated with cognitive impairment in Type 2 Diabetes Mellitus patients.

Materials and Methods: This case-control study was conducted at the diabetic center and neurology outpatient clinic at Prof. Dr. I.G.N.G Ngoerah Hospital in Denpasar, Indonesia between September and December 2022. Cases had a score of < 26 on the Montreal Cognitive Assessment questionnaire (Indonesian version) controls had a score ≥26. Vitamin D levels were assessed using serum 25-hydroxyvitamin D levels. The cut-off for vitamin D deficiency was obtained through the receiver operating curve characteristic.

Results: In total 31 cases and 31 controls were included. The cut-off for vitamin D deficiency was <24.6 ng/ml. Patients with T2DM and vitamin D deficiency had an increased association with cognitive impairment (OR 3.8; 95% CI [1.1 to 13.4]) compared to patients without vitamin D deficiency. Other independent factors associated with cognitive impairment in T2DM were low education levels (OR 5.4; 95% CI [1.3 to 22.2]) and diabetes duration of more than 5 years (OR 4.1; 95% CI [1.1 to 14.4]).

Conclusion: Vitamin D deficiency is one of the factors associated with cognitive impairment in T2DM patients.

Keywords: Cognitive impairment; type 2 diabetes mellitus; vitamin D (Siriraj Med J 2024; 76: 1-7)

INTRODUCTION

Type 2 diabetes mellitus (T2DM) carries a high risk of mortality and morbidity in the community.[1] Various complications can be caused by T2DM, including cognitive impairment.[2,3] Insulin dysregulation is a key element of neurodegeneration in T2DM. Insulin binds to its receptors on the blood-brain barrier and is transported into the central nervous system. Insulin appears to have a neurotropic role in the brain.[2]

Several previous studies indicate an association between vitamin D deficiency and a higher prevalence of diabetes.[4–6] Vitamin D is also reported to be associated with cognitive function.[7] This association is supported by the anti-inflammatory, antioxidant, and neuroprotective functions of vitamin D. These substances increase neurotrophic factors such as nerve growth factor (NGF) which maintains better brain health. Vitamin D also helps to prevent amyloid accumulation and supports amyloid clearance.[8]

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Evidence regarding an association between vitamin D status and dementia risk in patients with diabetes is scant, although several epidemiological studies have linked lower vitamin D concentrations to dementia risk in the general population. A recent cohort study showed that a higher serum vitamin D level in type 2 DM patients was associated with a lower risk of dementia.[9]

No studies have been published analysing the association between vitamin D levels and cognitive impairment in patients with T2DM in Indonesia . Therefore the aim of this study was to analyse the impact of vitamin D levels in T2DM patients with and without cognitive impairment

MATERIALS AND METHODS

The research was conducted at the neurology outpatient clinic and diabetic center of Prof. Dr. I.G.N.G Ngoerah Hospital from September to December 2022 using a case-control design. The study was reviewed and approved by the Institution Review Board of Faculty of Medicine Universitas Udayana/ RSUP Prof. Dr. I.G.N.G Ngoerah Denpasar No.2553/UN14.2.2.VII.14/LT/2022 on September, 22nd 2022. Written informed consent was obtained from each patient prior to the study.

Inclusion criteria were T2DM and age between 45 and 65 years. Exclusion criteria were chronic hepatic impairment, gastrointestinal disease (ulcerative colitis or Crohn's disease), having vitamin D supplementation regularly in the last 1 month, immobilization, history of stroke, central nervous system (CNS) infection, HIV-AIDS, brain tumor, Parkinson's disease, epilepsy, depression, pre-diabetic cognitive impairment, recurrent severe hypoglycemia, head trauma, heart failure, alcohol drinkers, and severe visual and hearing impairment.

The Montreal Cognitive Assessment questionnaire, Indonesian version, (MoCA-Ind) was applied to determine cognitive impairment. It is a brief, validated, and easy-to-use tool to identify mild and early Alzheimer's dementia with good sensitivity and specificity.[10,11] A scores of <26 indicate cognitive impairment[7]. The Hamilton Depression Rating Scale (HDRS) was applied to determine presences of depression (score of ≥8).[12] The Ascertain Dementia 8 – Indonesian version (AD 8-Ina) questionnaire answered by family or caregivers was applied to determine pre-diabetic cognitive impairment.[10]

All participants then underwent venous blood sampling by experts for laboratory examination of serum 25(OH)D levels measured in ng/ml using the Enzyme-Linked Immunosorbent Assay (ELISA) method in the Clinical Pathology Laboratory of Prof. Dr. I.G.N.G Ngoerah Hospital.

Potential confounding variables were poor glycemic control (HbA1c ≥7%), T2DM duration >5 years, hypertension, dyslipidemia, obesity, chronic kidney disease (CKD), and low education level (<12 years).

The data analysis was carried out using IBM SPSS Statistics version 25. All of the analyzed variables are presented in nominal variables. Bivariate associations were analysed using Chi-Square test. The cut-off for vitamin D deficiency was obtained through the receiver operating curve (ROC) characteristics. All variables with a significance value of less than 0.25 from the bivariate analysis will be included in the multivariate or logistic regression analysis. Logistic regression analysis was applied to explore associations of confounding variables with cognitive impairment. A p-value ≤ 0.05 was regarded as statistically significant.

RESULTS

There were 71 patients eligible for the study but 9 patients refused to participate. Thirty-one patients from each of the case and control groups were included in the study (Table 1). The ROC method yielded an Area Under the Curve (AUC) value of 75.3% [95% Confidence Interval (CI) 63.3 to 87.2%] (Fig 1). A vitamin D cut-off value of 24.6 ng/ml resulted in a sensitivity of 61.3% and specificity of 64.5% (Fig 2).

T2DM patients with vitamin D deficiency had a significantly higher risk of experiencing cognitive impairment compared to the control group (OR 2.8; 95% CI [1.1 to 8.1]; p=0.042) (Table 1). Confounding variables significantly associated with cognitive impairment in T2DM were education level, diabetes duration, hypertension, and gender (Table 2). The obesity variable has a significance value of less than 0.25 so it also be analyzed in the multivariate analysis. In the multivariable logistic regression analysis vitamin D deficiency, low education level, and T2DM duration >5 years were associated with cognitive impairments (Table 3).

DISCUSSION

The mean serum vitamin D level in the case group was significantly higher than in the control group (Table 1). These results are in line with a study by Rui-Hua et al. which found that the average vitamin D level in patients with T2DM with mild cognitive impairment (MCI) was 15.75 ng/ml and significantly lower than the normal cognitive group (23.04 ng/ml) (p<0.001).[7]

Vitamin D deficiency is associated with cognitive impairment in T2DM patients in this study. A cohort study involving 13,486 patients in the United Kingdom used a 20 ng/ml limit for all outcomes in measuring the association between vitamin D levels and the risk

TABLE 1. Characteristics of cases and controls.

Characteristics	Cases Cognitive Impairment (n= 31)	Controls Without Cognitive Impairment (n=31)	*p*
Age, (mean ± SD) years	55.1 ± 6.2	56.1 ± 5.2	0.507†
Gender, Female, n (%)	16 (52%)	8 (26%)	0.037*‡
Duration of education, median (25th; 75th percentile) years	12 (6 ; 15)	12 (12 ; 14)	0.217§
BMI, median (min-max) kg/m²	25.80 (19.7-36.7)	25.5 (18.3-36.7)	0.068‡
Occupation,			
Civil workers, n (%)	3 (9.7%)	2 (6.5%)	0.364‡
Teacher	1 (3.2%)	1 (3.2%)	
Unemployed	9 (29%)	4 (12.9%)	
Farmer	0 (0%)	1 (3.2%)	
Medical workers	3 (9.7%)	1 (3.2%)	
Entrepreneur	15 (48.4%)	22 (71%)	
MoCA-Ina score, median (min-max)	22 (11-25)	27 (26-30)	0.000*§
HbA1c, median (min-max) %	7.2 (5.2-14)	6.6 (5.9-14)	0.866§
Vitamin D serum, (mean±SD) ng/ml	20.5 ± 7	28.6 ± 9	0.000*†
Vitamin D category			
Deficiency, n (%)	20 (64.5%)	12 (38.7%)	0.042; OR (95% CI) 2.9 (1.1 to 8.1)
Without deficiency	11 (35.5%)	19 (61.3%)	

**p<0.05 †independent T-test, ‡chi-square test, §mann-whitney test.* BMI, Body Mass Index; MoCA-Ina, Montreal Cognitive Assessment-Indonesian Version; HbA1c, glycated hemoglobin; SD, standard deviation

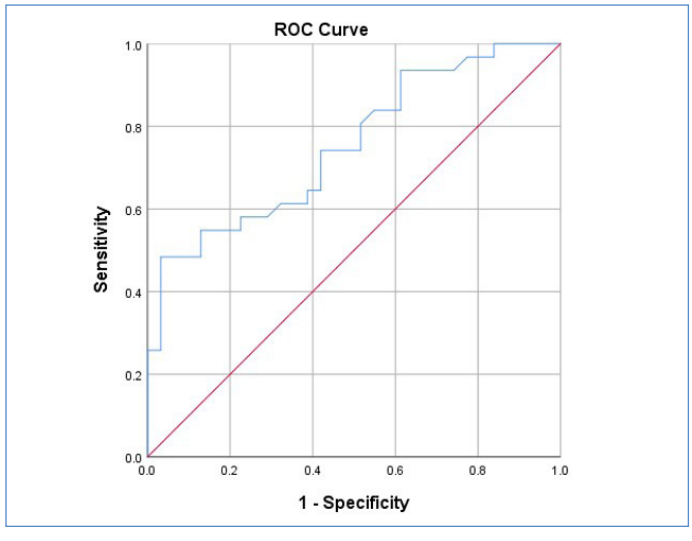

Fig 1. ROC characteristic of vitamin D level, and cognitive impairment in T2DM patients. The AUC based on this curve is 75.3%. ROC, receiver operating curve; AUC, area under the curve.

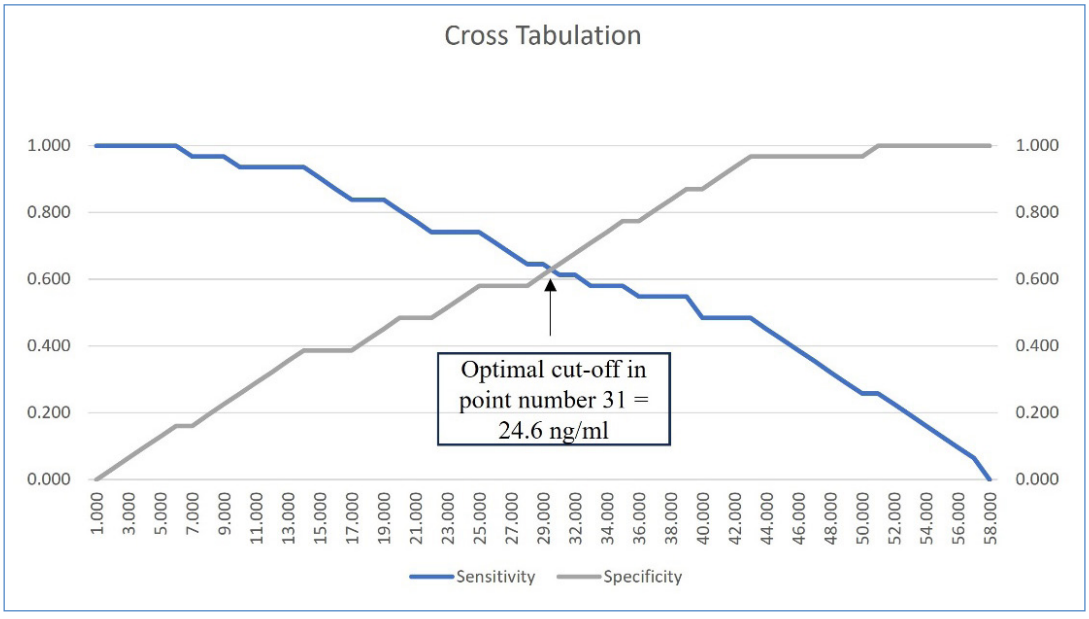

Fig 2. The results of the ROC coordinates for vitamin D deficiency cut-off level

TABLE 2. Results of the bivariate analysis between potential confounding variables and cognitive impairment in T2DM patients.

Variables	Cases n (%)	Controls n (%)	OR (95% CI)	*p*
Duration of education				
Low (<12 years)	13 (21%)	5 (16.1%)	3.8	0.025*
High (≥12 years)	18 (58.1%)	26 (83.9%)	(1.1 to 12.4)	
Duration of T2DM				
> 5 years	15 (48.4%)	7 (22.6%)	3.2	0.034*
≤ 5 years	16 (51.6%)	24 (77.4%)	(1.1 to 9.6)	
Glycemic control				
Poor	17 (54.8%)	13 (41.9%)	1.7	0.309
Good	14 (45.2%)	18 (58.1%)	(0.6 to 4.6)	
Hypertension				
Present	19 (61.3%)	11 (35.5%)	2.9	0.042*
Not present	12 (38.7%)	20 (64.5%)	(1.1 to 8.1)	
Dyslipidemia				
Present	11 (35.5%)	9 (29%)	1.3	0.587
Not present	20 (64.5%)	22 (71%)	(0.5 to 3.9)	
Obesity				
Present	10 (32.3%)	4 (12.9%)	3.2	0.068
Not present	21 (67,.7%)	27 (87.1%)	(0.9 to 11.7)	
CKD				
Present	7 (22.6%)	7 (22.6%)	1	1.000
Not present	24 (77.4%)	24 (77.4%)	(0.3 to 3.3)	
Gender				
Female	16 (51.6%)	8 (25.8%)	3.1	0.037*
Male	15 (48.4%)	23 (74.2%)	(1.1 to 8.9)	

*$p<0.05$. OR, Odd Ratio; CI, Confidence Interval; T2DM, type 2 Diabetes Mellitus; CKD, Chronic Kidney Disease.

