E-ISSN 2228-8082
Volume 76, Number 8, August 2024

136 YEAR SIRIRAJ

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Siriraj Medical Journal

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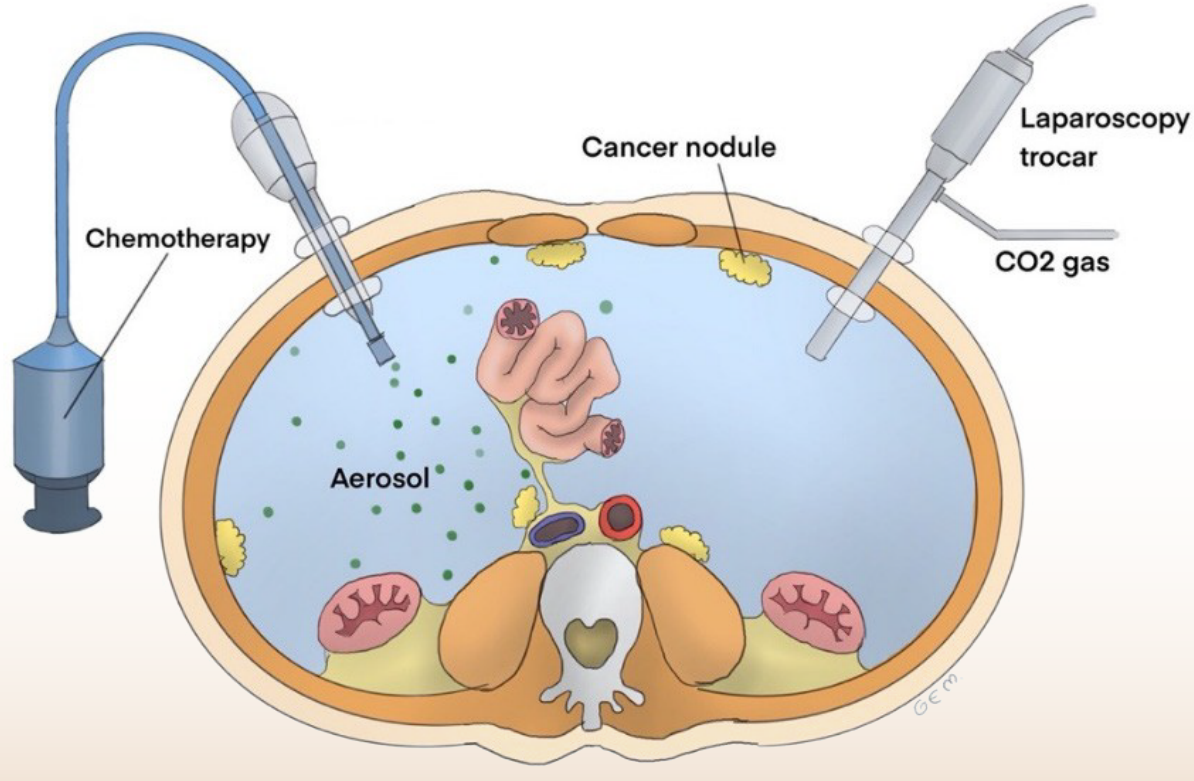
MONTHLY

ORIGINAL ARTICLE REVIEW ARTICLE



By Thita Intralawan, et al.

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SMJ
Siriraj Medical Journal
The world-leading biomedical science of Thailand
Volume 76 Number 8
August 2024

ORIGINAL ARTICLE

REVIEW ARTICLE

SIRIRAJ MEDICAL JOURNAL

https://he02.tci-thaijo.org/index.php/sirirajmedj/index

Office: His Majesty the King's 80th Birthday Anniversary 5th December 2007 Building (SIMR), 2nd Fl., Room No.207
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Incidence and Factors Associated with Breastfeeding at Six Months in Very-Low-Birthweight Infants: A Single-Center Prospective Study

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ABSTRACT

Objective: Primary objective was to determine success rate of breastfeeding (BF) at 6-month-postnatal age (PNA). Secondary objective was to explore factors associated with unsuccessful BF at 6-month-PNA in very-low-birth weight (VLBW) infants.

Materials and Methods: Single-center, prospective, observational study was conducted. Inclusion criteria were discharged VLBW infants and maternal desire for BF. We conducted telephone interviews to assess feeding type and volume every 2 months until 12-month-PNA and reasons for BF cessation.

Results: Eighty-nine VLBW infants were included. Mean (±standard deviation) maternal age was 31.4 ± 6.5 years. Median [P25, P75] gestational age was 29.0 [28.0, 31.5] weeks. At 6-month-PNA, 22 infants (24.7%) were exclusively breastfed (EBF), which decreased to 2 infants (2.2%) by 12 months. Rate of successful BF at 6 months was 55.1%. After controlling for potential confounders, factors associated with unsuccessful BF at 6 months were male [aOR (95% CI) 3.2 (1.1, 9.4), p = 0.04], longer hospitalization stays [aOR 1.0 (1.0, 1.1), p = 0.02], born via cesarean section [aOR 4.1 (1.1, 15.4), p = 0.04], maternal education below bachelor's degree [aOR 4.0 (1.1, 14.0), p = 0.03], and introduction of additional feeding types at hospital discharge [aOR 3.8 (1.2, 12.2), p = 0.03]. Main reason for unsuccessful breastfeeding at 6 months was inadequate milk supply (77.5%).

Conclusion: 55% of VLBW infants retained successful BF at 6 months. Main reason for unsuccessful BF was inadequate milk supply.

Keywords: Breastfeeding; cesarean section; maternal education; hospital discharge; very-low-birth weight infants (Siriraj Med J 2024; 76: 473-479)

INTRODUCTION

Breastfeeding (BF) is recognized as the gold standard for feeding infants.[1] Several studies have shown a correlation between extended BF and lower rates of infant morbidity and improved neurodevelopmental outcomes.[2-4] The World Health Organization and the American Academy of Pediatrics advocates exclusively breastfeeding until an infant is at least six months of age.[5,6] The advantage of human milk is particularly important for infants with very-low-birth weight (VLBW),[7,8] with studies indicating reduced incidences of severe conditions such as necrotizing enterocolitis, sepsis, and retinopathy of prematurity, as well as a lower mortality risk.[9-11] Furthermore, BF is associated with positive long-term developmental outcomes.[12] Therefore, it is important for hospitals to establish policies that promote BF in preterm infants

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https://doi.org/10.33192/smj.v76i8.268307

to improve short- and long-term outcomes. However, the success of BF depends on various factors, including the health conditions of both the infant and mother, BF techniques, and other support systems.

The prevalence of exclusive breastfeeding (EBF) (percentage of children under 6 months old fed only breast milk without any other liquids in the past 24 hours) varies across different regions. From 2015 to 2021, the average EBF rate in Southeast Asian countries was 48% compared to 26% in North America. In Thailand, the rate was only 14%.[13] At our institution, the rate of BF at 6 months reached 62%. Given that prematurity and low birth weight infants are linked to decreased rates of postnatal BF,[14] it can be inferred that the rate of EBF in VLBW infants would likely be even lower.

National or social culture can also influence the sustainability of BF. Several studies have demonstrated factors linked to successful BF at 6 months of age, including maternal intention,[15] supportive hospital policies,[16] psychological support,[17] socioeconomic status,[15,18] and social and workplace support.[19,20] These factors become more complicated for mothers of premature infants. Preterm infants typically suffer from various conditions from birth and require extended hospitalization stays, which can hinder adequate milk production and mother-infant bonding due to maternal stress and the complexities of postnatal care. Studied have found that milk expression volumes are lower in the absence of infants.[21] Additionally, the small size of their oropharyngeal structures and limited endurance complicate the establishment of BF. Some infants may also need fortification or supplemental formula to ensure proper nutrition and growth. Furthermore, the duration of maternity leave is often reduced by the extended hospital stay required at birth, making it more difficult to continue EBF for the recommended 6 months.

Given the relatively low rate of exclusive breastfeeding in Thailand, our study aimed to assess our specific context and investigate the factors leading to unsuccessful breastfeeding in VLBW infants up to 6 months postnatal age (PNA). The primary objective was to identify the rate of successful BF at 6 months. The secondary objective was to explore factors associated with unsuccessful BF at 6 months and the rate of successful BF at 12 months in VLBW infants.

MATERIALS AND METHODS

We conducted a prospective observational study at the Neonatal Division, Department of Pediatrics, Faculty of Medicine Siriraj Hospital in Bangkok, Thailand. Our institutional policy for BF in preterm infants follows the "Ten steps for promoting and protecting breastfeeding for vulnerable infants.[22] All preterm infants undergo an assessment for BF readiness once they are clinically stable, and their postmenstrual age reaches 32 weeks of gestation. The nursing staff provides education to mothers on BF techniques and assesses readiness until the infant is discharged from the hospital. Infants experiencing breastfeeding difficulties are referred to the lactation clinic for further evaluation and practice until mother feel confident in their BF ability. After hospital discharge, regular follow-up appointments at the lactation clinic are scheduled to ensure continued BF success.

The study's inclusion criteria included: 1) birth weight less than 1,500 g; 2) discharge before 4 months of PNA; 3) mothers with the intention to BF who were educated and assessed on BF techniques prior to discharge; and 4) maternal written consent. Infants were excluded if they had contraindications for BF, severe congenital anomalies or any conditions that could potentially impact BF, such as craniofacial anomalies or neurological conditions. Following hospital discharge, the study team made follow-up telephone calls using standardized questionnaires every two months up to 12 months of PNA. During these calls, information about the infants' current feeding types and experiences were collected from the mothers or primary guardians. Caregivers provided estimates of the type and volume of feedings. Missing data from any time point were excluded from the analysis.

Definitions

Exclusive breastfeeding (EBF) refers to a feeding practice in which the infant receives only breastmilk, whether directly from breastfeeding or through expressed breastmilk, with no additional infant formula.

Exclusive infant formula (EIF) refers to a feeding practice where the infant is fed solely with infant formula.

Predominant breastfeeding (PBF) refers to a feeding practice where breastmilk is more than half of the infant's total daily milk intake.

Predominant infant formula (PIF) refers to a feeding practice where infant formula accounts for more than half of the infant's total daily milk volume.

We defined successful BF as infants who were either EBF or PBF at the age of 6 months.