TABLE 3. Results of the multivariable logistic regression analysis to statistically predict cognitive impairment in patients with T2DM

Variables	B	S.E	*Adjusted* OR Final step	95% CI	*p*
Vitamin D deficiency	1.3	0.6	3.8	1.1 to 13.4	0.036
Duration of T2DM >5 years	1.4	0.6	4.1	1.2 to 14.4	0.030
Duration of education <12 years	1.7	0.7	5.4	1.3 to 22.2	0.019
Hypertension	1.3	0.6	3.5	1 to 12.3	0.050
Obesity	1.5	0.8	4.3	0.9 to 19.8	0.061

B, Beta; S.E, Standard Error; OR, Odd Ratio; CI, Confidence Interval; T2DM, type 2 Diabetes Mellitus

of dementia in T2DM. The results obtained from this 8-year cohort study showed that higher serum 25(OH)D levels were significantly associated with a lower risk of Alzheimer's dementia (AD), vascular dementia (VD), and all-cause dementia.[9]

The exact mechanism underlying the relationship between vitamin D and dementia in diabetics still needs further research, the most frequently suggested pathways from are the neurodegenerative and vascular pathways.[9] Experimental studies show that vitamin D can enhance the clearance of amyloid plaques by stimulating macrophages[13], in addition, vitamin D can suppress macrophage migration among patients with diabetes.[9]

In vivo studies demonstrated increased vitamin D receptors in diabetic mice neurons indicating that the vitamin D signaling system could be a potential therapeutic target for diabetic neuropathy.[14] In addition, there is mounting evidence that vitamin D can improve glycemic control, blood pressure, and lipid metabolism in diabetic patients.[9]

Vitamin D can play an important role in normal neural function supported by the presence of vitamin D3 25-hydroxylase and 25-hydroxyvitamin D3-1α-hydroxylase in brain tissue.[15] Observations showed that the cultured microglia of mice could produce $1,25(OH)_2D_3$, and there were findings of $1,25(OH)_2D_3$ in human cerebrospinal fluid.[16] $1,25(OH)_2D_3$ is thought to bind and act on vitamin D receptors found in the brain and spinal cord, while vitamin D receptor (VDR) gene expression was observed in neuronal and glial cells. It was found that $1,25(OH)_2D_3$ therapy increases choline acetyltransferase activity in the brain nuclei of mice.[17] Another relatively direct effect of vitamin D on normal neural function is through increased neurotrophin synthesis as demonstrated by the finding that $1,25(OH)_2D_3$ stimulates the synthesis of NGF, glial cell line-derived neurotrophic factor (GDNF), and neurotrophin 3 (NT3) in various non-clinical studies.[18]

Vitamin D appears to protect the brain from free radical-induced damage by inhibition of $1,25(OH)_2D_3$ inducible Nitric Oxide Synthase (iNOS) synthesis.[17] Moreover, protection against oxygen-derived free radicals can come from increasing glutathione levels through upregulation of gamma-glutamyl transpeptidase as seen in the mice brain treated with $1,25(OH)_2D_3$.[19]

Low education level and diabetes duration of more than 5 years were also significantly associated with risk of cognitive impairment. Educational level is widely used as an indicator of cognitive reserve capacity. Individuals with greater cognitive reserves can tolerate a higher neuropathological burden than those with smaller cognitive reserves.[20] A low education level is also associated with a lack of ability to control vascular risk factors, maintain healthy diets and a lack of affordability to access health services.[21]

A study by Sun et al. also found that T2DM patients experienced an average of MCI after having diabetes for 6.34±2.53 years, whereas patients who had severe cognitive dysfunction had an average of T2DM for 10.14±8.24 years. Along with diabetes duration, there is an increase of neuronal damage which comes from macrovascular and microvascular disease, oxidative stress, and insulin resistance.[22]

In this study glycemic control, hypertension, dyslipidemia, obesity, chronic kidney disease, and female gender were not associated with cognitive impairment in T2DM patients. Poor glycemic control is thought

to be one of the risk factors for cognitive impairment in patients with T2DM, however, previous studies still show contrasting results to date.[23,24] Analysis of mean HbA1c and fasting blood glucose over a certain period is suggested to be more important than static measurements.[25] Glycemic variability is not represented completely by HbA1c values especially in patients with good metabolic control.[26] Hypertension is a risk factor for cardio-cerebrovascular disease, cerebral small vessel disease (CSVD), and cerebral atrophy but the direct association between hypertension and cognitive decline is uncertain.[27]

The association between obesity and cognitive impairment was not significant. Both case and control groups in this study had a greater percentage of patients without obesity. A meta-analysis showed that being underweight, overweight, and obese in middle age increases the risk of dementia.[28] Obesity is stated by Xiu et al. not an independent factor of cognitive impairment in T2DM.[29]

Chronic kidney disease was not associated significantly with cognitive impairment in this study. This could be due to the incidentally balanced proportion of CKD sufferers in the case and control groups. The accumulation of advanced glycated end products (AGEs) triggers vascular endothelial dysfunction which can lead to increased fragility and permeability of cerebral vessels.[30] The direct neuronal toxicity effect of uremic toxins on the cerebral vasculature will accelerate vascular calcification and endothelial dysfunction.[31]

Female gender in multivariable analysis was not significantly related to cognitive impairment in T2DM. Results of previous research regarding the role of gender in cognitive impairment risk in T2DM are varying. That could be the result of different eligibility criterias and the presence of confounding factors.[32,33] A meta-analysis showed that women have a higher relative risk of developing vascular dementia associated with T2DM than men, however, in non-vascular dementia there was no difference. The exact underlying mechanism is unknown, increased exposure to endogenous estradiol especially in women with post-menopausal diabetes is thought to carry a higher risk of dementia.[34] The study by Espeland et al concluded that only the carrier status of the apoE-epsilon 4 gene influenced the degree of sex-related differences.[33] More in-depth research including assessment of the menopausal phase, lifestyle, and genetic factors still needed to evaluate the role of gender in the diabetics' cognitive function.

This study has some strengths and limitations. Vitamin D examination is highly available and applicable nowadays in many healthcare facilities at relatively affordable prices. The new limit value for vitamin D deficiency obtained from this study is expected to enrich the literature and provide a basis for further research on the prevention of cognitive impairment in T2DM patients. The limitation of this study is there were some confounding factors that could not be adjusted by design in this study since the research was carried out in a center referral hospital with a high complexity of cases. In addition, the sample size is limited, so it cannot be used to characterize the population as a whole.

In conclusion, vitamin D deficiency in T2DM patients is one of factors associated with cognitive impairment based on our study. Future research with a cohort design is needed to assess the causality relationship between vitamin D deficiency and cognitive impairment in diabetic patients.

Conflicts of interest

The authors have no potential conflicts of interest to disclose.

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Comparison between Lidocaine Spray and Oral Paracetamol for Pain Reduction during Amniocentesis in Second Trimester Pregnancy; A Randomize Controlled Trial

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ABSTRACT

Objective: The aim of this study was to compare the efficacy of lidocaine spray and oral paracetamol on pain reduction in pregnant women in the second trimester during amniocentesis.

Materials and Methods: This was a prospective randomized-controlled trial study conducted at Maternal and Fetal Medicine unit, Thammasat University Hospital, Pathum Thani, Thailand between June 2022 and April 2023. Participants were pregnant women who underwent amniocentesis during gestational age between 15 and 20 weeks. They were allocated into three groups namely lidocaine, paracetamol and control groups. Subjects in lidocaine group received 8 puffs of 10% lidocaine (80 mg) spray onto the marked puncture site for five minutes before amniocentesis and ingested 1 placebo tablet 1 hour before procedure. Paracetamol group ingested 650 mg paracetamol orally 1 hour before amniocentesis and received 8 puffs of normal saline spray on the marked puncture site. Control group received 8 puffs of normal saline spray onto the marked puncture site for five minutes before amniocentesis and ingested 1 placebo tablet 1 hour before amniocentesis. Expected pain (Te), during procedure (T0), 15 and 30 minutes after procedure (T15 and T30) were evaluated based on 10-cm visual analog scale (VAS).

Results: A total of 510 pregnant women were recruited and divided equally (170 cases per group). Mean maternal age was 36.1 years old. Demographic characters of three groups were comparable. Lidocaine had more pain reduction than paracetamol and control group at T0, T15 and T30 (at T0: 3.06±2.16 vs 3.96±2.42 vs 3.92±2.35, P value < 0.001, T15: 1.12±1.38 vs 1.92±1.47 vs 1.98±1.87, P value < 0.001, T30: 0.64±0.95 vs 1.33±0.97 vs 1.09±1.44, P value < 0.001). However, paracetamol had no significant difference in pain reduction compared to control group.

Conclusion: Lidocaine spray before amniocentesis had more efficacy on pain reduction during amniocentesis, 15 and 30 minutes after procedure.

Keywords: Lidocaine spray; paracetamol; amniocentesis; pain (Siriraj Med J 2024; 76: 8-13)

INTRODUCTION

Amniocentesis during the second trimester of pregnancy is the most common invasive prenatal procedure. Most common indications for amniocentesis were advanced maternal age, parental chromosome abnormalities, previous offspring with chromosome abnormalities and prior diagnosis of fetal malformations. This procedure consisted of transabdominal puncture under ultrasonographic guidance to obtain amniotic fluid. Pain from the procedure was frequently reported

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from previous literature.[1] Some pregnant women refuse to undergo amniocentesis when indicated due to fear of the pain during and after the procedure. Many pregnant women might request pain control to avoid pain during amniocentesis. Factors related to pain during amniocentesis included numbers of parity, gestational age, maternal body mass index (BMI), history of abdominal surgery and location of needle.[2]

There have been various prior studies regarding pain reduction in patients who underwent amniocentesis. Local anesthesia by using lidocaine (infiltration, spray and topical cream), oral paracetamol premedication and cryoanalgesia before amniocentesis had been reported to decrease procedural pain.[3-11]

Paracetamol is a common pain relieving medication and is safe for pregnancy. The peak effect of paracetamol was around 1 to 3 hour after ingestion.[12] Thanita and colleagues reported in 2018 that oral paracetamol one hour before amniocentesis could significantly reduce pain from the procedure than placebo group.[3]

Lidocaine is an amide anesthetic agent with a short onset of local anesthetic action, safe for pregnant women to use. Gordon and Elimian reported in 2007 and 2013 that local infiltration of 1% lidocaine could relieve pain from amniocentesis among pregnant women in the second trimester, compared to placebo with statistical significance.[4,5] Homkrun reported that application of lidocaine spray at amniocentetic puncture site before the procedure could significantly reduce pain compared to the placebo in 2019.[6] However Pongrojpaw reported in 2007 that application of lidocaine cream at the amniocentetic puncture site could not reduce pain from the procedure.[7]

Nonpharmacological pain reduction from amniocentesis, namely music therapy, aroma therapy and cryotherapy were also reported to possibly reduce pain.[13,14]

Lidocaine spray and oral paracetamol are both non-invasive and easy to apply. To date, there has been no comparative efficacy study between lidocaine spray and oral paracetamol for pain reduction during amniocentesis. The aim of this study was to compare the efficacy of pain reduction during amniocentesis between lidocaine spray and oral paracetamol.

MATERIALS AND METHODS

Participants

Pregnant women in the second trimester (gestational age between 15-20 weeks) who underwent genetic amniocentesis during June 2022 to April 2023 and had no severe congenital anomalies that were prior detected by ultrasonography were enrolled in this prospective randomized controlled trial at Maternal-Fetal Medicine Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Thammasat University Hospital, Pathum Thani, Thailand. The exclusion criteria were multifetal pregnancy, severe congenital anomaly detected previously by ultrasonography, contraindication to perform amniocentesis, more than one attempt of needle puncture during procedure, changing the puncture site due to fetal behavior, psychiatric disorder, skin infection at abdominal area, those who had side effects of paracetamol or lidocaine spray, and those who refused to participate in this study.

Trial design

This study was approved from Human Ethics Committee of Thammasat University (MTU-EC-OB-2-369/64) and registered with Thai Clinical Trials Registry. Thai clinical trials registry identification number is TCTR20220530009. Pregnant women who underwent second trimester amniocentesis were approached by certified Maternal Fetal Medicine (MFM) staffs. Pre-procedural counseling was performed, with the procedure being explained to the pregnant women with indications for genetic amniocentesis. After thorough counseling, signed informed consent was done after the study was explained and understood. The patients were recruited and randomized into three groups with simple random sampling methods. Inclusion and exclusion criteria were reviewed before informed consent was given by the patients. Eligible pregnant women were interviewed about demographic data including age, body weight, height, education, occupation, income, gestational age, parity, previous delivery, history of abortion, underlying illness, previous obstetrical or gynecological surgery, parity and history of genetic amniocentesis in the previous gestation. The visual analog scale (VAS) was used for evaluation before the procedure to qualify their anticipated pain level. The VAS is a subjective pain measuring method, which is recorded by making a mark along a 10-cm horizontal line (0 to 10) from no pain or anxiety (score 0) to the worst pain (score 10).

Interventions

All participants were divided into three groups, namely lidocaine, paracetamol and control group. The first group is lidocaine spray. The participants were sprayed with lidocaine spray 8 puffs for 15 minutes and ingested 1 placebo tablet 1 hour before procedure. The second group is paracetamol group. In this group the participants took paracetamol (Tylenol®) (650 mg) 1 tablet orally 1 hour and normal saline spray 8 puffs

15 minutes before procedure. Third group is the control group. The participants received 1 placebo tablet orally 1 hour before procedure and normal saline spray 8 puffs 15 minutes prior to procedure as shown in Fig 1.

All participants (3 groups) underwent ultrasonography to investigate gestational age, fetal anomalies, amniotic fluid and the location of placenta. Genetic amniocentesis procedure was performed by staffs at Maternal Fetal Medicine Units (MFM Units) under ultrasonographic continuous guidance, free-handed, antiseptic technique, using a 22-gauge spinal needle. Pain control methods (paracetamol tablet, lidocaine spray or placebo) were used during the procedure. Commonly, 18-20 mL of amniotic fluid was aspirated and collected in a sterile container. Fetal cardiac activity was auscultated immediately after procedure. The puncture site was covered with a waterproof occlusive dressing by an assistant nurse. Immediately after the intervention, the participants were interviewed to qualify their pain score before (Te: expected pain), during (T0), 15 minutes (T15) and 30 minutes (T30) after the amniocentesis by using the same VAS. Following the procedure, the participants were observed for 30 minutes. While the patients laid, post-procedural, any paracetamol tablet and lidocaine spray complications were observed and fetal heart sound was auscultated by the medical team before discharge. In this study all physicians, participants and nurses were blinded during the procedure. The data was opened after complete the study.

Sample size and statistical analysis

The sample size was calculated from standard deviation of post-procedure pain and anxiety of the control group (SD = 1.58), which was based on the study of Thanitha T. et al.[3] The alpha and beta were set at 0.05 and 0.10 respectively. The authors calculated that at least 154 subjects in each group would provide 80% power at the 0.05 significance level. Given a 10% dropout rate, the total participants to be recruited was 170 in each group.

Statistical analyses were performed by using statistic packaged for social science (SPSS Inc., Chicago, IL USA) for windows version 27. Continuous and category data were analyzed for statistical differences by using ANOVA and post hoc test (pairwise comparison of groups). when clinically applicable. A p-value of less than 0.05 indicates a statistically significant difference.

The primary outcome was a measurement of visual analogue scale (VAS) before amniocentesis, during the procedure, 15 minutes and 30 minutes after the procedure.

RESULTS

A total 510 pregnant women who underwent amniocentesis during the study period were recruited. They were divided in to three groups equally, namely lidocaine, paracetamol and control groups.

Table 1 shows mean maternal age was 36.1 years old. One-third of participants were nulliparous. Half of the participants had an education level equal to or more than a bachelor degree and less than of 10 percent of participants had experience of amniocentesis.