Statistical analysis

To estimate the required sample size, we used our overall EBF rate at 6 months which was 62%. With a type I error of 0.1, and using a Z-score of -1.65 with a margin of error of 0.1, we determined that a total of 91 VLBW infants were needed.

For the analysis of the incidence and rates of categorical

variables, we employed counts (percentage), mean±standard deviation (SD), or median [25th percentile, 75th percentile; P25, P75] depending on the nature and distribution of each variable. To explore factors associated with unsuccessful BF (either PIF or EIF), logistic regression analysis was used, with results presented as odds ratios (ORs) and 95% confidence intervals (95% CIs). Variables with a *p*-value <0.2 were further analyzed using multivariate logistic regression analysis and presented as adjusted odds ratios (aORs) with 95% CIs. All statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). A *p*-value <0.05 was considered statistically significant.

RESULTS

The study's protocol was approved by the institutional research ethics board, and maternal written consent was obtained prior to hospital discharge. Recruitment commenced in September 2018 but was prematurely concluded in August 2021 after 89 VLBW infants were enrolled. This early termination was the result of changes in hospital policy regarding maternal stays and visits during the COVID-19 pandemic, which influenced BF policy and maternal BF education. Table 1 demonstrates the demographic characteristics of mothers and infants involved in the study. The median [P25, P75] gestational age (GA) was 29.0 [28.0, 31.5] weeks. Among the infants, 13 (14.6%) were born before reaching 28 weeks GA. The median [P25, P75] birth weight (BW) was 1,150.0 g [970.0, 1,285.0], and 23 infants (25.8%) had a BW <1,000 g. The mean hospitalization duration was 65.9 ± 23.1 days, and 61 infants (68.5%) were breastfed at discharge. Out of all the mothers, 44 (54.3%) were primigravida, while 16 (19.8%) were pregnant with twins.

At 6 months postnatal age, 22 infants (24.7%) were EBF, but this decreased to just two infants (2.2%) by 12 months. Successful BF (either EBF or PBF) was accomplished by 49 infants (55.1%) at 6 months, and this rate subsequently decreased to 13 infants (14.6%) by the 12-month mark. The distribution of feeding types across the 12 months PNA is illustrated in Fig 1.

Table 2 outlines factors linked to unsuccessful BF at 6 months. Compared to infants who were successfully BF, those with unsuccessful BF outcomes had notably lower BW (1105.0 g [905.0, 1227.5] versus 1200.0 g [1045.0, 1310.0], $p = 0.02$), a higher incidence of being small-for-gestational age (SGA) (37.5% vs 18.4%, $p = 0.04$), longer hospitalization duration (71.9 ± 23.3 versus 61.0 ± 22.0, $p = 0.03$), a lower prevalence of mothers with bachelor's degrees (55.0% versus 32.7%, $p = 0.03$), and a greater frequency of introducing an additional type of feeding at hospital discharge (45.0% versus 20.4%, $p = 0.01$). However, after adjusting for potential confounders through multivariate logistic regression analysis, the factors significantly associated with unsuccessful BF at 6 months included male sex [aOR (95% CI) 3.2 (1.1, 9.4), $p = 0.04$], longer hospitalization stays [aOR 1.0 (1.0, 1.1), $p = 0.02$], born via cesarean section [aOR 4.1 (1.1, 15.4), $p = 0.04$], maternal education below a bachelor's degree [aOR 4.0 (1.1, 14.0), $p = 0.03$], and the introduction of an additional feeding type at hospital discharge [aOR 3.8 (1.2, 12.2), $p = 0.03$]. Table 3 presents maternal reasons for unsuccessful BF at 6 months, with the predominant reason being insufficient milk supply (77.5%), followed by concerns about the infant's health problems (10%).

DISCUSSION

While BF is considered the best option for preterm or low-birthweight infants, the likelihood of achieving and maintaining BF is typically lower for preterm infants compared to term infants.[14] This discrepancy can be attributed to potential postnatal illnesses and physiological immaturity, which leads to delayed initiation of BF, and longer time and effort required. At our center, despite an overall EBF rate of 62% at 6 months, the rate among VLBW infants was only 24.7%. Even when including both EBF or PBF as indicators of successful BF, the rate of 55% for VLBW infants is still lower than the overall rate. Therefore, despite efforts by the team to support BF, among this group, additional strategies are needed to promote the success rate of BF in VLBW infants.

The success of BF is associated with both infant and maternal factors. Characteristics such as male sex and being born via cesarean section have been identified as unmodified risk factors.[23] This may be due to male infants' higher susceptibility to hospital morbidities.[24] Our finding suggest that infants introduced to supplementary feeding type at discharge were also 3.8 times more likely to experience unsuccessful BF at 6-month mark. Moreover, a longer hospital stay, often indicative of a complicated illness, has been linked to challenges in establishing EBF after hospital discharge.[25] Therefore, infants facing significant health issues that prolongs their hospital stay and hinders BF before discharge require early and focused support from caregivers to encourage BF as a key part of discharge planning.[14] Interestingly, maternal education has a positive correlation with successful BF, which reinforces findings from previous studies.[14,18] Factors such as lower maternal socioeconomic status, maternal attitudes towards BF, and the level of social support have all been multifacetedly linked to BF outcomes at 6 months.[18] The most frequently cited reason for discontinuing BF was

TABLE 1. Maternal and infant demographic characteristics

Maternal (N=81)	
Age (years)	31.4 ± 6.5
Primigravida	44 (54.3)
Multifetal pregnancies	16 (19.8)
Cesarean section	58 (71.6)
Education below the bachelor's degree	34 (42.0)
Occupations	
Company employee	14 (17.3)
Self employed	40 (49.4)
Government official	6 (7.4)
Housewife	17 (21.0)
Parental income less than 15,000 THB/month	33 (40.7)
Live in Bangkok metropolitans (n=79)	68 (86.1)
Infant (N= 89)	
Gestational age (weeks)	29.0 [28.0, 31.5]
Birth weight (grams)	1150.0 [970.0, 1285.0]
Male sex	42 (47.2)
Twins	24 (27.0)
Small-for-gestational age	24 (27.0)
5-minute Apgar scores	9.0 [7.5, 9.0]
Days of hospitalization	65.9 ± 23.1
Feeding type at hospital discharge	
Breast feeding	61 (68.5)
Cup or spoon feeding	15 (16.9)
Tube feeding	8 (9.0)
Bottle feeding	5 (5.6)

Data is presented as mean±standard deviation, number (percentage), median [25th percentile, 75th percentile]

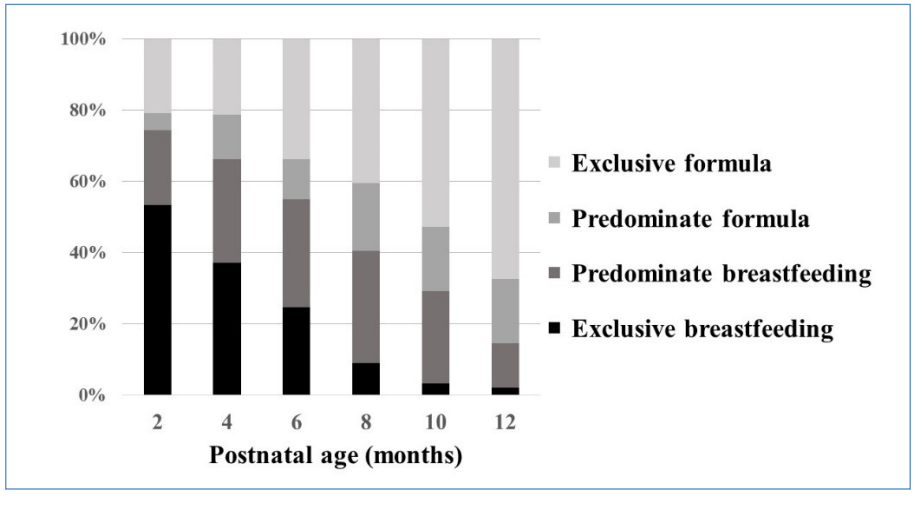

Fig 1. The proportion of feeding types over 12 months postnatal age (PNA)

TABLE 2. Factors associated with unsuccessful breastfeeding at 6 months of age (N=89)

	Unsuccessful BF (n=40)	Successful BF (n=49)	*p*	OR (95%CI)	Adjusted OR (95%CI)	*p*
Male sex	23 (57.5)	19 (38.8)	0.08	2.1 (0.9, 5.0)	3.2 (1.1, 9.4)	0.04*
Gestational age	29.5 [28.0, 31.0]	29.0 [28.5, 32.0]	0.61	0.9 (0.8, 1.1)		
Twins	11 (27.5)	13 (26.5)	0.92	1.1 (0.4, 2.7)		
Birth weight (grams)	1105.0 [905.0, 1227.5]	1200.0 [1045.0, 1310.0]	0.02*	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	0.74
Small-for-gestational age	15 (37.5)	9 (18.4)	0.04*	2.7 (1.0, 7.0)	2.5 (0.6, 10.8)	0.23
5-minute Apgar score	9.0 [8.0, 9.0]	8.0 [7.0, 9.0]	0.31	1.2 (0.9, 1.5)	1.4 (1.0, 1.9)	0.07
Days of hospitalization	71.9 ± 23.3	61.0 ± 22.0	0.03*	1.0 (1.0, 1.0)	1.0 (1.0, 1.1)	0.02*
Maternal age (years)	30.8 ± 6.5	31.3 ± 6.3	0.67	1.0 (0.9, 1.1)		
Cesarean section	32 (80.0)	31 (63.3)	0.08	2.3 (0.9, 6.1)	4.1 (1.1, 15.4)	0.04*
Multi-gravida	19 (47.5)	21 (42.9)	0.66	1.2 (0.5, 2.8)		
Occupation other than housewife	29 (72.5)	41 (83.7)	0.20	0.5 (0.2, 1.4)		
Maternal education below the bachelor's degree	22 (55.0)	16 (32.7)	0.03*	2.5 (1.1, 6.0)	4.0 (1.1, 14.0)	0.03*
Parental income >15,000 THB/month	21 (52.5)	17 (34.5)	0.09	2.1 (0.9, 4.9)	1.1 (0.3, 3.7)	0.85
Additional type of feeding at discharge	18 (45.0)	10 (20.4)	0.01*	3.2 (1.3, 8.1)	3.8 (1.2, 12.2)	0.03*
Living in Bangkok/Bangkok metropolitans	34 (85.0)	41 (87.2)	0.76	0.8 (0.2, 2.8)		

Unsuccessful breastfeeding (BF) was defined as a condition in which the infant received infant formula for at least a half of the total milk volume each day. Data is presented in numbers (percentage); odds ratio and 95% confidence interval, OR (95%CI). *p-value <0.05 was statistically significant.