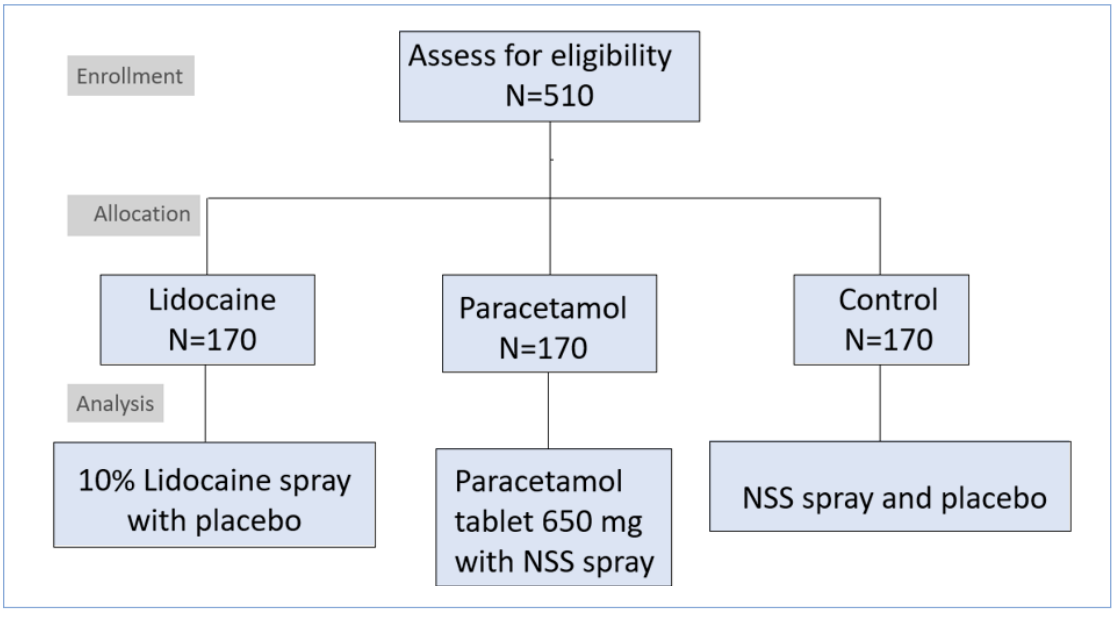

Fig 1. Flow chart of study.

Lidocaine: application of lidocaine spray at amniocentesis site, Paracetamol: ingestion of paracetamol tablet before amniocentesis, Control: application of normal saline spray at amniocentesis site and ingestion of paracetamol tablet before amniocentesis.

All physicians, participants and nurses were blinded during the procedure. The data was opened after complete the study.

TABLE 1. Demographic characters of amniocentesis cases (n=170 cases per group).

	Control	Paracetamol	Lidocaine	*p*-value
Age (years) (mean±SD)	36.22 ± 4.25	35.94 ± 4.32	35.81 ± 4.73	0.69
BMI (kg/m^2) (mean±SD)	24.51 ± 3.96	25.88 ± 4.20	25.39 ± 4.41	0.204
Nulliparity*	57 (33.5)	63 (37.1)	64 (37.6)	0.694
Education level*				0.06
≤ Secondary	102 (60)	89 (52.4)	82 (48.3)	
≥Bachelor	68 (40.0)	81 (47.6)	88 (51.8)	
Occupation*				0.067
Government officer	28 (16.5)	21 (12.4)	17 (10)	
Business owner	26 (15.3)	29 (17.1)	24 (14.1)	
Employee	105 (61.8)	108 (63.6)	116 (68.3)	
Housewife	11 (6.5)	12 (7.1)	13 (7.6)	
No history of surgery*	116 (68.2)	130 (76.5)	122 (71.8)	0.236
History	13 (7.6)	13 (7.6)	14 (8.2)	0.973
Indication				
Advanced age	139 (82.3)	140 (82.4)	144 (85.2)	
Family history	15 (8.9)	21 (12.4)	14 (8.3)	
Abnormal test	6 (3.6)	7 (4.1)	6 (3.6)	
Patient's need	3 (1.2)	2 (1.2)	3 (1.2)	
Previous abnormality	7 (4.1)	0 (0.0)	3 (1.8)	

*n(%), Control: no intervention before amniocentesis, Paracetamol: ingestion of paracetamol before amniocentesis, Lidocaine: application of lidocaine spray at amniocentesis site BMI: body mass index, C/S: cesarean delivery, History: History of amniocentesis, Control: no intervention before amniocentesis, Paracetamol: ingestion of paracetamol before amniocentesis, Lidocaine: application of lidocaine spray at amniocentesis site, Advance age: maternal age ≥ 35 years old, Family history: family history of chromosome abnormality, Abnormal screening test: Abnormal prenatal screening test, Previous abnormality: previous child with chromosome abnormality *n(%)

Demographic characteristics between the groups were comparable in terms of maternal age, BMI, parity, education, occupation, history of abdominal surgery at randomization. The majority of cases were advanced maternal age (95%).

Table 2 shows the VAS score among the three groups of participants. The expected pain (Te) and the pain during amniocentesis (T0) were comparable. However, the lidocaine group showed significantly lower value of VAS score at 15 and 30 minutes after the procedure compared to the control group and paracetamol group

Comparison of pain scores (VAS) during amniocentesis at timely manner: expected pain before amniocentesis (Te), during amniocentesis (T0), 15 minutes (T15) and 30 minutes after amniocentesis (T30) were presented in Fig 2.

DISCUSSION

Amniocentesis is a procedure that can cause mild to moderate pain. There are previous studies that investigated various pain reduction methods such as lidocaine, paracetamol premedication, aromatic therapy and cryoanalgesia.[3-14] The current study reported the efficacy of lidocaine spray for pain reduction during amniocentesis. Lidocaine spray shows pain reduction during amniocentesis at timely manner: expected pain before amniocentesis (Te), during amniocentesis (T0), 15 minutes (T15) and 30 minutes after amniocentesis (T30). While paracetamol did not show pain reduction during amniocentesis.

Lidocaine is the most effective and commonly used anesthetic agents which has various routes of administration (intravenous, cream, or spray). Its main mechanism

TABLE 2. Comparison pain score (VAS score) in amniocentesis among control, paracetamol and lidocaine group (n=170 cases per group).

	Control*	Paracetamol*	Lidocaine*	*p*-value (Bonferroni) Con vs Para	Con vs Lido	Para vs Lido	*p*-value (F-test)
Te	5.92 ± 2.18	6.15 ± 2.27	6.11 ± 1.81	0.984	0.710	0.601	0.58
T0	3.92 ± 2.35	3.96 ± 2.42	3.06 ± 2.16	0.987	0.003	0.002	< 0.001
T15	1.98 ± 1.87	1.92 ± 1.47	1.12 ± 1.38	0.943	< 0.001	< 0.001	< 0.001
T30	1.09 ± 1.44	1.33 ± 0.97	0.64 ± 0.95	0.166	0.001	< 0.001	< 0.001

VAS: visual analog scale (range 0-10), Control : no intervention before amniocentesis, Paracetamol: ingestion of paracetamol before amniocentesis, Lidocaine: application of lidocaine spray at amniocentesis site, * mean ± standard deviation(SD), Te: expected pain before amniocentesis, T0: pain during amniocentesis, T15: pain at 15 minutes after amniocentesis, T30: pain at 30 minutes after amniocentesis, Con vs Para: between control and paracetamol, Con vs Lido: between control and lidocaine group, Para vs Lido: between paracetamol and lidocaine group

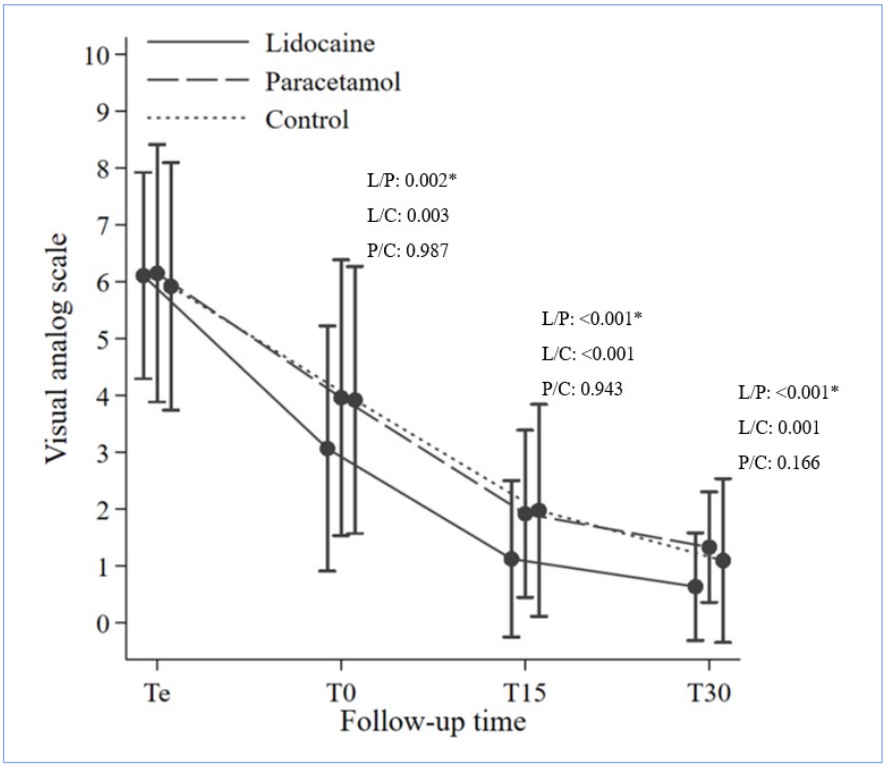

Fig 2. Comparison pain score (VAS score) in amniocentesis among control, paracetamol and lidocaine group.

Lidocaine: application of lidocaine spray at amniocentesis site, Paracetamol: ingestion of paracetamol tablet before amniocentesis, Control: application of normal saline spray at amniocentesis site and ingestion of paracetamol tablext before amniocentesis

*L/P: Lidocaine compare to paracetamol group, L/C: Lidocaine compare to control group, P/C : Paracetamol compare to control group

of action is blocking voltage-gated Na^+ channels.[15] From previous studies, lidocaine-prilocaine cream skin application[7] (Pongrojpaw et al. 2007) were not effective in reducing the pain in amniocentesis. However, Elimian et al. (2013)[5] has proved contrary. In 2019 Homkrun et al[6] reported that lidocaine spray can significantly decrease pain during amniocentesis. Due to different consistency of the product and drug component in previous study may affect the efficacy in pain reduction.

Paracetamol is an analgesic and antipyretic drug that is commonly used to relieve mild to moderate pain and is safe for pregnant women. Mechanism of action for relieve pain is it's bind to arachidonic acid which created N-arachidonyl-phynolamin (AM404) then AM404 stimulates Capsaicin receptor (TRPV1) and Canabinoid CB1 receptor in central nervous system which leads to relieve the pain.[16] In 2018, Thanita T.[3] reported that paracetamol 650 mg orally 1 hour before amniocentesis

compared with placebo could reduce pain during the procedure and 2 hours afterward.

Previous studies have shown that using lidocaine spray and paracetamol can reduce pain during amniocentesis but there is still no study that has compared the efficacy on pain reduction between lidocaine spray and paracetamol. According to this study result, the median procedural pain (T0) was lower in women who received lidocaine spray compared to paracetamol and control group and after 15 minutes and 30 minutes post procedure shows that lidocaine spray can significantly reduce pain. Conversely, neither the paracetamol nor control group had significant pain reduction during the procedure, 15 and 30 minutes after the procedure.

This study showed several strengths. First, this study is a prospective randomized controlled trial and was designed to have three arms. This allow the researcher to create a double blinded trial which can reduce the possible confounding bias that may occur. Moreover, this study involved a large number of participants and has comparable demographic characteristics in each group. However, there are still some limitations in this study. This study is a single center study. In addition, the participants took paracetamol (650 mg) 1 hour orally prior to amniocentesis while peak plasma level of paracetamol is 2 hours, which may affect the efficacy of paracetamol in pain reduction.

Also, the control group (placebo and normal saline spray) can have placebo effect or Hawthorne effect (the participants feel better due to realization of receiving therapy) that can make the comparison between paracetamol group and control group to have no significant difference in VAS score during and after amniocentesis.

From current study shows that lidocaine spray has efficacy in pain reduction during amniocentesis. The author suggests that lidocaine spray used before amniocentesis was recommend due to its profile, convenience and easy to use in clinical practice.

CONCLUSION

Lidocaine spray before amniocentesis had more efficacy on pain reduction than paracetamol during amniocentesis, 15 and 30 minutes after procedure.

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Clinical Characteristics and Survival of Pemphigoid and Pemphigus Patients in a Thai Population

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ABSTRACT

Objective: Pemphigoid and pemphigus are skin diseases with high morbidity and mortality. The research aims to study the clinical presentations, comorbidities, and medications used prior to diagnosis, as well as the survival rates and prognostic factors for pemphigoid and pemphigus patients.

Materials and Methods: The cohort study was conducted on retrospective data of patients who were treated at Naresuan University Hospital between 1 October 2012 and 30 September 2022.

Results: There were 30 pemphigoid patients and 44 pemphigus patients. Pemphigoid patients were on average older than pemphigus patients (76 years vs 52 years), have more skin blisters, and less oral cavity lesions. Neurological disease increases risk of being diagnosed as a bullous pemphigoid (odds ratio=4.6, p-value =0.051). After adjustment by neurologic disease and age at diagnosis, pemphigoid was not significantly associated with the use of any medications. The survival rate of pemphigus was 91.1% at 1 year and 82.2% at 5 years, while the survival rate of pemphigoid was 69.9% at 1 year, and 47.7% at 5 years. In multivariable Cox regression analysis, there was worse prognosis among pemphigoid and pemphigus patients that have comorbidity disease (adjusted HR= 3.13, p-value=0.057) and were older than 70 years (adj HR= 6.93, p-value=0.015).

Conclusion: Clinical characteristics of bullous pemphigoid and pemphigus were different such as age of onset, presence of blister and oral lesion. Neurological disease was a risk factor for developing bullous pemphigoid than pemphigus. Survival of pemphigoid patients was worse than pemphigus patients. However, this finding could be confounded by older age of pemphigoid patients.

Keywords: Autoimmune bullous disease; pemphigoid; pemphigus; survival rate; prognostic factor (Siriraj Med J 2024; 76: 14-20)

INTRODUCTION

Bullous pemphigoid and pemphigus are autoimmune bullous diseases caused by the presence of autoantibodies targeting bullous pemphigoid antigen (BP180, BP230) and desmoglein (DSG1, DSG3), respectively. Though prevalence of bullous disorder is quite low as 30 per 100,000 population in a study of a primary care area in Thailand[1], these are severe and poor prognosis skin disease with some distinct patterns of lesion locations, clinical presentations, and laboratory findings. Bullous pemphigoid was commonly found in elderly and pemphigus tend to have more oral lesions. The disease pathogenesis was the interaction between predisposing factors, such as human leukocyte antigen (HLA) genes, comorbidities, aging, and trigger factors.[2]

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Neurological disease was found to be associated with pemphigoid. Some medications such as aldosterone antagonists, DPP-4 inhibitors, anticholinergics and dopaminergic were associated with pemphigoid patients.[3]

Both diseases are skin diseases with high morbidity and mortality. In a study, the first-year mortality rate of pemphigoid was 31% and pemphigus was 24%.[4] A meta-analysis showed the pooled estimate of 1-year mortality rate of pemphigoid was 23.5%.[5]

The purposes of this research are to study differences in clinical manifestations, underlying diseases, comorbidities, prior drug use, survival rates at 1- and 5-year, and prognostic factors of pemphigoid and pemphigus diseases.

MATERIALS AND METHODS

The retrospective cohort study was conducted on patients with bullous pemphigoid and pemphigus who were diagnosed and treated at Naresuan University Hospital between 1 October 2012 and 30 September 2022. Ethical approval was allowed by the Naresuan University Institute Review Board.

All diagnosis of pemphigoid and pemphigus was confirmed by immunological laboratory findings of either positive direct immunofluorescence (DIF) test or positive indirect immunofluorescence (IIF) test.