TABLE 3. Maternal reasons of unsuccessful breastfeeding at 6 months of age (n =40)

Inadequate milk supply	31 (77.5)
Infant medical health problems	4 (10.0)
Stay at a different place	3 (7.5)
Return to work	2 (5.0)

inadequate milk supply, although no direct correlation was found with the mother's occupation or income. Therefore, caregivers should put more effort into early and regular pumping to maintain milk supply.

We prospectively determined successful BF in VLBW infants with a prespecified sample size. Despite concluding the study earlier than planned, we manage to recruit 98% of the required sample size and with no drop-outs over a 12-month period, which strengthens the internal validity of our results. Our approach to managing maternal breastfeeding in infants with metabolic bone diseases continues to prioritize maternal milk as the primary source of nutrition. We supplement other necessary minerals appropriately for each infant, whether through fortification or providing calcium and phosphate supplements, without resorting to formula to replace maternal milk. Consequently, the overall volume of maternal milk received within the 2-month study period remains dependent on maternal lactation capacity and other relevant factors we have investigated. However, we realize there were several limitations within our study. First, the potential for subjective assessment and recall bias could compromise the validity of our results, however, we chose a 2-month epoch for assessment to minimize any such bias. Second, our study included only infants whose mothers had expressed a desire to BF, which introduced a selection bias that could result in an overestimation of successful BF rates in general VLBW infants. Third, the requirement for mandatory consent meant that mothers were aware they would be subject to regular monitoring, which raised the possibility of ascertainment bias. However, we addressed this issue by discussing with mothers or primary caregivers at the time of consent and during each follow-up visit. We believe our extended long follow-up period should help nullify this effect and maintain our study's internal validity. It is also important to note that the study was conducted in a super tertiary care center equipped with a robust system and dedicated team to support BF before and after hospital discharge. Concurrently, there was an observed trend towards encountering infants with complex issues. Notably, infants with severe congenital anomalies or severe neurological deficits necessitate distinct nutritional management compared to generally VLBW infants. Factors such as breastfeeding techniques, volume, or frequency may influence maternal breastfeeding success or even maternal attitudes. Therefore, infants in this subgroup were designated as exclusion criteria to ensure that this study's outcomes represent the broader landscape of VLBW infants, thereby enhancing the generalizability of the results. Nevertheless, it is imperative to caution in extrapolating our findings to other secondary or tertiary care centers lacking similar BF support structures.

CONCLUSION

The success rate of BF in VLBW infants was 55%, which is lower than the broader average. The main maternal factor for unsuccessful BF was identified as inadequate milk supply. Several factors were linked to lower BF success rates, including being male, birth via cesarean section, and extended hospital stays. Additionally, mothers with education below a bachelor's degree were found to have a higher risk of unsuccessful BF. Factors linked to unsuccessful BF were related to infants' demographic characteristics and hospital-related outcomes rather than social factors.

ACKNOWLEDGEMENTS

We would like to thank all staff and nurses for their cooperation and support during this study. We also thank Mr. Aditya Rana for his English language editing.

Conflict of interest

All authors declare no conflicts of interest relating to any aspects of this study.

Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: RK and PT; data collection: PT and VC; analysis and interpretation of results: RK, NL, and PS; draft manuscript preparation and critical revision: RK, NL, and PS. All authors reviewed the results and approved the final version of the manuscript.

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Determining Perioperative Mortality in Patients with Ruptured Abdominal Aortic Aneurysm: Insights from a Retrospective Cohort Study

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ABSTRACT

Objective: This retrospective cohort study analyzed factors determining perioperative mortality in patients with ruptured abdominal aortic aneurysm (rAAA) undergoing open surgical repair (OSR) or endovascular aneurysm repair (EVAR).

Materials and Methods: 147 rAAA patients who underwent OSR (n = 37) or EVAR (n = 110) between 2000 and 2017 were included. Demographic data, intraoperative details, and perioperative complications were assessed. Logistic regression analysis identified factors associated with perioperative mortality. The primary endpoint was perioperative mortality rate, and the secondary endpoint focused on factors determining 30-day mortality.

Results: Overall perioperative mortality was 19.04% (28/147), with 8.1% (3/37) for OSR and 22.7% (25/110) for EVAR (p = 0.139). The non-survived group had more unfit patients (82.1% vs. 47.9%, p = 0.002), higher preoperative serum creatinine levels (1.8 ± 1.74 vs. 1.4 ± 5.89, p = 0.011), and higher rates of aortic balloon usage (64.3% vs. 22.7%, p<0.001) and cardiac arrest 28.6% vs. 3.4%, p < 0.001). Multivariable analysis identified age > 80 years (adjusted odds ratio [aOR] 9.785, p=0.003), unfit patient status (aOR, 3.35, p = 0.028), aortic balloon usage (aOR, 5.54, p = 0.036), postoperative myocardial infarction (aOR, 13.995, p < 0.001), postoperative congestive heart failure (aOR, 15.22, p = 0.038), and abdominal compartment syndrome (aOR, 23.397, p < 0.001) as independent predictors of 30-day mortality.

Conclusion: No significant difference in perioperative mortality was found between OSR and EVAR in rAAA patients. Several independent factors predicting 30-day mortality were identified, providing valuable insights for clinicians in predicting outcomes and improving patient care in rAAA cases.

Keywords: Ruptured abdominal aortic aneurysm; perioperative mortality factors (Siriraj Med J 2024; 76: 480-487)

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Received 13 November 2023 Revised 26 April 2024 Accepted 2 May 2024
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https://doi.org/10.33192/smj.v76i8.266315

INTRODUCTION

Rupture abdominal aortic aneurysm (rAAA) is a life-threatening condition in the field of surgery, demanding prompt intervention. Traditionally, open surgical repair (OSR) has been the established invasive treatment for rAAA. However, over the past two decades, endovascular aortic aneurysm repair (EVAR) has emerged as a proven method for reducing 30-day mortality in asymptomatic AAA repair[1,2] and has gained increasing popularity for rAAA management.[3,4]

Despite advancements in pre-hospital care, fast-track protocols, and endovascular technologies, it remains unclear whether there have been improvements in the outcomes related to 30-day mortality in rAAA.[5,6] Also, the existing literature lacks a comprehensive analysis of the specific factors contributing to perioperative mortality in both open and endovascular treatments for rAAA.

Therefore, the primary objective of this retrospective cohort study was to analyze the 30-day mortality rates and identify the factors that contribute to perioperative mortality in both OSR and EVAR for rAAA. By examining a large dataset of patients, this study aimed to provide valuable insights into the effectiveness of these treatment modalities and potentially guided clinical decision-making for better patient outcomes.

MATERIALS AND METHODS

Study design and ethical approval

This retrospective cohort study utilized data from a prospective database approved by the Siriraj Institution Review Board (SIRB Protocol no. 612/2561). The database included information on patients diagnosed with ruptured abdominal aortic aneurysm (rAAA) who underwent either open surgical repair (OSR) or endovascular aortic aneurysm repair (EVAR) at our institute from January 2000 to December 2017.

Patient selection

A total of 150 patients with rAAA were initially included in the study. However, three patients were excluded due to aortoenteric and aortocaval fistula diagnoses in two cases, and one case with missing data. The inclusion criteria consisted of patients aged 18–90 years old with a radiological diagnosis of rAAA or confirmation through intraoperative findings.

Preoperative factors

Various preoperative factors were considered, including age, gender, coronary arterial disease, chronic obstructive pulmonary disease, hypertension, dyslipidemia, type 2 diabetes, cerebrovascular disease, current smoking, unfit patient status, cardiac arrhythmia, antiplatelet drug usage, hemoglobin level, creatinine level, and coagulogram results. The selection of patients with rAAA, whether fit or unfit, has been previously described based on their cardiac, respiratory, and renal status in the UK EVAR 1 and 2 trials.[7]

Intraoperative factors

The treatment strategy (EVAR vs. OSR), intraoperative aortic balloon occlusion, cardiac arrest, intraoperative blood loss, intraoperative blood replacement, and procedure duration were analyzed as intraoperative factors. Efforts were made to stabilize patients' hemodynamic status before surgery through hypotensive resuscitation and limited fluid resuscitation to promptly diagnose issues and enable them to recover from a state of shock. The intraoperative aortic balloon occlusion was employed in case where patients were deemed unstable, specifically those who were unconscious or had low systolic blood pressure (less than 80 mmHg).

Postoperative factors

Postoperative factors included postoperative myocardial infarction, postoperative congestive heart failure, abdominal compartment syndrome, chest infection, ischemic colitis, and wound infection. These factors were examined to assess postoperative complications and outcomes.

Abdominal compartment syndrome (ACS) is characterized by the presence of intraabdominal pressure exceeding 20 mmHg, accompanied by the onset of organ dysfunction or failure.[8] The tool for measuring bladder pressure is a three-way Foley catheter using the patient's urine as pressure medium. A minimum of 25 mL should be instilled into the bladder, and the patient should be in the supine position.[9]

Outcome measures

The primary outcome measured in this study was the perioperative mortality rate. Additionally, secondary outcomes focused on identifying factors contributing to 30-day mortality and comparing postoperative complications and re-interventions between EVAR and OSR.

Statistical analysis

Data were recorded and analyzed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize the characteristics of the study population. Univariable analyses were initially conducted to examine the association between 30-day mortality and various factors. Categorical variables were analyzed using chi-square tests or Fisher's exact tests,

as appropriate. Continuous variables were compared using t-tests or Mann–Whitney U tests, depending on the distribution of the data. Factors that were found to be significant in the univariable analysis ($p < 0.05$) were then included in the multivariable logistic regression analysis. The multivariable analysis aimed to identify independent predictors of 30-day mortality. Variables were entered into the model using a stepwise selection method based on their significance in the univariable analysis and their clinical relevance. Adjusted odds ratios (aOR) with 95% confidence intervals (CIs) were calculated to quantify the strength of association between the independent predictors and the 30-day mortality. A *p-value* < 0.05 was considered statistically significant. Missing data were handled through complete case analysis, whereby cases with missing data were excluded from the specific analysis.