Data was obtained by reviewing medical records. The variables included gender, age of diagnosis, characteristic of skin blisters and oral cavity lesions, immunological laboratory results, prior drug use before diagnosis, comorbidity, treatment, and survival. Death status was confirmed by medical chart review and from the national death registration database.

Statistical analysis was done by using the STATA software version 18.0. Descriptive statistics were used to report demographic data, clinical characteristics, treatment, and treatment outcomes of pemphigoid and pemphigus patients. Prior medication use of pemphigoid and pemphigus patients were compared using univariable and multivariable logistic regression. The survival rate between pemphigoid and pemphigus patients was analyzed by the Kaplan-Meier method. The relationship between various factors and survival rates in patients with pemphigus and pemphigoid were analyzed with log-rank test statistics. Multivariable analysis for the effect of factors on survival was analyzed using Cox's proportional hazard model statistics presented by hazard ratio (HR).

RESULTS

Of 74 patients, there were 30 pemphigoid patients and 44 pemphigus patients. Pemphigus patients included 32 pemphigus vulgaris, 11 pemphigus foliaceus, and 1 pemphigus vegetans. There were 17 (57%) pemphigoid and 29 (63%) pemphigus female patients as shown in Table 1.

Pemphigoid patients were older than pemphigus patients on average. Approximately 76% of pemphigoid and 18% of pemphigus patients were 70 years or older than. The mean age of the pemphigoid patient was 75.3 years old (±13.9 SD) while for pemphigus was 52.4 years old (±18.8 SD), with a statistically significant difference at p-value 0.001. Skin vesicles appeared more in pemphigoid patients than pemphigus patients (75.8% versus 52.3%, p-value 0.043). Oral cavity lesions were more common in pemphigus patients than pemphigoid patients (40.9% versus 20.0%, p-value 0.051).

Neurologic diseases (cerebrovascular disease, dementia, Alzheimer, Parkinson) were present in 53% of pemphigoid and 9% of pemphigus patients. The odds ratio of neurologic disease for being pemphigoid was 11.42 (p-value <0.001) in univariable analysis and 4.64 (p-value=0.051) in multivariable analysis adjusted by age and gender.

Certain medications were more frequently used by pemphigoid patients than pemphigus patients, prior to their diagnosis. Some of those medications include angiotensin receptor blockers, calcium channel blockers, statins, biguanide, and non-steroidal anti-inflammatory drugs. However, in multivariable logistic regression analysis adjusted by age at diagnosis and neurologic disease, these were not statistically significant as shown in Table 2.

For the treatment, pemphigoid patients were treated with systemic corticosteroid in 23 cases (82.1%) and immunosuppressive therapy in 12 cases (40.0%). Pemphigus patients were treated with systemic corticosteroid in 41 cases (97.6%) and immunosuppressive therapy in 32 cases (72.7%). No patients were treated with biologic drug. Comorbidity disease (neurologic disease, diabetes mellitus, cancer, hypertension, and dyslipidemia) existed in 66% of pemphigoid patients and 25% of pemphigus patients.

In Table 3, the survival rate of pemphigoid patients at 1-year was 69.90% compared with 91.10 % for pemphigus patients as shown. While at 5-year, 47.7 % of pemphigoid patients and 82.2% of pemphigus patients survived. There was a statistically significant difference of survival rate between pemphigoid and pemphigus by log rank test. (p-value< 0.001). The Kaplan-Mier survival estimates curve was shown in Fig 1. The survival rate of autoimmune bullous disease (pemphigoid and pemphigus) also depends on age at diagnosis and the presence of comorbidity

TABLE 1. Characteristics of pemphigoid and pemphigus patients.

Characteristics	Pemphigoid (N=30)	Pemphigus (N=44)	Univariable Odds Ratio (pemphigoid as outcome)	p-value	Multivariable Odds Ratio	p-value
Gender						
Male	13 (43.3)	15 (34.1)	ref	0.42	ref	0.34
Female	17(56.7)	29 (65.9)	0.67(0.26-1.75)		0.54(0.15-1.92)	
Age						
Mean, SD	76.6, 12.4	52.4, 18.8				
Median	82.5,	54, 15-87				
Min-max	38-89					
Age group						
<60	4(13.3)	28(63.6)	Ref		Ref	0.833
60-69	3(10.0)	8(18.2)	1.28(.08-8.8)	0.801	1.23(.17-8.90)	0.001
>70	23(76.7)	8(18.2)	10.25(2.44-43.10)	0.001	11.25(2.57-49.22)	
Neurologic disease						
No	14(46.7)	40(90.9)	Ref	<0.001	Ref	0.051
Yes	16(53.3)	4(9.1)	11.42(3.26-40.02)		4.64(0.99-21.76)	

disease. The survival rate reduces from 96.8% among those less than 60 years old to 90.9% in 61–69-year group and 63.3% in those more than 70 years old. The presence of comorbidity reduces the 1-year survival of both diseases from 87.9% to 73.8%.

Prognostic factors of survival in pemphigoid and pemphigus patients were analyzed using univariable and multivariable cox regression as shown in Table 4. In univariable analysis, diagnosis of pemphigoid, age more than 70 and presence of comorbidity disease were associated with increasing hazard of death. However, in multivariable analysis, only age more than 70 years old was statistically significant associated with increasing hazard of death (hazard ratio= 4.57, p-value 0.015).

DISCUSSION

In our study, we found bullous pemphigoid patients slightly less frequent than pemphigus patients (30 cases versus 44 cases). It showed increase proportion of bullous pemphigoid when compare to the study in 2009 at Siriraj Hospital in Bangkok which found diagnosed pemphigoid (29.6% of autoimmune bullous disease) compared to pemphigus (63.3%).[6] A study in Singapore showed the relative incidence of pemphigoid versus pemphigus was 4:1.[4] The difference may reflect patient data coverage, referral bias, and aging structure with a rising incidence in bullous pemphigoid in older population. The age distribution of patients with both diseases significantly differed, with pemphigoid patients exhibiting a higher age than pemphigus patients. Clinical symptoms such as vesicles and oral lesions varied between the diseases. Vesicles were more pronounced in pemphigoid, while oral lesions were more common in pemphigus.

Previous study found some factors independently associated with pemphigoid such as major cognitive impairment, bedridden condition, Parkinson's disease, unipolar or bipolar disorder, and use of spironolactone or phenothiazines with aliphatic side chains.[7,8] In our study, we use pemphigus patients as a control. After controlling for age and gender, neurologic disease might increase risk of being diagnosed as pemphigoid versus pemphigus (odds ratio= 4.64, 95% CI 0.99-21.76, P-value=0.051). Previous studies found neurological disease were associated with BP.[8,9] A meta-analysis showed neurological disease increase risk of pemphigoid (RR 4.93, 95% CI: 3.62-6.70).[9] This is consistent with the finding of a study in Bangkok which showed pemphigoid patients had a significantly higher chance of having neurologic diseases compared

TABLE 2. Medications used prior to diagnosis in pemphigoid and pemphigus patients: frequency and odds ratio of being bullous pemphigoid by logistic regression.

Drug	Pemphigoid N= 30 n(%)	Pemphigus N= 44 n(%)	Univariable Odds Ratio (pemphigoid as outcome)	p-value	Multivariable Odds Ratio (adjusted by age and neurologic disease)	p-value
Angiotensin-converting -enzyme inhibitors (ACEi)	1 (3.3)	0 (0.0)	-	0.405	-	-
Angiotensin receptor blockers (ARBs)	7 (23.3)	1 (2.3)	13.08(1.51-12.9)	0.019	5.27 (0.54-50.89)	0.150
Calcium channel blockers (CCBs)	8 (26.7)	3 (6.8)	4.96(1.19-20.65)	0.027	1.82 (0.33-10.04)	0.490
Beta blocker	6 (20.0)	5 (11.4)	1.95(0.53-7.09)	0.331	0.63 (0.12-3.31)	0.589
Proton pump inhibitors	6 (20.0)	7 (15.9)	1.32(0.39-4.41)	0.650	0.37 (0.63-2.16)	0.271
Statins	12(40.0)	6(13.6)	4.22(1.36-13.05)	0.012	1.92 (0.48-7.72)	0.188
Warfarin	3(10.0)	1(2.3)	4.77 (0.47-8.31)	0.185	3.54(0.21-58.59)	0.318
Aspirin	6(20.0)	3(6.8)	3.41(0.78-14.92)	0.102	1.09 (0.168-7.17)	0.524
Clopidogrel	3(10.0)	0(0.0)	-	0.032	-	-
Anticholinergic	0(0.0)	0(0.0)	-	-	-	-
L-DOPA bromocriptine	2(6.7)	1(2.3)	3.07(0.265-35.49)	0.369	0.21(0.01-3.44)	0.275
Hypnotic sedative	2(6.7)	3(6.8)	0.97(0.153-6.22)	0.980	0.10 (0.01-1.03)	0.053
Sulfonylurea	3(10)	1(2.7)	4.77(0.47-48.31)	0.185	2.67 (0.089-79.64)	0.571
Thiazolidinediones	1(3.3)	0(0)	-	0.405	-	-
Biguanide	7(23.3)	2(4.6)	6.39(1.23-33.33)	0.028	5.17 (0.61-43.51)	0.130
DDP-4 inhibitor	2(6.7)	0(0)	-	0.161	-	-
Loop diuretics	0(0)	1(2.3)	-	1.000	-	-
NSAIDs	8(26.7)	3(6.8)	4.96(1.19-20.65)	0.027	2.69(0.45-16.08)	0.276
Alpha blocker	1(3.3)	1(2.7)	1.48(0.08-24.66)	0.784	0.13(0.01-3.27)	0.218
Anticonvulsant	2(6.6)	3(6.8)	0.97(0.15-6.22)	0.980	0.15 (0.02-1.48)	0.106

TABLE 3. 1- and 5-year survival probability in pemphigoid patients and pemphigus Patients.

	Survival probability				P-value
	1-year	95%CI	5-year	95%CI	(Log-rank test)
Pemphigoid	0.691	0.489 - 0.826	0.427	0.227- 0.613	<0.001
Pemphigus	0.907	0.770 -0.964	0.813	0.642 - 0.907	
Age					<0.001
<60	0.968	0.798- 0.995	0.827	0.598- 0.932	
61-69	0.909	0.508-0.986	0.818	0.447-0.951	
>=70	0.633	0.435-0.778	0.436	0.247-0.610	
Comorbidity					0.006
Present	0.738	0.544-0.859	0.4595	0.260-0.638	
Absent	0.879	0.734-0.948	0.8173	0.650-0.909	

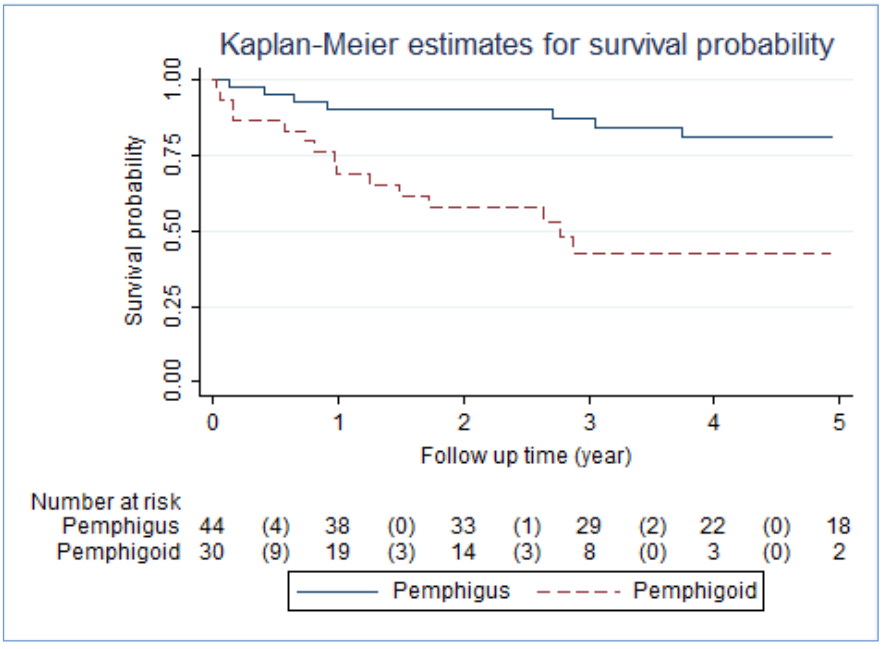

Fig 1. Survival curve of pemphigoid patients compared to pemphigus patients.

TABLE 4. Prognostic factors of survival in pemphigoid and pemphigus patients, univariable and multivariable cox regression

Characteristics	Univariable hazard ratio	p-value	Multivariable hazard ratio	p-value
Type of bullous disease				
Pemphigus	Ref.		Ref.	
Pemphigoid	4.10 (1.76- 9.58)	0.001	1.51 (0.54-4.26)	0.427
Age				
<60	Ref.		Ref	
61-69	1.59(0.29-8.75)	0.589	0.95(0.16-5.49)	0.955
>=70	6.93 (2.34-20.48)	<0.001	4.57 (1.34-15.51)	0.015
Comorbidity				
Absent	Ref.		Ref	
Present	3.13 (1.33-7.33)	0.008	2.46 (0.97-6.22)	0.057

with other autoimmune vesiculobullous disease patients (adjusted odd ratios =4.00 , 95% CI 2.00-13.30).[6] It was postulated that genetic background, regulatory T cell dysfunction, aging and triggering factors such as trauma, irradiation, infection, neurological diseases, hematological malignancies, and certain drugs synergistically induce the breakdown of immune tolerance to BP180/COL17, and result in the production of autoantibodies and the onset of pemphigoid.[10]

A meta-analysis suggested that aldosterone antagonists, dipeptidyl peptidase 4 inhibitors, anticholinergics, and dopaminergic medications are associated with bullous pemphigoid.[11] Drug intake, which may potentially induce pemphigus, includes D-penicillamine[12], angiotensin-converting enzyme inhibitors, angiotensin receptor blockers[13], beta blockers, cephalosporins, phenylbutazone, pyritinol, and thiopronine.[14] In our study, drug use prior to diagnosis: ARBs, CCBs, statins, clopidogrel, biguanides, and NSAIDs pemphigoid were more frequently used in pemphigoid patients than in pemphigus patients. However, after adjustment by cerebrovascular disease and age, there are no drugs that were statistically significant at p-value less than 0.05. This negative finding of association may be due to small sample size or adjustment with confounding effects by age.

In our study the mortality rate after diagnosis of pemphigoid was higher than pemphigus (at one-year 31.9% vs 9.7%: at 5-year 57.2% vs 19.7%). A study in Singapore found the 1-year mortality of pemphigoid and pemphigus were nearly similar at 31% and 24%.[4] A prospective study in Switzerland found the 1-year, 2-year and 5-year probabilities of death in pemphigoid patients were 26.7%, 37.1%, and 60.8%.[15] A study in Songkhla, Thailand found that the 1-year, 3-year and 5-year overall mortality rates of pemphigoid patients were 28.1% , 55.7% and 71.9%.[16] The 1-year, and 3-year overall mortality rates of pemphigoid patients were 25.8% and 43.0% from a study in Morocco.[17] For pemphigus, the 1-, 2-, and 5-year overall survival rates were 92%, 88%, and 77% in a French multicenter study with 249 patients.[18]

In our analysis for prognostic factor of survival in pemphigoid and pemphigus patients, being diagnosed as pemphigoid, older age of initial diagnosis at 75 years old or more and having comorbidity disease were the prognostic factors that increase death in pemphigoid and pemphigus patients in univariable cox regression analysis. In multivariable analysis only the age of diagnosis more than 75 years old was statistically significant. This could explain that pemphigoid is not more severe than pemphigus but rather confounded by older age. A cohort study in France found the prognosis of patients with pemphigoid is influenced by age and Karnofsky score.[19]

There are some limitations of the study due to the small sample size. The comparison drawn between pemphigoid and pemphigus patients in our study might not fully capture the comparative of pemphigoid cases with the general population. The retrospective nature of the study relying on medical records could introduce information bias by missing information.

Overall, this research provides insights into the attributes, prognoses, and associated factors for survival of pemphigoid and pemphigus patients. Bullous pemphigoid incidence should increase as society becomes older. The treatment outcome is still unfavorable especially for pemphigoid. The new treatment such as biologic and topical treatment might reduce the mortality.[20,21] The findings highlight the need for further study of the pathogenesis of disease, novel treatment, and larger population studies with more comprehensive controls for confounding variables.

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Prevalence and Characteristics of Medicinal Cannabis Use among Chronic Pain Patients; A Post-Legalization Study in a Tertiary Care Setting in Thailand

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ABSTRACT

Objective: Cannabinoid products have been applied for numerous medical conditions, including chronic pain. Thailand was the first country in South East Asia to legalize medical cannabinoids. This study aims to explore prevalence, characters, attitude, side effects of medical cannabinoid use, and pain-related outcome among the chronic cancer and non-cancer pain population at Siriraj Hospital.

Materials and Methods: 200 chronic cancer pain and 670 chronic noncancer pain patients were collected by questionnaires and interviews. Data included demographic data, clinical diagnosis, pain treatment, knowledge, attitude, pattern of use, side effects and quality of life of cannabinoid extracts.

Results: Prevalence of active cannabis user was 15% in chronic cancer pain and 3.1% in noncancer pain. Oil extract sublingual was the most common form. Pain control was the most common initial reason for usage. No serious side effects were reported. Common side effects were dry oral mucosa, drowsiness, and headache. The most common source was obtained from friends. 36% of the patients believed they had enough understanding of medical cannabis, while 68.5% agreed that it is appropriate to use in Thailand. In cancer patients, the Edmonton Symptom Assessment System (ESAS) subscale for lack of appetite, anxiety, and subscale for a brief pain inventory (BPI) for enjoyment of life were higher among active users. In patients with noncancer pain, only the mood subscale BPI was lower among active users.

Conclusion: Medical cannabis usage is common compared with general population in Thai patients with chronic pain and may be associated with increased pain interference and cancer-related symptoms. Nonmedical license prescription and nonmedical license cannabis products were common in Thailand.

Keywords: Cannabis; prevalence; chronic pain; quality of life; side effect of cannabis; cancer pain; noncancer pain (Siriraj Med J 2024; 76: 21-30)

INTRODUCTION

Cannabinoids, cannabis, and cannabis-based products have been used for medical purposes for a variety of conditions such as Parkinson's disease, Alzheimer's disease, spasticity associated with multiple sclerosis, and childhood seizure disorder.[1,2] In a prospective study of pain and palliative medicine, several studies demonstrated cannabinoid products as adjunctive treatment in related conditions such as neuropathic pain, cancer pain, chemotherapy-induced nausea and

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vomiting, and probably anticancer treatment.[3-6] However, clinical application remains controversial due to the limited evidence of benefit, potential harm, and legal/regulatory issues around the world.[7-11]

Public interest in cannabinoid products has increased globally and has been accelerated by legalization for medicinal and recreational purposes in many countries.[11-16] In Thailand, cannabinoid products have been classified as controlled substances since the early 1930s. (Ref) However, in February 2019, Thailand was the first country in South East Asia to legalize the use of medicinal cannabis for therapeutic and research purposes.[17,18]

Although the Thai government established a multilevel system of safeguards that includes the implementation of standards on manufacture and prescribing, and monitoring and evaluation[7,18], the first survey one year after legalization showed that off-labeled products were still common and illegal products were easily obtained.[8,19] Some patients consume cannabinoid products without proper knowledge of indication, dose, route, and possible interaction with other medications, which can cause several unwanted effects, drug abuse, and life-threatening conditions.[10,20-22]

This is the subsequent research from our initial survey.[8] The main objective of this study is to explore the prevalence of medical cannabinoid use among chronic pain patients in a tertiary care pain center in Thailand. Secondary research questions aim to explore the characteristic of medicinal cannabis use, including preparation, common route of administration, common side effects, symptoms, and pain-related interference among chronic cancer patients and noncancer pain patients.

MATERIALS AND METHODS

This single-center cross-sectional study was conducted from June 2020 to July 2021. After approval of the institutional review board (IRB number Si 172/2020), 200 patients with chronic cancer pain and 670 patients with chronic noncancer pain who attended the pain or palliative clinic at Siriraj Hospital were interviewed. Data were collected using questionnaires, including Likert scales and open-ended questions focused on attitude, basic knowledge about medical cannabis, and descriptive data on cannabis use, such as formulation and side effects. The inclusion criteria required subjects to be 18 years or older with pain for more than 3 months. Patients who refused to participate and those with cognitive impairment were excluded. Demographic data, diagnosis, intensity of pain, current analgesic medications, and cannabis use patterns were also obtained by interview or review of medical records. Pain-related interference and symptoms were evaluated using the Brief Pain Inventory and Edmonton Symptom Assessment System, Thai version.[23,24]

A brief pain inventory (BPI) was used to assess the severity of pain and the impact of this pain on the daily functioning of the patient ranging from 0 to 10. The higher the score means more interference from pain. Pain- related disability is the total sum of BPI in each modality. The Thai version (BPI-T) was also validated for use in patients with chronic pain.[24]

The Edmonton Symptom Assessment System (ESAS) was used to rate the intensity of common symptoms experienced by the cancer patient. Scoring from 0 to 10, the higher the score, the more intense the symptoms. The Thai version of the ESAS achieved good levels of validity and internal consistency.[23]

Statistical analysis

Demographic data were represented in descriptive analysis. Categorical variables were presented as counts and percent. Continuous and normal variables were presented as means with standard deviation or medians with an interquartile range (IQR). Comparison between group responses was made using the chi-square or Fisher's exact test. The P-value < 0.05 was considered statistically significant. Data analyzes were performed using PASW Statistics version 18 (SPSS, Inc., Chicago, IL, USA).

RESULTS

The 870 participants has an average age of 58 years with a female predominance (57% in the cancer group and 65.7% in the noncancer group).62% in the cancer group and 68.7% in the noncancer group had a higher education level (>12 years of education, equal to or greater than high school). Demographic data are presented in Table 1.

Prevalence

The prevalence of current users was 5.86%; 15% for cancer patients, and 3.1% for noncancer patients. The average duration of treatment among current users was 75 days for cancer and 120 days for noncancer patients. 25.5% of cancer patients and 5.2%of noncancer patients used medicinal cannabis for an average of 30 and 75 days, respectively. 57%of cancer patients and 90% of noncancer patients had never used cannabis products.

Characteristic of the current users

Breast cancer was the most common primary cancer in current users (N=5) and noncurrent users (N=25) among cancer patients, while spinal stenosis was the most common diagnosis in current users

TABLE 1. Demographic data of cancer (N=200) and noncancer groups (N=670) (p value).

Variable	Cancer(N=200) Mean±SD	N (%)	Non-cancer(N=670) Mean±SD	N (%)
Age (years)	59.55 ± 12.87		58.13±16.34	
Sex				
Male		86 (43)		230 (34.3)
Female		114 (57)		440 (65.7)
Education				
Lower education level		76(38)		210(31.3)
Higher education level		124(62)		460(68.7)
Duration of diagnosis (months)	12(6-48)		24(7-48)	

Values are presented by Mean±SD and number (percent), Lower education, ≤12 years of education or junior high school; Higher education, >12 years of education

(N =3) and nonusers (N = 72) among noncancer patients. The average pain score and maximum pain score trend towards higher in current users in both cancer and non-cancer patients, but did not reach statistical significance. There were no statistically significant differences in age, sex, education level, duration of diagnosis, number of treatments (surgery, chemotherapy, radiation), PPS score (Palliative performance scale), opioid consumption, and current conventional pain medication between current and noncurrent cannabis users in cancer and noncancer patients. (Supplemental Table 1 and 2)

Compared to noncancer patients, cancer patients who received cannabis were more likely to receive opioids (step 3 analgesic ladder) (80% vs 0%) and more likely to receive strong opioids in greater opioid dose of opioid consumption (average morphine equivalent dose per day of 30 mg). However, there were no significant differences in sex, age, education, duration of diagnosis, and pain score. (Supplemental Table 3)

Symptoms and pain-related interference among current users

Cancer patients

Compared to noncurrent users, current users in the cancer group reported a trend towards a higher pain score (average pain score 4.8 ± 2.28 VS 4.35 ± 2.48, P 0.361) and pain interference score (BPI) (36.5 VS 31, P 0.064) and statistically significant higher cancer-related symptoms (ESAS) (34 VS 27, P 0.017). All BPI and ESAS subscales tend to be higher or the same in current users. Additionally, the subscale of enjoyment of life from BPI, lack of appetite, and anxiety from ESAS was significantly higher in current users. (Figs 1&2)

Noncancer patients

Unlike cancer patients, current users in noncancer patients reported a trend toward a higher pain score (average pain score 5.29 ± 1.95 VS 4.56 ± 2.07, P 0.112), but a trend toward a lower pain interference score (BPI) (24 VS 29, P 0.503) and related symptoms (ESAS) (19 VS 24, P 0.445). There is no difference in BPI and ESAS subscale, expect mood subscale from BPI which were statistically significant lower in current users. (Figs 3&4)

Formulation and sources of cannabis products

Oil extract was the most common formulation in both cancer and non-cancer participants (79.1% N=68, 71.9% N=46). Cancer and noncancer cannabis users had statistically significant differences in tablet and tea formulation (P= 0.0.381, 0.105). Only 39.5% of cancer and 32.9% of noncancer patients obtained a medical cannabis license, either from the hospital or from registered practitioners. The main source of cannabis came from a neighbor or acquaintance (61.6% in cancer and 65.6% in non-cancer). No statistically significant differences were detected in the source of cannabis between the two groups. (Table 2)

Reasons to use and to continue

Pain control was the most common initial indication in both groups (45.3% and 53.1%, in cancer and noncancer patients, respectively) followed by the belief in adjuvants in insomnia treatment (37.2% and 25%). Palliative care and cure cancer purposes were statistically significantly higher in cancer compared to noncancer users (P=0.0001). However, users reported that sleeping aid was the most common benefit of medicinal cannabis in both groups

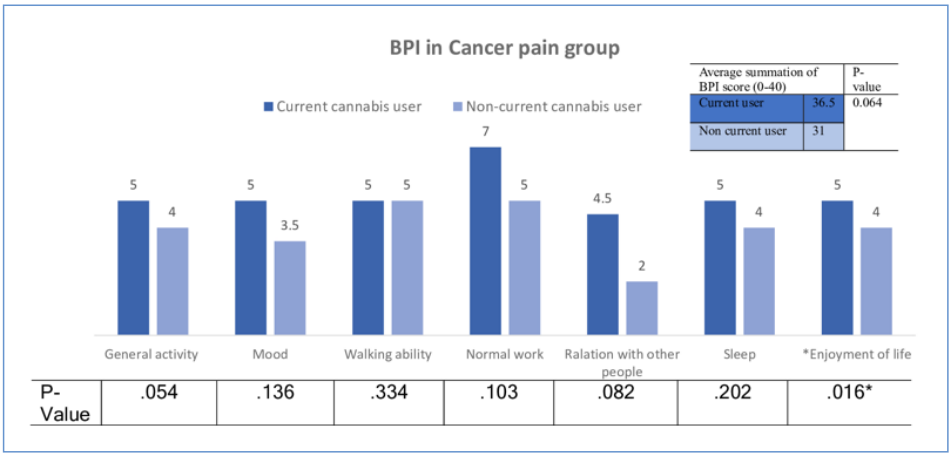

Fig 1. Comparison of noncurrent users and current users in the cancer group according to the Brief Pain Inventory score (BPI), Number above the bar represent average score (0-10) in each subscale, *=P<.05

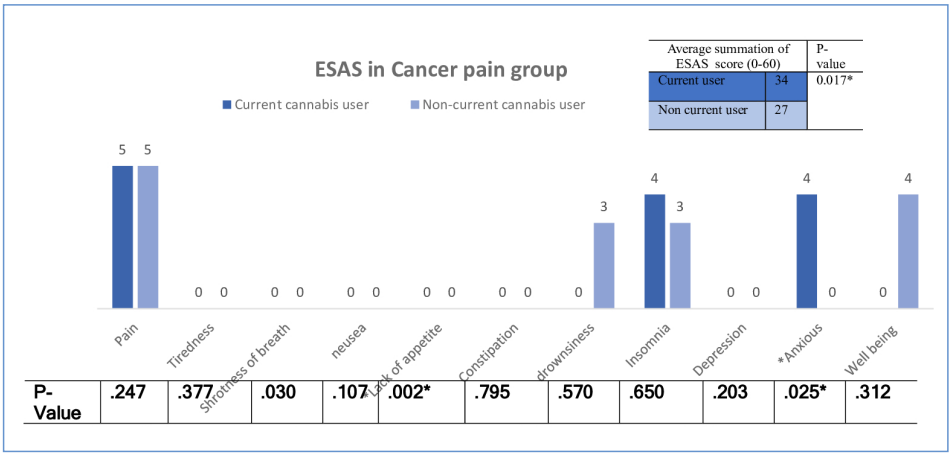

Fig 2. Comparison of the noncurrent users and the current users in the cancer group according to the Edmonton symptom assessment system (ESAS), Number above the bar represent average score (0-10) in each subscale, *=P<.05

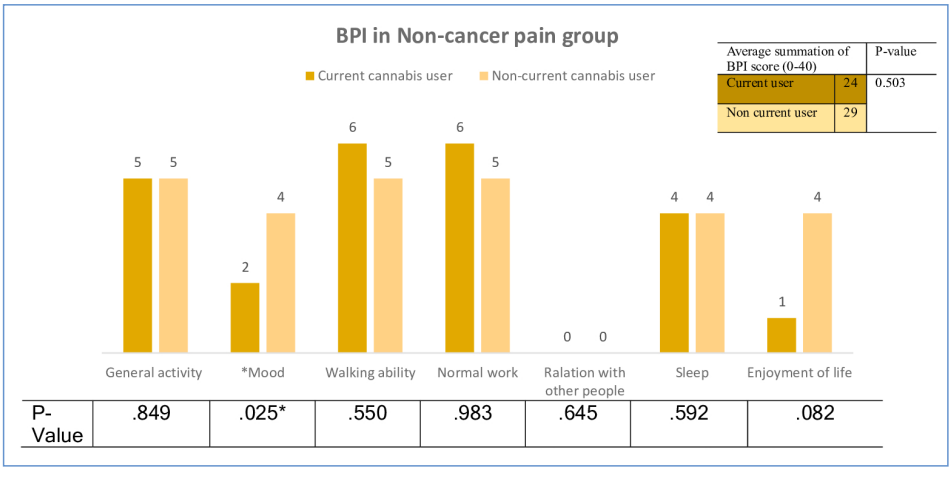

Fig 3. Comparison of the noncurrent users and the current users in the Noncancer group according to the Brief Pain Inventory score (BPI), Number above the bar represent average score (0-10) in each subscale, *=P<.05

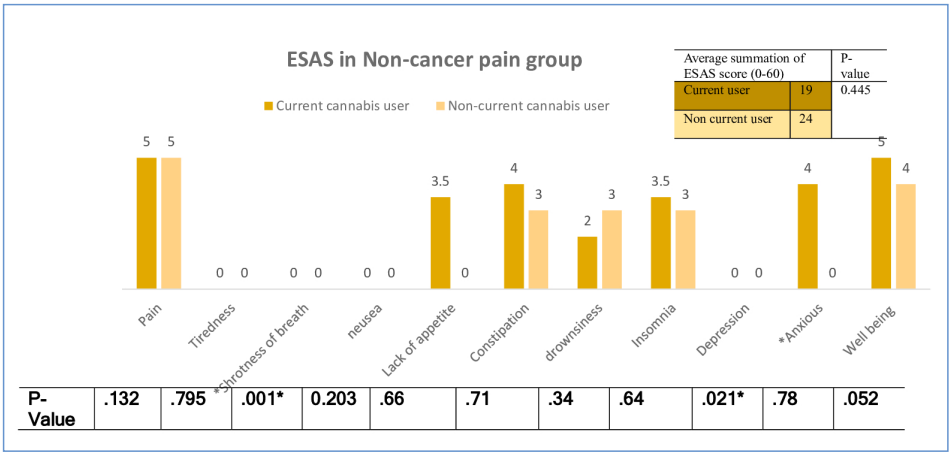

Fig 4. Comparison of the noncurrent users and the current users in the Noncancer group according to the Edmonton symptom assessment system (ESAS), Number above the bar represent average score (0-10) in each subscale, *=P<.05

TABLE 2. Formulation and sources of cannabis products in cancer (N=200) and noncancer groups (N=670).