RESULTS

Of the 37 patients in the OSR group, 34 survived while 3 patients died within 30 days after the operation. Among the 110 patients who underwent EVAR, 85 survived and 25 patients died within 30 days after the operation. The overall 30-day mortality for rAAA was 19%, with 22.7% for EVAR and 8.1% for OSR ($p = 0.139$).

We analyzed a total of 147 patients, comprising 119 patients in the survived group and 28 patients in the non-survived group. The mean age of the survived group was 70.33±12.2 years old, while the average age was 74.82±8.8 years old for the non-survived group ($p = 0.069$). The most common comorbidity in both groups was hypertension. However, there was a significant difference in the percentage of unfit patients, with 47.9% of the patients in the survived group being classed as unfit compared to 82.1% in the non-survived group ($p = 0.002$) (Table 1). The definition of the unfit patient status was based on the UK EVAR 1 and 2 trials[7], which considered cardiac, respiratory, and renal conditions.

In terms of preoperative blood chemistry, we found a significant difference in the level of serum creatinine (mg/dL) between the survived group (1.40±5.89) and the non-survived group (1.80±1.74), ($p = 0.011$). Additionally, there were no significant differences in the level of hemoglobin (g/dL) and coagulogram levels between both groups (Table 1).

For intraoperative details (Table 2), there was no statistically significant difference between the survived and non-survived groups in EVAR treatment ($p = 0.086$). However, the usage of intraoperative aortic balloon occlusion was significantly higher in the non-survived group (18 patients, 64.3%) compared to the survived group (27 patients, 22.7%) ($p < 0.001$). Additionally, the percentage of cardiac arrest was significantly higher in the non-survived group (8 patients, 28.6%) compared to the survived group (4 patients, 3.4%) ($p < 0.001$).

Regarding early postoperative complications (Table 3), we observed a statistically significant increase in postoperative congestive heart failure and myocardial infarction in the non-survived group compared to the survived group (10.7% vs. 0.8%, $p = 0.022$ and 53.6% vs. 10.1%, $p < 0.001$, respectively). Similarly, the incidence of abdominal compartment syndrome was significantly higher in the non-survived group than in the survived group (53.6% vs. 12.6%, $p < 0.001$).

Table 4 presents the crude and adjusted odds ratios (95% CI) for the factors associated with 30-day mortality. Logistic regression analysis was performed to determine the statistical significance of these factors. Age > 80 years old (aOR, 9.785; 95% CI, 2.128–45.008; $p = 0.003$), unfit patient status (aOR, 3.35; 95% CI, 1.136–9.893; $p = 0.028$), aortic balloon usage (aOR, 5.54; 95% CI, 1.116–27.54; $p = 0.036$), postoperative myocardial infarction (aOR, 13.995; 95% CI, 3.171–61.767; $p < 0.001$), postoperative congestive heart failure (aOR, 15.22; 95% CI, 1.163–199.2; $p = 0.038$), and abdominal compartment syndrome (aOR, 23.397; 95% CI, 5.551–98.614; $p < 0.001$) were independent predictors of 30-day mortality.

When comparing EVAR and OSR (Table 5), differences in procedural characteristics were observed. The length of the procedure was significantly shorter in the EVAR group (155 minutes) compared to the OSR group (245 minutes) ($p < 0.001$). Intraoperative blood loss was also significantly lower in the EVAR group (300 ml) compared to the OSR group (3500 ml) ($p < 0.001$). Similarly, the EVAR group required significantly less intraoperative blood replacement (1 unit) compared to the OSR group (7 units) ($p < 0.001$).

DISCUSSION

In this study, we aimed to analyze the perioperative mortality rates and factors influencing mortality in patients undergoing OSR and EVAR for rAAA. Our findings indicate that perioperative mortality is higher in OSR, but there was no statistically significant difference between OSR and EVAR. Several factors were identified as independent predictors of 30-day mortality in rAAA, including an unfit patient status, age over 80 years old, intraoperative aortic balloon usage, postoperative myocardial infarction, postoperative congestive heart failure, and abdominal compartment syndrome. Below, we discuss these findings in detail and explore their implications.

The absence of a significant difference in perioperative

TABLE 1. Baseline characteristics of the patients with ruptured AAA.

Baseline characteristics	Survived (n=119)	Non-survived (n=28)	*p*-value
Age, mean (SD) years	70.33 (12.2)	74.82 (8.8)	0.069
Male gender, no (%)	103 (86.6%)	24 (85.7%)	1.000
Coronary arterial disease, no (%)	20 (16.8%)	5 (17.9%)	1.000
COPD, no (%)	12 (10.1%)	3 (10.7%)	1.000
Hypertension, no (%)	93 (78.2%)	20 (71.4%)	0.610
Dyslipidemia, no (%)	35 (29.4%)	7 (25%)	0.816
Type 2 Diabetes, no (%)	26 (21.8%)	5 (17.9%)	0.835
Cerebrovascular disease, no (%)	10 (8.4%)	1 (3.6%)	0.635
Current smoking, no (%)	17 (14.3%)	6 (21.4%)	0.387
Unfit patient status, no (%)	57 (47.9%)	23 (82.1%)	***0.002***
Cardiac arrhythmia, no (%)	8 (6.7%)	1 (3.6%)	1.000
Antiplatelet drug, no (%)	28 (23.5%)	7 (25%)	1.000
Hemoglobin level, mean (SD) g/dl	9.59 (2.05)	9.80 (2.69)	0.657
Creatinine level, mean (SD) mg/dl	1.4 (5.89)	1.8 (1.74)	***0.011***
PT, mean (SD) sec	14.5 (3.11)	14.5 (2.51)	0.964
APTT, mean (SD) sec	28.7 (16.7)	29 (9.64)	0.501

Abbreviation: no, number; SD, standard deviation; COPD, chronic obstructive pulmonary disease; PT, prothrombin time; PTT, partial thromboplastin time.
A *p*-value<0.05 indicates statistical significance.

TABLE 2. Intraoperative variables of the patients with ruptured AAA.

Intraoperative variables	Survived (n=119)	Non-survived (n=28)	*p*-value
EVAR treatment, no (%)	85 (71.4%)	25 (89.3%)	0.086
Aortic balloon occlusion, no (%)	27 (22.7%)	18 (64.3%)	***<0.001***
Cardiac arrest, no (%)	4 (3.4%)	8 (28.6%)	***<0.001***
Intraoperative blood loss, median (Min–Max) ml	425 (20–14900)	500 (50–21000)	0.195
Intraoperative blood replacement, median (Min–Max) unit	2 (0–19)	2.5 (0–17)	0.270
Length of procedure, median (Min–Max) mins	170 (50–530)	207.5 (90–590)	0.061

A *p*-value<0.05 indicates statistical significance.

TABLE 3. Postoperative complications of the patients with ruptured AAA.

Baseline characteristics	Survived (n=119)	Non-survives (n=28)	*p*-value
Congestive heart failure	1 (0.8%)	3 (10.7%)	***0.022***
Postoperative myocardial infarction	12 (10.1%)	15 (53.6%)	***<0.001***
Abdominal compartment syndrome	15 (12.6%)	15 (53.6%)	***<0.001***
Chest infection	29 (24.4%)	8 (28.6%)	0.827
Ischemic colitis	8 (6.7%)	3 (10.7%)	0.734
Wound infection	6 (5.0%)	1 (3.6%)	1.000

A *p*-value<0.05 indicates statistical significance.

TABLE 4. Results from logistic regression analysis of the factors associated mortality in the patients with ruptured AAA.

Factors	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age > 80 years old	3.284 (1.257–8.579)	***0.015***	9.785 (2.128–45.008)	***0.003***
Unfit patient status	2.739 (0.830–9.032)	0.098	3.352 (1.136–9.893)	***0.028***
Creatinine level >1.3 mg/dl	0.974 (0.876–1.083)	0.626		
EVAR treatment	3.313 (0.679–16.16)	0.139	3.241 (0.667–15.75)	0.145
Aortic balloon usage	2.379 (0.730–7.752)	0.150	5.543 (1.116–27.54)	***0.036***
Cardiac arrest	11.5 (3.163–41.81)	***< 0.001***	9.87 (0.96–78.7)	0.087
Postoperative Myocardial infarction	10.29 (3.968–26.67)	***< 0.001***	13.995 (3.171–61.767)	***< 0.001***
Abdominal compartment syndrome	8 (3.191–20.05)	***< 0.001***	23.397 (5.551–98.614)	***< 0.001***
Postoperative congestive heart failure	15.9 (1.2–211.6)	***0.036***	15.22 (1.163–199.2)	***0.038***

A *p*-value<0.05 indicates statistical significance.

mortality rates between OSR and EVAR in our study aligns with previous research in this field. For instance, the AJAX trial[10] conducted in the Netherlands reported a 30-day mortality rate of 21% for EVAR compared to 25% for OSR (p = 0.66), with an overall perioperative mortality of 23.2%. Similarly, the ECAR trial[11] conducted in France reported a 30-day mortality rate of 18% for EVAR compared to 24% for OSR (p = 0.239), with an overall perioperative mortality of 20.5%. On the other hand, the IMPROVE trial[12] conducted in the UK reported a 30-day mortality rate of 35.4% for EVAR compared to 37.4% for OSR (p = 0.62), with an overall perioperative mortality of 36.3%. These trials collectively suggest that both OSR and EVAR are viable treatment options for rAAA patients, as they yield similar outcomes in terms of perioperative mortality.

TABLE 5. Comparison results of endovascular and open repair in the patients with ruptured AAA.

Variables	EVAR (n=110)	Open surgical repair (n=37)	*p*-value
Unfit status	71 (64.5%)	9 (24.3%)	***<0.001***
Length of procedure, median (Min–Max) minutes	155 (50–590)	245 (95–530)	***<0.001***
Intraoperative blood loss, median (Min–Max) ml	300 (20–2100)	3500 (500–8500)	***<0.001***
Intraoperative blood replacement, median (Min–Max) units	1 (0–19)	7 (3–24)	***<0.001***
Aortic balloon occlusion usage	30 (27.3%)	15 (40.5%)	0.191
Perioperative complications	54 (49.1%)	22 (59.5%)	0.367
Abdominal compartment syndrome	22 (20%)	8 (21.6%)	0.978
Perioperative re-interventions	22 (20%)	4 (10.8%)	0.309
Length of ICU stay, median (Min–Max) days	2 (0–90)	5 (0–80)	0.637
Length of Hospital stay, median (Min–Max) days	13.5 (1–180)	15 (1–120)	0.527

A *p*-value<0.05 indicates statistical significance.