	Cancer(N=200) N (%)	Non-Cancer (N=670) N (%)	P-Value
Cannabis formulation			
Inhale	5(5.8)	9(14.1)	.971
Topical cream	1(1.2)	3(4.7)	.313
Oil extract sublingually Oil extract	68(79.1)	46(71.9)	.3379
Tablet	6(7.0)	0(0)	.0381
Spray	1(1.2)	3(4.7)	0.313
Tea	9(10.5)	0(0)	.0105
Source of cannabis			
Hospital or clinic	9(10.5)	4(6.3)	.5589
Registered medical doctor	10(11.6)	9(14.1)	.8047
Registered Thai traditional medicine practitioners	15(17.4)	8(12.5)	.4964
Online	9(10.5)	7(10.9)	1.000
Home made	2(2.3)	1(1.6)	1.000
Neighbor/Acquaintance	53(61.6)	42(65.6)	.7231

Values are presented as number (percent)

(46.5% and 46.9%), while pain control was ranked as the second most common benefit in the cancer group (22.1%) and the third in the noncancer group (18.8%). The noncancer users continued to use cannabis believing in its advantage as a natural product and unspecified perspectives that was statistically significant compared to the other groups (P=0.0052, 0.0004). Finally, pain control was ranked as the second most common reason, after sleeping aid, to continue using medicinal cannabis among cancer patients (26.7%) and the most common reason to continue for noncancer patients. The only reason to continue using cannabis that was statistically significant between cancer and noncancer group was for an alternative purpose (P=0.0314).

Side effects

Most of the cannabis participants reported no side effects (48.8% and 40.6%). The most common side effects among cancer patients were drowsiness (27.9%), followed by dry mouth (23.3%) and intoxication (14%). The most common side effects among noncancer patients were headache (25%) that was statistically significant compared to cancer users (P=0.004), followed by dry mouth (21.9%), and drowsiness (17.2%). Serious side effects such as confusion / hallucination were reported in 4 persons (6.3%) in the noncancer group and 3 persons (3.5%) in the cancer group. (Table 3)

Attitude towards and knowledge about medicinal cannabis

Most of the participants (68.5% in cancer and 62.2% in noncancer patients) agreed that it was appropriate to use medical cannabis in the current context of Thailand closely monitored as narcotics (51% in cancer and 49.3% in noncancer patients). However, the majority of them also disagreed or were uncertain if they had enough understanding about medical cannabis. Number (30%) of patients with cancer pain and number (23.4%) noncancer believed that cannabis products can cure cancer. Most of the patients believed that cannabis can be used with other drugs without drug interaction and that a small amount should not cause serious side effects. Finally, most of the participants agreed that administration should be under medical supervision. (Table 4&5)

DISCUSSION

This observational cross-sectional study showed that the prevalence of active cannabis users in patients with chronic pain was much higher than in the general population.[20] Surprisingly, the prevalence of current users among cancer patients was not only higher than that of noncancer patients, but was also associated with a higher cancer-related symptoms score and a trend toward higher pain intensity and pain interference, compared to noncurrent users. In contrast, symptoms

TABLE 3. Cannabis use in cancer (N=200) and noncancer groups (N=670).

	Cancer (N=200) N (%)	Non-Cancer (N=670) N (%)	P-value
Initial indication(s) of use			
As indicated by the Department of Medical Service			
Pain control	39 (45.3)	34 (53.1)	.4096
Palliative care	26 (30.2)	1 (1.6)	.0001
Not indicated by the Department of Medical Service.			
Insomnia	32(37.2)	16 (25)	.1565
Cure cancer	26 (30.2)	0 (0)	.0001
Appetite	14 (16.3)	5 (7.8)	.143
Mood	9 (10.5)	5 (7.8)	.7779
Others	0 (0)	2 (3.1)	.1804
Cannabinoid advantage from the user's perspective			
Sleep	40 (46.5)	30 (46.9)	1
Pain control	19(22.1)	12 (18.8)	.6864
Appetite	13 (15.1)	5 (7.8)	.2101
Mood	13 (15.1)	14 (21.9)	.2931
Curative	0 (0)	2 (3.1)	.1804
Organic	0 (0)	6 (9.4)	.0052
Unspecified	1 (1.2)	11(17.2)	.0004
Reason(s) for continuation			
Insomnia	14 (46.7)	4 (19)	.0769
Pain control	8 (26.7)	6 (28.6)	1.000
Appetite	3 (10)	2 (9.5)	1.000
Mood	0 (0)	1 (4.8)	0.4267
Cure cancer	1 (3.3)	-	-
Alternative	0 (0)	4 (19)	.0314
Unspecified	4 (13.3)	1(4.8)	.3938
Side effect			
No side effects	42 (48.8)	26 (40.6)	.3262
Irritable	4 (4.7)	3 (4.7)	1.000
Dry mouth	20 (23.3)	14(21.9)	1.000
Confusion/Hallucination	3 (3.5)	4 (6.3)	.4605
Drowsiness	24 (27.9)	11 (17.2)	.1716
Headache	4 (4.7)	16 (25)	.0004
Palpitation	5 (5.8)	2 (3.1)	.6992
Feeling drunk/intoxicated	12 (14)	4 (6.3)	.1822
Constipation	3 (3.5)	1 (1.6)	.6363
Others	3 (3.5)	0 (0)	.2612

TABLE 4. Attitude towards medical cannabinoid in cancer (N=200) and noncancer groups (N=670).

I believe	Cancer group (N=200) N (%)	Non-cancer group (N=670) N (%)
I have enough understanding of medical cannabis		
Agree	72 (36)	246 (36.7)
Uncertain	75 (37.5)	281 (41.9)
Disagree	53 (26.5)	143 (21.3)
Medical cannabis usage is appropriate in Thailand		
Agree	137 (68.5)	417 (62.2)
Uncertain	46 (23)	197 (29.4)
Disagree	17 (8.5)	56 (8.4)
Medical cannabis is safe		
Without medical supervision	12 (6.1)	13 (1.9)
Under Thai traditional doctor's supervision	31 (15.7)	93 (13.9)
Under the supervision of the physician	44 (22.2)	202 (30.2)
Closely monitored as narcotics	101(51)	330 (49.3)
Disagree	10 (5.1)	32 (4.8)

Values are presented as number (percent)

TABLE 5. Basic knowledge of cannabis in cancer (N=200) and noncancer groups (N=670).

Cannabis	Cancer group (N=200)			Non-cancer group (N=670)		
	Agree	Uncertain	Disagree	Agree	Uncertain	Disagree
is narcotic	122 (61)	33 (16.5)	45 (22.5)	414 (61.8)	132 (19.7)	124 (18.5)
can be in possession without permission	71 (35.5)	23 (11.5)	106 (53)	135 (20.1)	119 (17.8)	416 (62.1)
can cure cancer	60 (30)	96 (48)	44 (22)	157 (23.4)	395 (59)	118 (17.6)
can relieve cancer pain	117(58.5)	64 (32)	19 (9.5)	334 (49.9)	290(43.3)	46 (6.9)
can reduce nausea/vomiting from chemotherapy	54 (27)	121 (60.5)	25 (12.5)	113 (16.9)	478 (71.3)	79 (11.8)
can be used with other medications without drug interaction	112 (56)	74 (37)	14 (7)	349 (52.1)	287 (42.8)	34 (5.1)
should be under medical supervision	189 (94.5)	3 (1.5)	8 (4)	622 (92.8)	35 (5.2)	13 (1.9)
Recreational use should be legal	74 (37)	25 (12.5)	101 (50.5)	243 (36.3)	103 (15.4)	324 (48.4)
The small amount of use should not cause serious side effects.	134 (67)	39 (19.5)	27 (13.5)	365 (54.5)	205 (30.6)	100 (14.9)
can be used safely in patients with heart disease, liver disease, kidney disease, and psychiatric conditions.	65 (32.5)	101 (50.5)	34 (17)	192 (28.7)	371 (55.4)	107 (16)

Values are presented as number (percent)

and pain interference in current users trend toward the opposite direction in noncancer patients. Off-label use and illegal procurement were easy and common.[8,14,19] However, adverse events have been reported, and terrible adverse events are not uncommon.[19,21,22]

Among the nearly 60 chemicals extracted from Cannabis Sativa L., the two main compounds are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (Δ9-THC)[25,26], which act on immune cells and the central nervous system, resulting in modulation of memory, emotion, pain, movement, and caused psychoactive effects.[27] Although phytocannabinoids were theoretically beneficial for a variety of conditions, including seizures and spasticity; the clinical benefits, especially pain management, are controversial.[28] Furthermore, the optimal route, dose range, composition of cannabinoids, and therapeutic efficacy in each disease have not been elucidated.[4,7,9,18,29-32] Lastly, the potential harm and long-term side effect is concerning.[33-35]

In Thailand, phytocannabinoid was previously used for various types of condition as part of Thai traditional medicine until it was declared a controlled substance in the early 1930s. Subsequently, cannabis was found in the three most common uses of illicit substances together with Kratom and yaba (met-amphetamine tablet).[36] After the Narcotic act of 2019, which legalized medicinal cannabis in Thailand, was introduced, there was an increasing prevalence of cannabis use from 2.6 to 10.6 per 100,000 patients in 2018 to 2019.[10,17] Among the chronic pain population in our study, the overall prevalence of active cannabis use was 5.86%; 3.1% in chronic noncancer and 15% in cancer patients.

The analysis comparing the characteristics of current users and noncurrent users found that there is no difference in terms of sex, age, education or pain intensity, but the diagnosis of patients (cancer or noncancer) is the only significant factor associated with use. However, our data showed that the proportion of patients who used pain relievers was comparable between cancer and noncancer patients (45.3% vs 53.1%). The higher incidence of the current use in cancer patients is possibly due to non-pain indications such as for palliative care (30.2% vs. 1.6%) or believe that medical cannabis can cure cancer (30.2% vs 0%).

Our data showed that 30% of cancer patients believed that medical cannabis can cure cancer and 30.2% used medical cannabis (MC) for this reason, which is not recommended by Thai or international authorities.[5-7,18,31,37] Furthermore, about a third of the patients in both cancer and noncancer pain group were uncertain of basic knowledge, including the prospective of cannabis-cancer, drug interactions, and use in liver or kidney disease. Assanangkornchai found that the main source from which the respondents obtained information on MC was from friends and relatives (78.3%), followed by social networks (32.9%) and only 15.4% reported receiving information from healthcare providers or government organizations. Most of the patients obtained MC products from illegal sources and without supervision (about 2/3), in conjunction with a survey study in four regions of Thailand by Assanangkornchai et al.[19] This information highlights the fact that public perception and education on medical cannabis is vital and must contribute to prevalence, nature of use, and outcome in the Thai population.

As this study was conducted in the pain center, it is not surprising that the most common reason for using medical cannabis was to control pain in both cancer and noncancer patients (45.3%,53.1%), which is consistent with the meta-analysis by Kosiba et al.[30] and a systematic review by Pratt et al.[33] However, pain control was ranked after sleep aid and mood control in terms of benefit from the user's point of view in both cancer and noncancer patients. Pain was not the most common reason to continue using medical cannabis in cancer patients, but it remains the top reason among noncancer patients. Medical cannabis as an alternative treatment was significantly higher in non-cannabis users in our study, which could be explained by that noncancer group as chronic pain progression, some patients tried a variety of regimens on the market together with the standard medical treatment compared to cancer groups that at the time, if diagnosis needed to be strict with the standard medical regimen. This result showed that the analgesic benefit of medical cannabis between cancer patients and noncancer patients may be different. Oil extraction is the most common formulation, and the recommendation is to use only a few drops sublingually as to bypass first pass hepatic mechanism and direct to the systemic absorption because cannabis has poor oral bioavailability (only 10-20% with lower in combination with food consumption).[38] Also from this reason and low amount of consumption, most cannabis users reported no side effects. Further research is needed to explain why headache was statistically significant in the noncancer group in our study.

Among cancer patients, the current medical cannabis user in the cancer group reported a trend toward a higher pain score, pain interference and a statistically significant higher subscale of interference of enjoyment of life from BPI, lack of appetite, and anxiety, and total cancer-related symptoms from ESAS. In contrast, the

current user in the noncancer group reported a trend toward a lower BPI and ESAS subscale, except the mood subscale from BPI which was statistically significantly lower. The associations of a worse outcome among medical cannabis users in cancer patients are possibly due to the different population, the different nature of the disease, or different types of pain (nociceptive and neuropathic). Even if this association can cause the use of MC or the result of the use of MC in cancer patients, these results raise questions about the overall effectiveness of MC, especially among cancer pain patients. Further research with a confounding factor-controlled prospective cohort study is needed to answer this question.

Legalization was not only associated with an increase in the prevalence of cannabis exposure[20], adverse events from cannabis use also increased after legalization.[8,19] Although most of the participants in our study reported no side effects or minor side effects (dry mouth, drowsiness), severe adverse events such as confusion or hallucination were common.[33] The early report right after the legalization of the National Poison Center reported severe adverse events such as seizures, altered consciousness, and coma patients who underwent brain imaging or tracheal intubation for ventilator support.[39] Furthermore, the long-term follow-up and monitoring of serious adverse outcomes such as psychosis, traffic accidents, abuse, and addiction have not been elucidated in this study and will be required in the future.