Our study identified several factors that independently predicted 30-day mortality in patients with rAAA who did not survive the perioperative period. Notably, we found that an unfit patient status was associated with a high mortality rate after both open surgical repair (OSR) and endovascular aneurysm repair (EVAR). This highlights the importance of carefully assessing patient fitness and comorbidities when considering treatment options for rAAA. Our findings align with a previous EVAR trial[13] focused on the elective treatment of AAA in unfit patients, emphasizing the significance of patient fitness in determining outcomes.

An advanced age, explicitly being over 80 years old, was also identified as a significant predictor of increased mortality risk in rAAA patients. This finding is consistent with Antonopoulos CN et al.[14], who reported that age over 80 years old was associated with in-hospital mortality after OSR and EVAR in rAAA. This result suggests that the patient age should be considered when evaluating the risks and benefits of different treatment options in this population.

The use of aortic balloon occlusion during the procedure was identified as a parameter that predicted 30-day mortality, indicating the potential impact of intraoperative interventions on patient survival. Similar to our findings, several articles[15-20] have discussed the use of intraoperative aortic balloon in rAAA, which is associated with high perioperative mortality rates. For instance, Mehta M et al.[18] demonstrated that the use of aortic balloon occlusion in hemodynamically unstable rAAA patients was associated with a 33% increased risk of death.

Holst J et al. [20] also found that aortic balloon occlusion in hemodynamically unstable patients treated with EVAR resulted in a 27% increased risk of death. Furthermore, if a patient requires aortic balloon occlusion during the operation, postoperative care and monitoring will be more focused on the patient's general condition and potential complications related to balloon occlusion, such as aortic dissection or distal embolization to visceral organs. These considerations are crucial for intensive care unit management and ensuring optimal patient outcomes.

Postoperative complications, such as myocardial infarction, congestive heart failure, and abdominal compartment syndrome, were also found to be associated with a significantly higher risk of 30-day mortality. Myocardial infarction and other cardiac complications frequently contribute to mortality in patients with rAAA.[21] Abdominal compartment syndrome, often a

result of intraoperative hypotension and the use of aortic balloon occlusion, is also associated with a high 30-day mortality rate. Previous studies[19,22,23] have indicated that the occurrence of this complication is correlated with a preoperative blood pressure below 70 mmHg, the application of aortic balloon occlusion, and intraoperative blood replacement exceeding 5 units.[23] These findings emphasize the importance of vigilant postoperative monitoring and the prompt management of complications to improve patient outcomes.

While our study provides valuable insights, it has certain limitations to note too. First, it was conducted in a single-center setting, which may limit the generalizability of our findings. Multi-center studies with larger sample sizes are needed to validate and apply our results to a broader population. Second, the retrospective nature of our study introduces the possibility of selection bias and confounding variables. Although statistical adjustments were made, residual confounding factors cannot be ruled out. A prospective study design or a randomized controlled trial would provide stronger evidence and minimize the impact of confounding factors.

Additionally, our study focused solely on perioperative mortality rates and did not consider long-term outcomes, such as overall survival or quality of life. Evaluating these long-term outcomes would provide a more comprehensive understanding of the effectiveness of OSR and EVAR in managing rAAA. Lastly, the study period spanned several years, during which advancements in surgical techniques, perioperative care, and imaging modalities may have occurred. These temporal changes could influence the outcomes and potentially limit the generalizability of our findings to current clinical practice.

CONCLUSION

In conclusion, our study enhances the understanding of perioperative mortality and the factors influencing outcomes in rAAA patients undergoing OSR and EVAR. The absence of a significant difference in perioperative mortality rates between the two treatment modalities suggests their viability as treatment options. However, individual patient characteristics and predictive factors, such as an unfit patient status, age over 80 years old, intraoperative aortic balloon interventions, postoperative myocardial infarction, postoperative congestive heart failure, and abdominal compartment syndrome, must be considered when making treatment decisions. Future research should further investigate the impact of these factors and develop strategies for improving the outcomes in this high-risk patient population.

ACKNOWLEDGEMENTS

The authors thank Surut Chalermjitt, Sommapun Jueakaew, Aphanan Phiromyaphorn, and Wannaporn Paemueang for their assistance with data collection. We also thank Dr. Supaporn Kulsitthiboon, for his technical editing.

Conflicts of Interest Declaration

All authors declare that they have no personal or professional conflicts of interest, and received no financial support from the companies that produce and distribute the drugs, devices, or materials described in this report.

Funding Disclosure

This study did not receive any financial support.

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Vitamin D Deficiency as a Factor Associated with Neuropathic Pain in Multibacillary Type Morbus Hansen

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ABSTRACT

Objective: Morbus Hansen (MH), caused by Mycobacterium leprae, is marked by neuropathic pain. Prior studies link low vitamin D levels to diabetic neuropathic pain, yet research on its role in MH-related neuropathic pain is limited. This study investigates the role of vitamin D deficiency in MH-related neuropathic pain.

Materials and Methods: An analytical cross-sectional study was conducted among multibacillary (MB) MH patients at Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali from April to August 2023. Neuropathic pain was assessed using the Douleur Neuropathique 4 (DN4) questionnaire, while serum 25(OH)D levels determined vitamin D status. The cutoff for deficiency was determined via ROC curve analysis.

Results: Among 42 participants, those without neuropathic pain exhibited higher mean serum vitamin D levels than those with neuropathic pain (28.69 ± 8.16 vs. 22.11 ± 9.54 ng/ml; p=0.021). The ROC curve identified a cutoff value of 30.25 ng/ml, categorizing participants into vitamin D deficiency (<30.25 ng/ml) and non-deficiency (≥30.25 ng/ml) groups. Bivariate analysis revealed a heightened incidence of neuropathic pain among MH patients with serum vitamin D levels below the designated cutoff point (OR: 6.60; 95%CI: 1.484-29.355; p=0.022). Multivariate analysis indicated that two variables significantly correlated with neuropathic pain in MH patients: vitamin D deficiency (OR: 14.337; 95%CI: 2.431-84.542; p=0.003) and peripheral nerve enlargement (OR: 12.564; 95%CI: 2.096-75.307; p=0.006).

Conclusion: Disparities in average vitamin D levels were observed between MH patients with and without neuropathic pain. Vitamin D deficiency, alongside peripheral nerve enlargement, emerged as significant risk factors for neuropathic pain in MH patients.

Keywords: Morbus hansen; multibacillary; neuropathic pain; serum vitamin D; vitamin D deficiency (Siriraj Med J 2024; 76: 488-496)

INTRODUCTION

Morbus Hansen (MH) is a chronic infectious disease caused by *Mycobacterium leprae*, with one of its complications being neuropathic pain. A complete neurological examination is crucial for the early detection of neuropathic pain, including nerve conduction tests capable of detecting nerve damage before symptoms manifest. However, apart from the associated costs, such

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Received 9 April 2024 Revised 1 May 2024 Accepted 20 May 2024
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https://doi.org/10.33192/smj.v76i8.268656

examinations are not universally available, necessitating the exploration of more cost-effective diagnostic alternatives. Vitamin D has been extensively studied in relation to neuropathic pain, particularly in the context of diabetic neuropathic pain. Clinical trial studies by Martin et al. have demonstrated that vitamin D supplementation, in conjunction with exercise, can alleviate symptoms and complications of diabetic neuropathy.[1] Additionally, a meta-analysis by Qu et al. found lower vitamin D levels in individuals with diabetic neuropathic pain compared to healthy subjects, suggesting that vitamin D deficiency increases the risk of diabetic neuropathic pain and that vitamin D supplementation is effective in mitigating its progression.[1,2]

The role of vitamin D in individuals with MH has been explored predominantly as an immunomodulator. Vitamin D levels influence bacterial indices in multibacillary (MB) MH patients. Toruan et al. revealed an intracrine vitamin D disorder in MB MH patients, leading to compromised macrophage phagocytosis of mycobacteria.[3] In their study, the mean serum vitamin D level was 19.15 ± 3.25 in the paucibacillary (PB) type and 14.85 ± 4.26 in the MB type. Moreover, Rusyati et al. observed that lower plasma vitamin D receptor levels correlated with higher bacterial index numbers in MH patients.[4] Vitamin D plays a pivotal role in improving axonogenesis and sensory responses in peripheral nerves. It upregulates the expression of vitamin D receptors, particularly in small-diameter neurons, while downregulating the expression of L-type calcium channels. Furthermore, vitamin D activates the expression of calcium-binding proteins and increases calcium-buffering molecules in cells, thus shielding them from damage and apoptosis.[5,6]

Vitamin D exerts a modulatory effect on inflammation associated with chronic pain by inhibiting nitric oxide synthesis, which contributes to oxidative stress.[7,8] In vitro studies demonstrate that vitamin D controls the expression of the Nerve Growth Factor (NGF) gene in Schwann cells. Calcitriol and vitamin D analogs increase the binding of activator protein-1 (AP-1) to the NGF promoter, stimulating NGF production. NGF, typically produced by basal keratinocytes in normal skin, binds strongly to the Trk A receptor on nociceptor nerve fibers, enhancing their sensitivity, particularly during inflammation.[9] Vitamin D augments NGF production and prevents a decrease in NGF levels, providing the necessary neuroprotective effect for nerve growth, especially in the peripheral nervous system (sympathetic and sensory nerves). Elevated NGF levels also inhibit the release of substance P and calcitonin gene-related peptide (CGRP), mitigating pain.[5,6,10–18] Patients with low vitamin D levels experience impaired nociceptor function and increased nerve damage, resulting in a lower pain threshold. Correcting vitamin D levels can raise the pain threshold once again.[2,11,19–21]

The mechanisms and manifestations of neuropathic pain in MH closely resemble those observed in individuals with diabetes mellitus. Although prior studies have extensively explored the association between low serum vitamin D levels and diabetic neuropathic pain, research directly evaluating the relationship between vitamin D levels and MH neuropathic pain remains scarce. Thus, investigating this correlation presents an intriguing avenue for further exploration.