The Thai government subsequently initiated many strategies and regulations to mitigate the possible adverse outcomes of medical cannabis, including the implementation of standards around the manufacture and prescribing and a monitoring and evaluation system.[17] However, despite the limited availability of standard preparations produced by the government Pharmaceutical Organization (GPO) and approved manufacturers, the illegal nonstandardized product was the main source of medical cannabis in our study. This problem may be the result of the limited availability and accessibility of legal products and law enforcement. Furthermore, the Thai FDA found variability in Δ^9THC content in MC products, which could be one of the confounders of benefits and side effects in our research.[17]

There were several limitations in this study. First, as a single-center observation study in a tertiary care center, it could not represent prevalence in other settings or across the country. Furthermore, since there is still no standard dose and form recommendation for specific diseases in the use of medical cannabis, this observational study did not have control over the dose, route, and form of medical cannabis that can contribute to variability in individual side effects and responses from cannabis.[29,31,32,35] Lastly, since most of the medical cannabis in this study was an illegal product, the ingredient of medical cannabis was unknown, which can also contribute to the variable of the effect and side effects. More quantitative control research is needed to explore the effect of medicinal cannabis among chronic cancer and noncancer patients.

After legalization, the use of medical cannabis in chronic pain patients in Thailand is prevalent. Use among cancer patients is more common than among non cancer patients and may be associated with greater pain interference and cancer-related symptoms. Nonmedical license prescription and nonmedical cannabis license products were common. Although most of the patients in our study reported no side effects, minor adverse events were frequently reported. Improving public education, law enforcement, and monitoring long-term adverse outcomes is needed to ensure the safety of the use of medicinal cannabis.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Comparative Study of PDA Ligation in the OR versus in the NICU: A 10-Year Retrospective Cohort Study

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ABSTRACT

Objective: This study aimed to compare the outcomes of PDA (patent ductus arteriosus) ligation performed in NICU (neonatal intensive care unit) versus OR (operating room) and identify relevant influencing factors.

Materials and Methods: In this retrospective review, spanning a decade (2012-2021) of NICU patients at Siriraj Hospital who underwent PDA ligation, patients were categorized into two groups: OR and NICU. Baseline clinical characteristics, operative details, and postoperative results (including hospital mortality, cause of death, and complications) were collected and analyzed.

Results: A total of 118 patients were included, with 52 patients in the OR group and 66 patients in the NICU group. There were no statistically significant differences in postoperative outcomes between the two groups. The hospital mortality rates were 1.9% (1/52) and 10.6% (7/66), respectively (p = 0.08). Post hoc multivariable binary logistic regression analysis further confirmed that the location of PDA ligation was not associated with hospital mortality. However, higher oxygen requirements and lower postmenstrual age (PMA) were found to be independently associated with hospital mortality (OR 1.10, p =0.02 and OR 0.82, p<0.01 respectively). Hypothermia, defined as a body temperature less than 36C, was more prevalent in the OR group (30.8% vs 16.7%, p=0.07). Other postoperative complications were not statistically different between the two groups. Lastly, no case of surgical site infection was observed in the NICU group.

Conclusion: PDA ligation can be safely and effectively performed in the NICU with comparable hospital mortality, potentially offering better temperature control, and without an increased risk of complications, including surgical site infection.

Keywords: Patent ductus arteriosus; Patent ductus arteriosus ligation; NICU surgery; Bedside surgery (Siriraj Med J 2024; 76: 31-39)

INTRODUCTION

Patent ductus arteriosus (PDA) is the most common congenital cardiac defect in newborns, particularly among premature infants.[1] Hemodynamically significant PDA can lead to impaired cardiac and respiratory function, resulting in increased morbidity and mortality.[2] When medication trials fail or are contraindicated, PDA ligation is the standard of care.

Traditionally, PDA ligation has been exclusively performed in the operating room (OR), which involves transporting newborns across buildings and subjecting them to less monitored and controlled conditions. Transporting these sick newborns to the operating theater can result in various negative consequences, such as inadequate monitoring, hemodynamic instability, temperature instability, respiratory compromise, and dislodgment

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of intravenous access sites. To minimize transportation-related risks, PDA ligation can be performed bedside in neonatal intensive care units (NICUs).[3]

However, PDA ligation in NICU also carries risks, such as limited availability of equipment, poor surgical lighting, less sterile surgical fields, and lack of cardiopulmonary bypass standby. A study by Mallick et al.[4] has demonstrated the safety and feasibility of performing several procedures in NICU, including PDA ligation. Several studies have also reported outcomes of bedside PDA ligation in NICUs, with hospital mortality rates ranging from 4.20% to 19.20%.[5-8]

To the best of our knowledge, only one study directly compares PDA ligation performed in the OR to the same procedure performed in the NICU. The retrospective cohort study (n = 189) was conducted in 2018 by Lisa K. Lee et al.[9] from the University of California, Los Angeles, reported outcomes and compared PDA ligation in the NICU with ligation in the OR. After adjusting for baseline patient characteristics using mixed effect models and propensity score matching, hospital mortality rates were 14.3% and 5.1%, respectively, which were not significant. Hemodynamic instability upon arrival to the NICU was statistically more prevalent in the OR group. Other outcomes, including perioperative hypothermia, loss of vascular access, sepsis arising after PDA ligation, change in saturation, days requiring ventilator support, and length of stay after PDA ligation, were not statistically significant.

At our center, PDA ligation has been performed in the OR for over sixty years (since 1956), but bedside PDA ligation in the NICU was only initiated within the last decade. This study aims to evaluate hospital mortality and other outcomes of PDA ligation in our NICU patient cohort performed both in the NICU and in the OR over a ten-year period (2012-2021), compare outcomes of both groups, and identify factors that may be associated with differences in the outcomes.

MATERIALS AND METHODS

A retrospective chart review of all NICU patients who had undergone PDA ligation in a ten-year period (2012-2021) at Siriraj Hospital was performed. Approval from the Institutional review board (IRB) was obtained. Patients were initially identified through hospital summary records and subsequently cross-referenced with operating room records. The exclusion criteria included patients who underwent concomitant procedures in addition to PDA ligation, patients not originally from the NICU and patients with incomplete medical records. Data was obtained from a variety of sources, including operative notes, anesthetic records, progress notes, nursing flow sheets, and discharge summary notes.

Patients were categorized into two groups, the OR group and the NICU group, based on the location where PDA ligation was performed. The choice of the location was a collaborative judgment of neonatologists, anesthesiologists and attending cardiothoracic surgeons. In the OR group, newborns were transferred from the NICU to the operating room. During the transfer, all newborns were enclosed in neonatal transport 'Isolette TI500' (Dräger, Lübeck, Germany) units and were manually ventilated using a bag-valve mask.

In the NICU group, newborns underwent the surgery in a radiant warmer, Babyleo TN500 model (Drägerwerk AG & Co. Lübeck, Germany). Surgical instruments were obtained from the OR, and the surgeon used a wearable headlight to enhance visualization.

In both groups, PDA ligation was performed by the same team, consisting of a cardiothoracic surgeon, a cardiothoracic anesthesiologist and scrub nurses. Patients were positioned in the right lateral decubitus position and a posterolateral approach was employed in all cases.

Baseline clinical characteristic data included the following parameters: gestational age (GA), postmenstrual age (PMA), postnatal age, birthweight, weight at the time of procedure, PDA size, concomitant cardiac lesions, preoperative comorbidities, ventilator support parameters (types and settings), inotropic support and details of medication administered for PDA closure trials (drug, number of courses given).

Operative details encompassed incision type and surgical technique, anesthetic approach (intravenous and/or inhalation), intraoperative findings (PDA size and other findings), blood loss, and immediate complications.

Postoperative outcomes included hospital mortality, causes of death, length of stay in the NICU, length of hospital stay and postoperative complications (surgical site infection, cultured-confirmed postoperative sepsis, bleeding, pneumothorax, chylothorax, recurrent laryngeal nerve injury, phrenic nerve injury), body temperature, hypothermia (defined as body temperature below 36C Celsius), and changes in oxygen saturation and hemodynamic instability.

Oxygen saturation changes and hemodynamic instability definition were defined as follows:

For oxygen saturation changes, measurements were measured at two distinct time points:

1) Saturation changes after arrival at the OR: between the last recorded SpO2 at the ward and upon arrival at the OR (for NICU group; last NICU record and first anesthetic record)

2) Saturation changes after returning to the NICU:

between the last recorded SpO2 in the OR and upon arrival to the NICU (for NICU group: first NICU record after surgery and last anesthetic record).

Hemodynamic instability, defined as a change in mean arterial pressure (MAP) greater than 20%, was measured at three different time points:

1) Between the last recorded MAP at the ward and upon arrival at the OR (for NICU group: last NICU record and first anesthetic record).

2) Between the last recorded MAP at the ward and the lowest intraoperative MAP

3) Between the last recorded MAP in the OR and upon arrival to the NICU (for NICU group, first NICU record after surgery and last anesthetic record).

Statistical analyses were conducted using SPSS Statistics version 26 (IBM, Armonk, NY). Descriptive statistics were employed to characterize patient baseline clinical variables and outcomes. To compare variables, Chi-square tests or Fisher's exact test were used for categorical variables, while Student's t-test or Wilcoxon-Mann-Whitney Test were used for continuous variables. Univariable analyses were performed through binary logistic regression, followed by subsequent multivariable binary logistic regression analyses to assess factors associated with primary outcome.

RESULTS

Out of the 130 patients initially identified, 12 were excluded due to concomitant procedures or for not being part of the NICU cohort (Fig 1). The remaining 118 patients, including 66 in the NICU group and 52 in the OR group, were analyzed.

Baseline characteristics (Table 1): There were no significant differences in gender between the two groups ($p = 0.56$). Half of all patients (53%) were classified as extremely low birth weight (ELBW) infants, with very low birth weight (VLBW) infants making up the second-highest proportion (31%). The NICU group exhibitied significantly lower birth weights than the OR group (972 gm versus 1261 gm, $p < 0.01$), significantly lower mean body weights at the time of surgery (1193 gm versus 1442 gm, $p < 0.01$), and also significantly lower gestational age compared to the OR group (27.8 weeks versus 29.2 weeks, $p = 0.02$). Postnatal age, measured as the number of days since birth at the time of surgery, did not significantly differ between the two groups, with the NICU and OR groups having mean ages of 23.9 and 24.6 days respectively ($p = 0.52$).

Regarding concomitant cardiac lesions, there was no significant difference in the percentage of newborns with PFO/ASD (Patent foramen ovale/Atrial septal defect) and VSD (Ventricular septal defect) ($p = 0.37$ and 0.85, respectively). Hypertrophic cardiomyopathy, cardiac rhabdomyoma, and common atrium were also rarely identified in this study.

Both groups exhibited a median of approximately 5 preoperative comorbidities, without significant differences observed between them ($p = 0.51$). Although there were tendencies for a higher prevalence of certain comorbidities (such as Transient tachypnea of the newborn (TTN), Pulmonary hemorrhage, Acute kidney injury (AKI), Sepsis, and Persistent pulmonary hypertension of the newborn (PPHN)) in the NICU group, only the incidence of intraventricular hemorrhage (IVH) showed a statistically significant difference, being notably higher in the NICU group (53.0% vs 19.2%, $p < 0.01$).

Nearly all patients (98.3%) received invasive respiratory support (Conventional ventilator or High frequency oscillatory ventilation - HFOV). The NICU group had a significantly higher percentage of patients

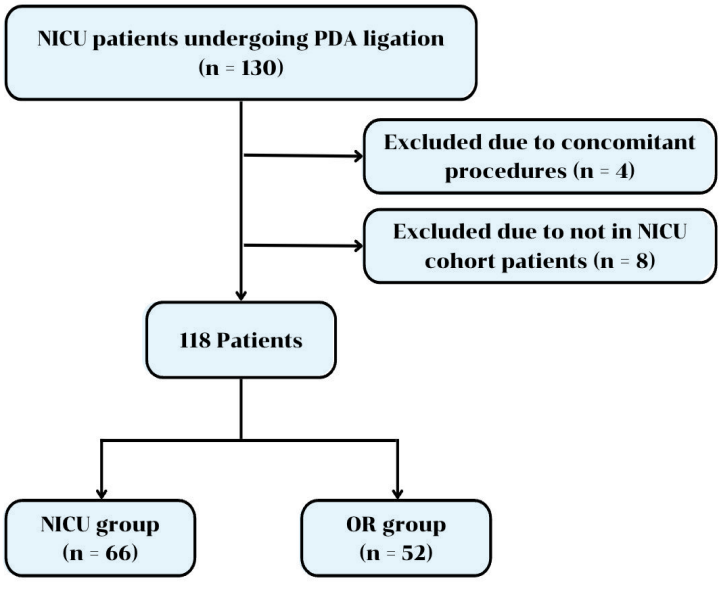

Fig 1. Flow diagram of the patient selection process.

TABLE 1. Baseline characteristics.

	NICU (n = 66)	OR (n = 52)	p value
Sex (Male, n (%))	24 (46.2%)	34 (51.5%)	0.56
Birthweight (grams, median (Q1, Q3))	850 (660, 1070)	1050 (875, 1415)	<0.01
NBW (n (%))	1 (1.5%)	2 (3.8%)	0.09
LBW (<2,500 gm) (n (%))	6 (9.1%)	9 (17.3%)	
VLBW (<1,500 gm) (n (%))	17 (25.8%)	20 (38.5%)	
ELBW (<1,000 gm) (n (%))	42 (63.6%)	21 (40.4%)	
Weight at time of procedure (grams, median (Q1, Q3))	1110 (800, 1302)	1295 (1043, 1683)	<0.01
GA (weeks, median (Q1, Q3))	27.1 (26.1, 28.7)	28.0 (26.6, 31.6)	0.02
PMA at time of procedure (weeks, median (Q1, Q3))	30.7 (28.7, 32.1)	32.7 (30.7, 35.0)	<0.01
Postnatal age (days, median (Q1, Q3))	21.0 (16.0, 31.0)	24.0 (16.0, 32.0)	0.52
Other congenital cardiac lesions			
PFO/ASD (n (%))	30 (45.5%)	28 (53.8%)	0.37
VSD (n (%))	3 (4.5%)	2 (3.8%)	0.85
Other lesions			
Hypertrophic cardiomyopathy	0	1	
Cardiac rhabdomyoma	0	1	
Common atrium	1	0	
Number of comorbidities**			
Number of comorbidities	5 (IQR 4 - 6)	5 (IQR 4 - 6)	0.51
IVH (n (%))	35 (53%)	10 (19.2%)	<0.01
ROP (n (%))	3 (4.5%)	2 (3.8%)	0.85
RDS (n (%))	50 (75.8%)	41 (78.8%)	0.69
TTN (n (%))	10 (15.2%)	4 (7.7%)	0.21
BPD (n (%))	4 (6.1%)	9 (17.3%)	0.05
AOP (n (%))	13 (19.7%)	17 (32.7%)	0.16
Pulmonary hemorrhage (n (%))	18 (27.3%)	10 (19.2%)	0.31
AKI (n (%))	18 (27.3%)	7 (13.5%)	0.07
Hyperbilirubinemia (n (%))	61 (92.4%)	48 (92.3%)	0.98
NEC (n (%))	12 (18.2%)	13 (25%)	0.37
Anemia (n (%))	44 (66.7%)	34 (65.4%)	0.88
Sepsis (n (%))	49 (74.2%)	34 (65.4%)	0.30
Pneumonia (n (%))	14 (21.2%)	18 (34.6%)	0.104
PPHN (n (%))	3 (4.5%)	1 (1.9%)	0.44
Ventilation requirement			
HFNC (n (%))	1 (1.5%)	1 (1.9%)	<0.01
Conventional (n (%))	38 (57.6%)	50 (96.2%)	
HFOV (n (%))	27 (40.9%)	1 (1.9%)	