MATERIALS AND METHODS

Study design

An analytical observational study with a cross-sectional design was conducted at the neurologist clinic and the skin and genital clinic at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Bali from April to August 2023. This research received approval and ethical clearance from the Research Ethics Commission, Faculty of Medicine, Universitas Udayana (No: 1130/UN14.2.2.VII.14/LT/2023).

Participant selection

Prior to participation, written informed consent was obtained from all enrolled individuals. Inclusion criteria encompassed individuals diagnosed with multibacillary (MB) type Morbus Hansen (MH) who were aged 18 years or older. Exclusion criteria comprised patients with chronic kidney disease, chronic liver disease, diabetes mellitus, HIV/AIDS infection, entrapment neuropathy, history of stroke, multiple sclerosis, undergoing chemotherapy, diagnosed with malignancy, alcoholism, or taking regular medication within the preceding 30 days, including vitamin D supplements, phenytoin, phenobarbital, carbamazepine, and cholestyramine.

Neuropathic pain assessment

Neuropathic pain assessment was conducted using the Douleur Neuropathique 4 (DN4) questionnaire, comprising 7 pain description questions and 3 clinical examinations with sensitivity and specificity rates ranging from 82% to 95% and 78% to 97%, respectively. The questionnaire was administered by trained neurologists following rigorous training and standardization procedures to ensure consistency and accuracy in data collection.

Vitamin D assessment

Venous blood samples were collected from all participants by highly trained phlebotomists, utilizing

aseptic techniques and adhering strictly to established protocols to minimize the risk of contamination and ensure the integrity of the samples. The samples were processed and analyzed for the quantification of serum 25-hydroxyvitamin D [25(OH)D] levels in ng/ml using the highly sensitive and precise enzyme-linked immunosorbent assay (ELISA) method validated and standardized in the Clinical Pathology laboratory at Prof. Dr. I.G.N.G. Ngoerah General Hospital.

Statistical analysis

Statistical analysis was performed using the SPSS 25 for Windows program, with serum 25(OH)D levels considered the independent variable and MH neuropathic pain as the dependent variable. Numerical variables and data were presented as mean or median based on the results of the normality test using the Shapiro-Wilk test. Bivariate analysis utilized the independent parametric t-test for comparison. The threshold for vitamin D deficiency was determined through the receiver operating characteristic (ROC) curve. Variables with a significance value of less than 0.25 from multivariate selection were subjected to multivariate logistic regression analysis to explore associations of confounding variables with neuropathic pain. A p-value ≤0.05 was deemed statistically significant.

RESULTS

In the study, 42 participants meeting the criteria were categorized into two groups: those experiencing neuropathic pain and those without (Table 1). The ROC curve (Fig 1) demonstrates the diagnostic capability of serum vitamin D levels, as the curve surpasses the 50% line. The area under the curve (AUC) value obtained was 71.4% (95%CI: 0.558-0.871; p=0.017), indicating moderate diagnostic efficacy. The ROC coordinates revealed a cut-off value for vitamin D of 30.25 ng/ml using the Youden index, with a sensitivity of 52.4% and a specificity of 85.7%.

The disparity in mean serum vitamin D levels between MH patients with and without neuropathic pain was evaluated using the unpaired T test. Patients without MH neuropathic pain exhibited a higher mean serum vitamin D level of 28.69 ± 8.16 ng/ml (p=0.021). Bivariate analysis examined the relationship between serum vitamin D levels (independent variable) and neuropathic pain in MH patients (dependent variable) using a cut-off point of 30.25 ng/ml. The hypothesis was tested using an unpaired categorical comparative test employing the Chi-square method (Table 2). Additionally, bivariate analysis explored other factors influencing neuropathic pain in MH patients, including gender, body mass index, leprosy reaction, compliance with multidrug therapy (MDT), medication status, peripheral nerve enlargement, and Pittsburgh Sleep Quality Index (PSQI) (Table 3).

Variables such as onset of diagnosis, peripheral nerve enlargement, leprosy reaction, and MDT treatment status exhibited significance in multivariate selection with a p-value <0.25 (Table 4), prompting further analysis in multivariate regression. The final stage of multivariate analysis identified two variables significantly associated with neuropathic pain in MH patients: vitamin D deficiency (OR: 11.398; 95%CI: 2.140-60.698; p=0.004), and peripheral nerve enlargement (OR: 5.68; 95%CI: 1.104-29.213; p=0.038) (Table 5). Although due to the nature of the study, several confounding factors such as duration and severity of MH, comorbidities, and sun exposure could deviate the results.

DISCUSSION

Our study, consistent with prior research, found a predominance of male participants (71.4%), aligning with systematic reviews indicating a higher susceptibility of men to Morbus Hansen (MH) infection. This gender disparity may be attributed to differences in health-seeking behaviors between genders, potentially leading to increased male exposure to MH disease.[22] Using the DN4 screening tool, our research identified tingling (50%) and electric shock sensations (40.5%) as the most frequently reported symptoms.[23] According to Toh et al., patients in Nepal predominantly reported tingling sensations (90%), followed by burning sensations and numbness at 80%.[24] Discrepancies in study results may arise from subjective complaints, limited participants, and variations in screening tools. In MH patients, vitamin D levels have been linked to bacterial indices, with Toruan et al.[3] reporting a mean of 14.85 ± 4.26 ng/ml. In our study, we observed higher levels, averaging 25.4 ± 9.383 ng/ml, possibly due to Indonesia's tropical climate and increased sunlight exposure. Among MH patients with neuropathic pain, mean serum vitamin D levels were lower (22.11 ± 9.54 ng/ml), with a mean difference of 6.586 ± 2.74. Prior studies have explored the association between vitamin D and neuropathic pain, particularly in diabetic neuropathy, where lower vitamin D levels were correlated with neuropathic pain. Vitamin D deficiency can impact nerve growth factor (NGF), myelin production, and inflammatory factors, contributing to axonal and myelin damage and hyperexcitability, ultimately leading to MH neuropathic pain.[9,11,25–27]

Bivariate analysis in our study revealed a significant association between low vitamin D levels and MH neuropathic pain, with a 6.6 times greater risk observed

TABLE 1. Basic characteristics of research participants.

Variables	Neuropathic Pain (n=21)	Without Neuropathic Pain (n=21)
Age (years) (median (min-max)	43 (23-63)	37 (20-81)
Educational Background		
Elementary School	5 (23.8%)	1 (4.8%)
Junior High School	1 (4.8%)	4 (19%)
Senior High School	6 (28.6%)	11 (52.4%)
University	9 (42.9%)	5 (23.8%)
Marital Status		
Single	4 (19%)	7 (33.3%)
Married	17 (81%)	14 (66.7%)
Employment		
Farmer/Labor	3 (14.3%)	3 (14.3%)
Self-employed	5 (23.8%)	3 (14.3%)
Private Employee	7 (33.3%)	9 (42.9%)
Government Employee	2 (9.5%)	0 (0%)
Others	4 (19%)	6 (28.6%)
Numeric Pain Rating Scale (median (min-max)	2 (0-6)	1 (0-5)
Nerve Enlargement		
N. Auricularis	3 (14.3%)	13 (61.5%)
N. Ulnaris	12 (57.1%)	4 (19%)
N. Peroneus	2 (9.5%)	10 (47.6%)
N. Tibialis	9 (42.9%)	8 (38.1%)
DASS- 21		
Depression		
Normal (0-9)	19 (90.5%)	19 (90.5%)
Mild (10-13)	2 (9.5%)	2 (9.5%)
Anxiety		
Normal (0-7)	21 (100%)	20 (95.2%)
Mild (8-9)	0 (0%)	1 (4.8%)
Stress		
Normal (0-14)	21 (100%)	21 (100%)

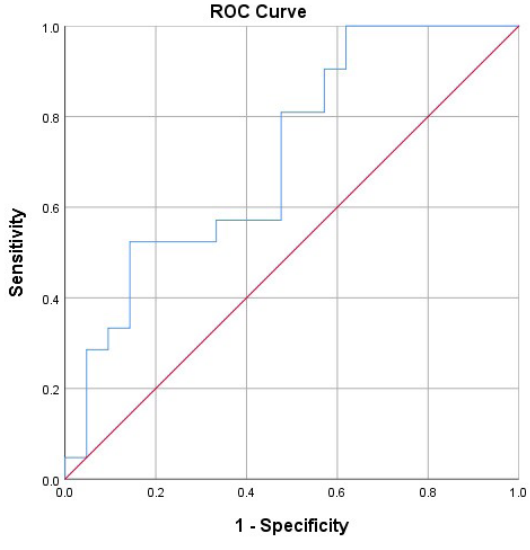

Fig 1. Results of the ROC Procedure - Serum Vitamin D Level Values for MH neuropathic pain

TABLE 2. Bivariate analysis of serum vitamin D levels with neuropathic pain in MH patients.

Variables	Neuropathic Pain	Without Neuropathic Pain	OR (95%CI)	p-value
Serum Vitamin D ng/ml (mean ± SD)	22.11 ± 9.54	28.69 ± 8.16		0.021*
Vitamin D Deficiency (<30.25)	18 (85.7%)	10 (47.6%)	6.6	
Vitamin D No deficiency (≥30.25)	3 (14.3%)	11 (52.4%)	(1.484 - 29.355)	0.022*

TABLE 3. Bivariate analysis of covariate variables with neuropathic pain in MH Patients.

Variables	Neuropathic Pain n (%)	Without Neuropathic Pain n (%)	OR (95%CI)	p-value
Gender				
Male	14 (66.7)	16 (76.2)	0.625	0.733
Female	7 (33.3)	5 (23.8)	(0.161-2.419)	
Body Mass Index				
Overweight-Obesitas	7 (33.3)	4 (19)	2.125	0.483
Underweight-Normoweight	14 (66.7)	17 (81)	(0.515-8.77)	
Leprosy Reaction				
Yes	13 (61.9)	8 (38.1)	2.641	0.217
No	8 (38.1)	13 (61.9)	(0.76-9.176)	
Onset of Diagnosis				
≥ 1 year	10 (47.6)	5 (23.8)	2.909	0.198
< 1 year	11 (52.4)	16 (76.2)	(0.777-10.887)	
MDT Compliance				
Poor	2 (9.5)	2 (9.5)	1	1.00
Good	19 (90.5)	19 (90.5)	(0.127-7.850)	
Treatment Status				
On Treatment	16 (76.2)	19 (90.5)	0.377	0.410
Release from Treatment	5 (23.8)	2 (9.5)	(0.057-1.977)	
Peripheral Nerve Enlargement				
Yes	17 (81)	13 (61.9)	2.615	0.306
No	4 (19)	8 (38.1)	(0.644-10.614)	
Vitamin B Supplementation				
No	16 (76.2)	15 (71.4)	1.28	1.000
Yes	5 (23.8)	6 (28.6)	(0.322-5.088)	
PSQI				
Poor Sleep (>5)	8 (38.1)	5 (23.8)	1.969	0.504
Good Sleep (≤5)	13 (61.9)	16 (76.2)	(0.518-7.488)	

TABLE 4. Multivariate logistic regression selection analysis.