TABLE 1. Baseline characteristics. (Continue)

	NICU (n = 66)	OR (n = 52)	p value
HFNC			
FiO2 (%)	- 0.21	- 0.25	N/A
Flow (LPM)	- 5	- 4	
Conventional			
FiO2 (%)	- 0.31	- 0.29	0.47
PIP (cmH2O)	- 16.2	- 13.7	0.04
PEEP(cmH2O)	- 5.3	- 4.7	0.01
HFOV			
FiO2 (%)	- 0.33	- 0.5	N/A
MAP (cmH2O)	- 14.1	- 12.0	
Inotropic requirement (n (%))	42 (63.6%)	28 (53.8%)	0.28
Dopamine (n (%))	4 (6.1%)	1 (1.9%)	0.38
(5/118)	Mean dose 11.8	Mean dose 12.0	N/A
Dobutamine (n (%))	40 (60.6%)	27 (51.9%)	0.35
(67/118)	Mean dose 8.6	Mean dose 9.2	0.41
Milrinone (n (%))	3 (4.5%)	1 (1.9%)	0.63
(4/118)	Mean dose 0.2	Mean dose 0.3	N/A
Norepinephrine (n (%))	1 (1.5%)	0 (0%)	1.000
(1/118)	Mean dose 0.4	Mean dose N/A	0.38
Modified inotropic score* (median, (Q1, Q3))**	6 (0, 10)	6 (IQR 0, 10)	0.65
Medical closure trials	34 (51.5%)	20 (38.5%)	0.16
NSAIDs	22 (33.3%)	20 (38.5%)	0.56
Indomethacin	11 (16.7%)	17 (32.7%)	<0.01
Ibuprofen	12 (18.2%)	12 (18.2%)	0.12
Paracetamol	19 (28.8%)	0	<0.01
Number of courses (median, (Q1, Q3))	1 (0, 2)	0 (0, 1)	0.03
0	32 (48.5%)	32 (61.5%)	-
1	16 (24.2%)	16 (30.8%)	-
2	16 (24.2%)	2 (3.8%)	p < 0.05
3	2 (3.0%)	2 (3.8%)	-
PDA size (mm, mean, (SD))	3.3 (1.3)	3.8 (1.0)	0.01
Anesthetic technique			
Total IV (n, (%))	66 (100%)	8 (15.4%)	
IV with Inhalation (n, (%))	0	43 (82.7%)	

requiring HFOV ventilatory support compared to the OR group (40.9% vs 1.9%, p < 0.01). There were no significant differences in FiO2 between patients receiving conventional ventilation in the NICU and OR groups (0.31 vs 0.29, p=0.35). However, the NICU group had significantly higher PIP (16.2 vs 13.7, p=0.04) and PEEP (5.3 vs 4.7, p=0.01) compared to the OR group.

Inotropic support was required in 59.3% of all patients (63.6% vs 53.8% in NICU and OR group respectively, p = 0.28), and dobutamine was the dominant inotrope used (56.8%). The median of modified inotropic scores did not differ between the two groups (6 vs 6 for the NICU and OR group, respectively, p = 0.65).

In this study, medical closure attempts of PDA were made in 45.8% of all patients. There was a trend towards more patients in the NICU group receiving medical closure trials (51.5% vs 38.5%), but this difference was not statistically significant (p = 0.16). The most frequently used drugs for medical closure were NSAIDs (Nonsteroidal anti-inflammatory drugs - Indomethacin, Ibuprofen), which were administered to 35.6% of all patients. Paracetamol was found to be exclusively used in the NICU group, with 19 patients (28.8%) receiving this medication.

In the NICU group, all patients received total intravenous anesthesia, while in the OR group, 82.7% of patients received a combination of inhalation and intravenous anesthesia, and the remaining 15.4% received total intravenous anesthesia.

Postoperative outcomes (Table 2&3)

The study revealed that hospital mortality rates in the NICU group were higher than those in the OR group (10.6% vs. 1.9%). However, this difference was not statistically significant (p = 0.08). Of the eight hospital mortalities, none were PDA-related. The predominant cause was respiratory-related issues, accounting for five deaths: three due to ARDS and two to BPD. Additionally, there were two fatalities from septicemia and one from PPHN.

After conducting both univariable and multivariable binary logistic regression analyses, the location of PDA ligation-whether in the NICU or OR-was not found to be associated with hospital mortality. Nevertheless, lower PMA and higher FiO2 emerged as independent predictors of hospital mortality (OR 0.82, p < 0.01 and OR = 1.10, p = 0.02, respectively). Other factors were not found to be associated with mortality.

Postoperative complications, including infection, sepsis, bleeding, pneumothorax, chylothorax, nerve injury, and rib fractures, were not statistically different between the two groups. There were no cases with surgical site infection in the NICU group.

However, postoperative temperature was significantly lower in the OR group (36.2 C vs 36.5 C, p = 0.04), and hypothermia was more prevalent in the OR group, although it did not reach statistical significance (30.8% vs 16.7% for OR group and NICU group, respectively, p = 0.07).

Following arrival in the OR, the change in oxygen saturation was +1% in the NICU group and +3% in the OR group (p = 0.01). Upon return to the NICU, the change in oxygen saturation was 0% for the NICU group and -2% for the OR group (p < 0.01). Hemodynamic instability at OR arrival, during the operation, and when returning to the NICU was more pronounced in the OR group, with incidences of 23.5%, 32.7%, and 35.3%, respectively, compared to 18.8%, 24.2%, and 28.1% in the NICU group. However, these differences did not reach statistical significance, with p-values of 0.53, 0.33, and 0.41, respectively.

The study also found that hospital and NICU length of stays were longer in the NICU group (138.3 vs 99.8 days, p<0.01 and 92.6 vs 59.1 days, p<0.01, respectively).

DISCUSSION

Consistent with other studies[9-13], the patients in the NICU group were more premature and had lower weight, which may suggest a preference for bedside surgery for smaller patients due to perceived risks associated with

TABLE 2. Independent predictors of hospital mortality.

Factors	Unadjusted OR	p-value	Adjusted OR	p-value
PMA	0.96 (0.74-1.23)	0.74	0.82 (0.74-0.91)	<0.01
FiO2	1.11 (1.05-1.18)	0.001	1.10 (1.02-1.19)	0.02

(Adjusted for PMA, Weight at time of surgery, Location of PDA ligation, Number of comorbidities, FiO2, PIP, HFOV, PDA size)

TABLE 3. Postoperative data.

	NICU (n=66)	OR (n=52)	p value
Hospital mortality (n (%))	7 (10.6%)	1 (1.9%)	0.08
Cause of death			
PDA-related (n (%))	0 (0.0%)	0 (0.0%)	
ARDS (n (%))	2 (3.0%)	1 (1.9%)	
BPD (n (%))	2 (3.0%)	0 (0.0%)	
Septicemia (n (%))	2 (3.0%)	0 (0.0%)	
PPHN (n (%))	1 (1.5%)	0 (0.0%)	
Complications			
Surgical site infection (n (%))	0	2 (3.8%)	0.19
CS-confirmed sepsis (n (%))	9 (13.6%)	6 (11.5%)	0.73
Bleeding (n (%))	0	0	
Pneumothorax (n (%))	2 (3.0%)	1 (1.9%)	1.00
Chylothorax (n (%))	2 (3.0%)	2 (3.8%)	1.00
Recurrent laryngeal nerve injury (n (%))	1 (1.5%)	3 (5.8%)	0.32
Phrenic nerve injury (n (%))	1 (1.5%)	1 (1.9%)	1.00
Rib fracture (n (%))	1 (1.5%)	2 (3.8%)	0.58
Body temp (C, median (Q1, Q3))	36.5 (36.0, 37.0)	36.2 (35.8, 36.6)	0.04
Hypothermia (<36C, n (%))	11 (16.7%)	16 (30.8%)	0.07
Saturation change after arrival at OR (% (Q1, Q3))	1 % (-1, 3)	3 % (0, 5)	0.01
Saturation change after return to NICU (% (Q1, Q3))	0 % (-2, 2)	-2 % (-5, 0) %	<0.01
Hemodynamic instability after arrival (n (%))	12 (18.8%)	12 (23.5%)	0.53
Hemodynamic instability intraoperative (n (%))	16 (24.2%)	17 (32.7%)	0.33
Hemodynamic instability after return (n (%))	18 (28.1%)	18 (35.3%)	0.41
Length of stay in NICU (days (Q1, Q3))	78 (49, 105)	51 (39, 78)	<0.01
Length of NICU stay after the procedure (days, (Q1, Q3))	57 (28.5, 81)	30 (12, 52)	<0.01
Total hospital stay (days, (Q1, Q3))	125 (92, 179)	91 (70, 119)	<0.01

transporting them to the operating room. Also, IVH was more prevalent in the NICU group, possibly due to the group having more premature gestational ages.

Additionally, nearly half of the NICU group required HFOV or a higher setting of conventional ventilator. This reflects that those patients were younger and more severely ill, which is also consistent with findings from other studies.[9,10,13] Other preoperative comorbidities and inotropic support between the two groups were not significantly different.

The predominant use of paracetamol in the NICU group may be due to the high prevalence of contraindications for NSAIDs, such as intraventricular hemorrhage (IVH), which was significantly more common in the NICU group. In addition, there was an increase in paracetamol usage in later years of this study. This trend is supported by recent evidence from El-Meshed et al, which demonstrated that paracetamol is as effective as NSAIDs but with fewer side effects.

The mortality rates observed in this study (10.6% vs 1.9%, NICU and OR group, p=0.08) were comparable to those reported in contemporary studies (14.3% vs 5.1% by Lisa K. Lee).[9] These findings suggest that the location of surgery does not affect hospital mortality. Additionally, respiratory-related causes were the most common reported mortalities (5 deaths), with two deaths

attributed to septicemia, which occurred exclusively in the NICU group. The absence of surgical site infections in the NICU group suggests that septicemia cases were caused by sources other than surgical site infections.

Table 4 presents hospital mortality rates stratified by year and location of operation (OR or NICU). In recent years, PDA ligation has been conducted more frequently in the NICU than in the OR. However, the low rate of hospital mortality limits the potential for further meaningful analysis.

TABLE 4. . PDA ligation location trends in recent years.

		Hospital mortality			
Year		No	Yes	Total (n, (%))	p value
2011	NICU (n, (%))	0 (0%)	0 (0%)	0 (0%)	NA
	OR (n, (%))	2 (100%)	0 (0%)	2 (100%)	
	Total (n, (%))	2 (100%)	0 (0%)	2 (100%)	
2012	NICU (n, (%))	0 (0%)	0 (0%)	0 (0%)	NA
	OR (n, (%))	8 (88.89%)	1 (1.11%)	9 (100%)	
	Total (n, (%))	8 (88.89%)	1 (1.11%)	9 (100%)	
2013	NICU (n, (%))	0 (0%)	0 (0%)	0 (0%)	NA
	OR (n, (%))	4 (100%)	0 (0%)	4 (100%)	
	Total (n, (%))	4 (100%)	0 (0%)	4 (100%)	
2014	NICU (n, (%))	2 (50%)	2 (50%)	4 (26.67%)	0.01
	OR (n, (%))	11 (100%)	0 (0%)	11 (73.33%)	
	Total (n, (%))	13 (86.67%)	2 (13.33%)	15 (100%)	
2015	NICU (n, (%))	1 (100%)	0 (0%)	1 (6.67%)	NA
	OR (n, (%))	14 (100%)	0 (0%)	14 (93.33 %)	
	Total (n, (%))	15 (100%)	0 (0%)	15 (100%)	
2016	NICU (n, (%))	5 (83.33%)	1 (16.67%)	6 (60%)	0.39
	OR (n, (%))	4 (100%)	0 (0%)	4 (40%)	
	Total (n, (%))	9 (90%)	1 (10%)	10 (100%)	
2017	NICU (n, (%))	12 (85.71%)	2 (14.29%)	14 (82.35%)	0.49
	OR (n, (%))	3 (100%)	0 (0%)	3 (17.65%)	
	Total (n, (%))	15 (88.24%)	2 (11.76%)	17 (100%)	
2018	NICU (n, (%))	6 (100%)	0 (0%)	6 (66.67%)	NA
	OR (n, (%))	3 (100%)	0 (0%)	3 (33.33%)	
	Total (n, (%))	9 (100%)	0 (0%)	9 (100%)	
2019	NICU (n, (%))	12 (100%)	0 (0%)	12 (100%)	NA
	OR (n, (%))	0 (0%)	0 (0%)	0 (0%)	
	Total (n, (%))	12 (100%)	0 (0%)	12 (100%)	
2020	NICU (n, (%))	12 (92.31%)	1 (7.69%)	13 (86.67%)	0.69
	OR (n, (%))	2 (100%)	0 (0%)	2 (13.33%)	
	Total (n, (%))	14 (93.33%)	1 (6.67%)	15 (100%)	
2021	NICU (n, (%))	9 (90%)	1 (10%)	10 (100%)	NA
	OR (n, (%))	0 (0%)	0 (0%)	0 (0%)	
	Total (n, (%))	9 (90%)	1 (10%)	10 (100%)	
Total	NICU (n, (%))	59 (89.39%)	7 (10.61%)	66 (55.93%)	0.06
	OR (n, (%))	51 (98.08%)	1 (1.92%)	52 (44.07%)	
	Total (n, (%))	110 (93.22%)	8 (6.78%)	118 (100%)	

The incidence of surgical site infections was comparable between the two groups, with no statistically significant difference observed (0% vs 3.8%, p=0.19). This finding, along with similar findings from other studies, including those by Gavilanes et al. in 1997 and Lisa K. Lee in 2018, reaffirmed that the location of the operation, whether in the OR or NICU, does not appear to increase the risk of surgical site infections.[9,14]

The OR group had a lower postoperative body temperature, possibly due to factors like transportation and temperature control during the operation. The OR group also had a higher incidence of hypothermia, defined as a body temperature under 36C, but the difference (16.7% vs 30.8%) did not reach statistical significance (p=0.07). This suggests that PDA ligation in the NICU might offer better temperature control, though the difference in hypothermia rates was not statistically significant.

This study identified statistically significant differences in oxygen saturation at various time points; however, the differences observed were clinically insignificant (-2% to 3%). These findings are consistent with previous research.[9] Additionally, while there was a trend towards a higher incidence of hemodynamic instability in the OR group, the difference was not statistically significant. This contrasts with a study by Lisa K. Lee, which reported a significantly higher incidence of hemodynamic instability in the OR group upon returning to the NICU, suggesting a need for further research to specifically address hemodynamic instability during transportation of newborns to the operating room.

Limitations: Firstly, this study was retrospective and relies on existing medical records, which may have been incomplete or of varying quality. Additionally, the decision to perform PDA ligation in the NICU or OR was not randomized, introducing selection bias. Furthermore, the incidence of mortality was relatively low, making it difficult to conduct further analysis on factors that may affect the outcome.

CONCLUSION

PDA ligation can be safely and effectively performed in the NICU with comparable hospital mortality, potentially providing better temperature control, and without an increased risk of complications, including surgical site infection.

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