Variables	Adjusted OR	95%CI	p-value
Onset of Diagnosis	2.909	0.777-10.887	0.113*
Peripheral Nerve Enlargement	2.615	0.644-10.614	0.179*
Leprosy Reaction	2.641	0.76-9.176	0.127*
MDT Treatment Status	0.337	0.057-1.977	0.228*
MDT Compliance	1.00	0.127-7.850	1.00
Vitamin D Deficiency	6.6	1.484-29.355	0.013*

NB:
*: statistically significant
Abbreviations: OR: Odds Ratio; CI: Confidence Interval

TABLE 5. Multivariate logistic regression analysis.

Variables	Adjusted OR	95%CI	p-value
Onset of Diagnosis	1.641	0.206-13.061	0.640
Peripheral Nerve Enlargement	5.680	1.104-29.213	0.038*
Leprosy Reaction	4.341	0.775-24.329	0.095
MDT Treatment Status	0.220	0.010-4.704	0.333
Vitamin D Deficiency	11.398	2.140-60.698	0.004*

NB:
*: statistically significant

among MH patients with vitamin D deficiency compared to those without (OR 6.6; CI 95% [1.484-29.355]). This finding aligns with Alam et al.'s study, which reported a 9.8 times increased risk of neuropathic pain in individuals with diabetes mellitus and vitamin D deficiency.[25] Vitamin D plays a crucial role in peripheral nerves by enhancing axonogenesis, sensory responses, and the expression of vitamin D receptors, particularly in small diameter neurons. Additionally, it activates calcium-binding proteins, enhances cellular calcium buffering, modulates inflammation, inhibits nitric oxide synthesis, and reduces oxidative stress.[5,6] Moreover, vitamin D contributes to neuroprotection by promoting nerve growth factor (NGF) production and preventing declines in NGF levels, crucial for peripheral nerve growth and pain modulation.[28] Elevated NGF levels can also inhibit the release of substance P and calcitonin gene-related peptide (CGRP), further influencing pain sensation.[7,8] In a study by Tiago et al., leprosy reaction emerged as a significant risk factor for neuropathic pain occurrence.[22] Lockwood et al. demonstrated that during leprosy reactions, M. leprae antigens trigger chronic neuritis and ectopic nerve activity, leading to chronic neuropathic pain in MH patients.[29] In our study, 61.9% of patients experiencing leprosy reactions reported neuropathic pain; however, bivariate analysis did not yield significance (p = 0.217). This suggests that neuropathic pain may not solely stem from the host's immune response but also from direct Schwann cell damage by M. leprae. The prevalence of neuropathic pain is notably higher in patients with longer MH diagnoses due to persistent nerve inflammation and M. leprae antigen presence.[22] Interestingly, in our

study, neuropathic pain incidence was similar among patients diagnosed with MH for less or more than one year, with no significant relationship observed (p = 0.198). However, Faridi et al. reported a correlation between MH disease duration and neuropathic pain incidence.[30] These discrepancies highlight the complex etiology of neuropathic pain in MH, warranting further investigation. MDT therapy does not guarantee prevention of neuropathic pain in MH patients. Even after completing treatment, patients may still experience neuropathic pain, as observed in studies by Pitta et al.[31] and Riecher et al.[32] Approximately 23.8% of patients experiencing neuropathic pain had completed MDT, consistent with findings from Mumbai.[32] However, Faridi et al. reported a 1.75 times increased risk of MH neuropathic pain at the initiation of antimicrobial therapy compared to after therapy. The majority of neuropathic pain patients in their study were still undergoing MDT, suggesting potential contributions from dead bacterial cells in nerve inflammation.[30,33] However, bivariate analysis in our study did not yield a significant result (p=0.41).

In a study by Giesel et al., nerve enlargement was prevalent in MH cases associated with neuropathic pain, with a higher incidence of sensory disturbances.[23] In our study, 81% of neuropathic pain patients exhibited peripheral nerve enlargement, indicating ongoing nerve inflammation contributing to neuropathic pain. Neuropathic pain can lead to psychological issues such as anxiety, depression, and sleep disorders, impacting patients' quality of life. While approximately 50% of MH patients with neuropathic pain reported insomnia in Giesel et al.'s study[23], only about 61.9% of our study's neuropathic pain patients reported sleep disorders. Bivariate analysis did not yield significance (p = 0.504), possibly due to variations in diagnostic tools. In assessments using the Hamilton Depression scale, depression rates were observed to be approximately 70%, 72.1%, and 77.8% in MH patients with neuropathic pain, diabetic neuropathic pain, and post-herpetic neuralgia patients, respectively. However, in our study utilizing the Depression Anxiety Stress Scales 21 (DASS-21), only four patients exhibited mild depression, with one patient experiencing mild anxiety and no reported stress. It is plausible that our study's assessment spanned varying periods of MH occurrence, which might have hindered a comprehensive depiction of depression within a singular period.[23] Multivariate analysis employing logistic regression revealed that independent risk factors for neuropathic pain in MH included vitamin D deficiency and peripheral nerve enlargement. Conversely, the presence of leprosy reactions, duration of MH affliction, and MDT treatment status did not exhibit statistically significant relationships with neuropathic pain in MB type MH. In this study, vitamin D deficiency (OR 11.398; CI 95% [2.140-60.698]; p=0.004) was identified as a more significant risk factor for neuropathic pain in MH compared to peripheral nerve enlargement (OR 5.68; CI 95% [1.104-29.213]; p=0.038). Within MH, there is an escalation in free radicals and other inflammatory responses, which contribute to macrophage activity, axonal damage, demyelination, and subsequent nerve ischemia. These processes, including peripheral nerve enlargement, can lead to neuropathic pain. However, our findings suggest that vitamin D deficiency poses a greater risk for neuropathic pain manifestation in MH patients compared to peripheral nerve enlargement.

This study is pioneering in exploring the relationship between vitamin D deficiency and MH neuropathic pain in Indonesia, offering valuable insights into risk factors for MB type MH. Employing multivariate analysis, the study expands understanding beyond vitamin D deficiency alone. Additionally, the widespread availability of vitamin D tests enhances the study's practical relevance in medical practice. Establishing a cut-off value for vitamin D deficiency at 30.25 ng/ml provides a basis for future research on neuropathic pain prevention.

However, inherent limitations exist. The study's sample size was constrained by the scarcity of diagnosed MB type MH cases, affecting statistical power and generalizability. Due to the challenge of long-term patient follow-up, a cross-sectional design was employed, preventing the establishment of causal relationships. Nerve conduction studies, considered a gold standard, were not incorporated due to resource constraints, potentially limiting the depth of pain assessment. While some risk factors were matched, resource constraints in a tertiary hospital limited adjustment for all confounding factors. Factors like sunscreen usage and clothing materials may introduce bias in vitamin D level assessments.

CONCLUSION

Neuropathic pain prevalence in this study is 50%, with MB type MH patients having serum vitamin D deficiency below 30.25 ng/ml facing a significant risk. Specifically, individuals with deficient vitamin D levels are 11.398 times more likely to experience neuropathic pain. However, given the limited sample size and cross-sectional study design, caution is warranted in interpreting the results. Early diagnosis of neuropathic pain is crucial, as it often goes undetected, leading to inadequate treatment. Ongoing research aims to identify predictive factors for neuropathic pain, offering potential interventions to alleviate symptoms in MH patients.

ACKNOWLEDGEMENT

None declared

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions

Conceptualization, Formal Analysis, Project administration, Writing – original draft, C.T.; Data curation, Writing – review & editing, B.G.; Investigation Visualization, K.T.; Methodology, A.M., Resources, K.W.; Software, A.S.; Supervision, Validation, I.W.

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Developing Cerebral Palsy Screening of Functional Abilities in School (CPS –FAS)

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ABSTRACT

Objective: This study aimed to determine the psychometric property of a newly developed functional abilities screening tool for children with cerebral palsy (CP) in special education units.

Materials and Methods: This study was designed as a cross-sectional study. The tool for cerebral palsy screening of functional abilities in school (CPS-FAS) was established by surveying 28 pediatric physical therapists and holding focus group discussions with them. The CPS-FAS tool was used to evaluate content validity, reliability, and discriminative ability with 30 school-age children with CP at levels 1-3 of the Gross Motor Function Classification System (GMFCS).

Results: The CPS-FAS generation process established 21 activity-problem screening items for children with CP, which had good content validity (index of item-objective congruence (IOC) = 1), good internal consistency ($\alpha = 0.92$), and showed significant differences between GMFCS levels 1 and 3 ($p > 0.001$) and GMFCS levels 2 and 3 ($p > 0.001$).

Conclusion: The CPS-FAS tool can be applied to school-age children with CP in a special education unit to screen such children for activity problems that affect school living without environmental obstruction and language barriers, and it only takes a short time (10-15 minutes) to complete.

Keywords: Cerebral palsy; functional ability; special education school (Siriraj Med J 2024; 76: 497-503)

INTRODUCTION

Cerebral palsy (CP) is a neurological condition causing abnormal developmental pathologies affecting 1.6-3.4 children out of every 1000.[1] The most common problem is motor disability, which is demonstrated through abnormal muscle tone, muscle weakness, joint deformity, mental retardation, and impaired cognition.[2,3] It is a persistent disorder associated with posture and movement control of the body which means children with CP have difficulty in physical activity and is the cause of social exclusion.[4,5] Their health and disabilities mean children with CP have more barriers to participating, studying, and socializing. Therefore, children with CP have a significantly lower quality of life than typical children.[6-8]

Gross motor function deficits are an important participation restriction and lead to discriminatory education practices. The participation, motor function, and stress of children with CP are very different from those of typical children, so providing a normal environment and mainstream education system for them might be not suitable. Therefore, there is a special education system which can support special needs and optimize approaches to remove the children's barriers.[9,10] A special education program is a modified program that involves unique tools, techniques, and instructional arrangements that are driven by multidisciplinary teams to move toward less discrimination against disabled children.[11-13]

Physical therapists (PTs) in special education have an important role in interacting with overall health

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Received 23 January 2024 Revised 20 February 2024 Accepted 31 March 2024
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https://doi.org/10.33192/smj.v76i8.267459

conditions, such as bodily functions, activities, participation, and other impacted factors, for improving children's academic performance and estimating the levels of caregiver management required in school[14,15] A previous survey study on special education units showed that PTs used motor impairment assessment tools for admission screening, estimating children's performance, and planning rehabilitation plans and follow-up treatment. However, PTs still faced obstacles in the assessment process and had to integrate items or domains from various standard tools to solve their problems. They needed clear instructions and an appropriate scoring system, and they needed to be able to complete the assessment within a short time and document the social participation aspect.[16] All these gaps found among PTs should be filled, and their requirements should also be integrated into a new simple and validated tool for children with CP.

An appropriate clinical tool is the most important item required to address the motor function problems of children with CP and decrease the size of the differences between those children and typical children. Therefore, this study aims to develop a physical therapy screening tool to define the problematic functional activities in school-based children with CP, which will lead to more accurate decisions for further in-depth physical examination and regulation of guidelines for Individualized Education Programs (IEPs).

MATERIALS AND METHODS

The cerebral palsy screening of functional abilities in school (CPS-FAS) tool was developed from a surveying process and a focus group discussion process with pediatric physical therapists (PTs). The tool was tested for its psychometric properties and discriminative ability in children with CP. The study process is shown in (Fig 1). The study was approved by the Human Research Ethics Committee of Srinakarinwirot University (Certification number PTPT2021-004), the Physical Therapy Department of Srinakarinwirot University (Certification number SWUEC/E/G-212-2564), and the Human Research Ethics Committee of Bangkok (Certification number U004hh/66).

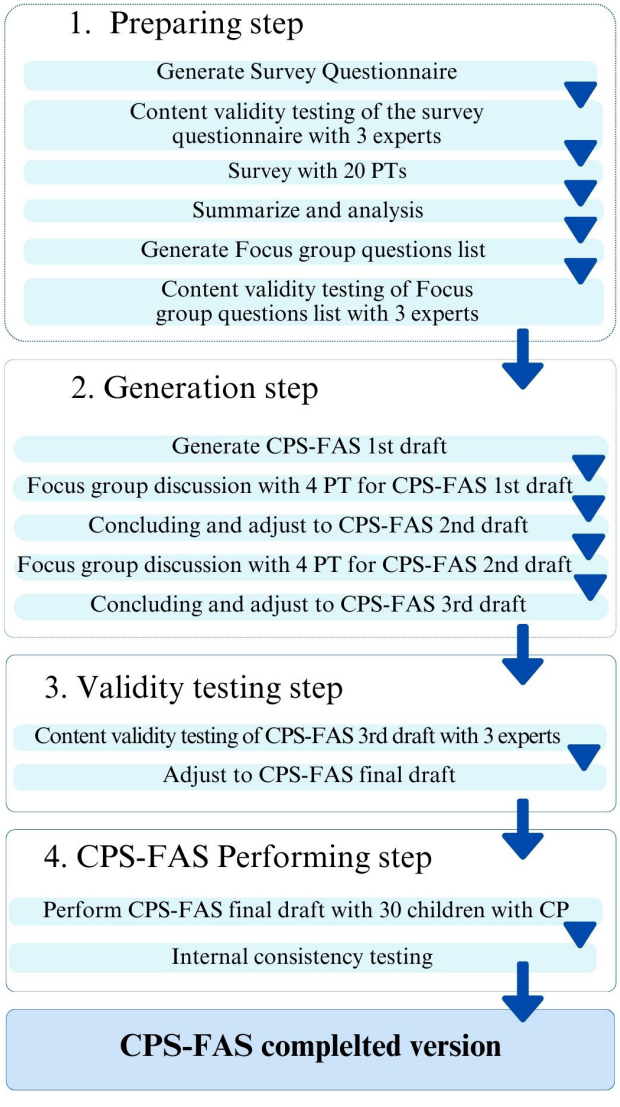

Fig 1. The process of cerebral palsy screening of functional abilities in school tool development.

Boys and girls (n=30) who had been diagnosed with CP were selected by purposive sampling according to the following inclusion criteria: studied in school grades 1-12, had CP at GMFCS levels 1-3, and were able to cooperate. They were selected to evaluate the content validity, internal consistency, and GMFCS-level discriminative ability of the CPS-FAS tool. Participants were excluded if consent had not been given by parents or legal guardians; they were in ill health; they could not move their extremities or were under weight-bearing restrictions after surgery; they had unstable epilepsy or had changed doses of anti-epileptic medication; or they had additional disabilities such as blindness or deafness.

To define school-based PT obstructions, the author created the following survey with closed and open-ended questions: Requirements of PTs in Special Education Units. The authors ensured content validity and understanding of the language of the survey questionnaire with three experts who analyzed the correspondence between the questions and the objectives by using the index of IOC. The coefficient (IOC=0.67-1) of the survey questionnaire was acceptable. Then, the survey questionnaire was applied with 12 special education units in Thailand and was submitted via Google Forms by PTs who had more than 1 year of experience (n=20) and had been recruited by purposive sampling. The author waited for 2 weeks to receive the responses and then analyzed the answers. The summary was used to generate the first draft of the CPS-FAS tool.

The online focus group discussion was an item-detail adjustment process. The question list was established based on the results of the survey that had been content validated by three experts (IOC = 0.67-1). This process was divided into two rounds with researchers and senior pediatric PTs (n=8). In the first round, the first draft of the CPS-FAS tool was sent to the senior lecturer of PTs in the pediatric field (n=4). Then, the results were used to adjust item details for the second draft. In the second round, the second draft of the CPS-FAS tool was sent to senior pediatric PTs in the special education units (n=4). Then, the results from the focus group discussion were used to develop the third draft.

The third draft from the focus group discussion was analyzed for content validity. The content validity was tested by three experts who had more than 2 years experience as pediatric PTs. This analysis resulted in the final draft of the CPS-FAS tool. The final draft of the CPS-FAS tool was used on children with CP (n=30) to evaluate the internal consistency of each item and the total consistency of all items. The total CPS-FAS score of 30 children with CP was used to define differences between levels 1-3 of the GMFCS.

Statistical analyses

Descriptive statistics were used to explain the participants' demographic data, CP type, GMFCS level, other characteristics, and the results of CPS-FAS as frequency, mean, and standard deviation values. The index of item-objective congruence (IOC) was used to test the content validity. The expected coefficient was greater than 0.5. Cronbach's alpha coefficient was used to evaluate the internal consistency of the items of the CPS-FAS tool. The expected coefficient (α) was greater than 0.8. The group difference was analyzed using the Kruskal-Wallis test, analysis of variance (ANOVA) tests, and the Bonferroni post-hoc test. The level of significant difference was set at $p < 0.05$ and 95% confidence intervals. For all of the analyses, SPSS software, version 22.0, was used (SPSS Inc., Chicago, IL).

RESULTS

The CPS-FAS tool is a newly developed tool that responds to the needs of PTs in special education units and helps remove obstructions to psychometric testing. The CPS-FAS tool has acceptable content validity (IOC=0.67-1).

The CPS-FAS tool consists of three parts: Part 1: Basic profile (name, caregiver's name, GMFCS level, study level, usage of gait aids, disabilities, other personal health issues, and body chart); Part 2: Screening scale (related to motor functions and activities in school, and consisting of 21 items); see detail in (Table 1) and Part 3: Tool instruction (suggested starting position, main idea of each item and decision criteria). The scaling system uses a 4-point ordinal scale to score the level of children's abilities and each level has a specific definition, ranging from 3, which means they are able to complete that function, to 0, which means they are unable to complete that function. The highest possible score is 63.

The demographics and characteristics of participants are presented in (Table 2). The 30 children with CP consisted of 14 boys and 16 girls. The mean age was 13.13 years (range = 8–18 years), and the median was 13 years. The participants' levels were diagnosed and classified according to the Gross Motor Function Classification System (GMFCS) by physicians.

The statistically significant differences between the total CPS-FAS scores at the three GMFCS levels were confirmed by the Kruskal-Wallis test ($p<0.001$), and the ANOVA test ($F=42.786$, $p<0.001$). From the pairwise comparison between groups, differences were found between GMFCS levels 1 and 3 ($p > 0.001$) and GMFCS levels 2 and 3 ($p > 0.001$); see detail in (Table 3) and (Fig 2).

TABLE 1. The items of CPS-FAS.

Items
Sit on a chair with stability
Co-ordination of eyes and hands
Reach in sitting with stability
Co-ordination of both hands
Co-ordination of upper extremities
Co-ordination of lower extremities
Stand up from a chair
Stand with stability
Reach in standing with stability
Walk on a flat surface for a distance of 2 meters with a safety
Gait pattern on a flat surface for a distance of 2 meters
Walk in a narrow lens 30-centimeters for a distance of 2 meters
Cross objects at ankle level
Upstairs 3 steps
Downstairs 3 steps
Wheelchair using
Transfer to toilet
Hygiene care in the toilet
Bathing
Grooming
Eating

Note: CPS-FAS mean cerebral palsy screening of functional abilities in school

The reliability testing of the CPS-FAS tool involved each item related to the tool's objective. The statistics showed the CPS-FAS tool had a Cronbach's alpha of 0.921 based on all items, and a Cronbach's alpha of 0.917 based on standardized items.

DISCUSSION

Currently, each special education unit has its own diverse structure; even though all special education units have the same policy, they work differently. Therefore, some special education units established their own tool to fill their gaps, but the tools lacked psychometric properties. Some units did not establish their own tools, but instead, they chose to use standard tools, such as GMFM, and selected some dimensions that were related; however, half of them thought GMFM was uncomprehendable and selected other tools, such as the Gross Motor Function Classification System (GMFCS), visual analogue scale (VAS), modified Ashworth scale (MAS), Functional Independence Measure for Children (WeeFIM), and Barthel ADL index to be used together. Moreover, the survey results showed PTs in special education units had a lack of experience in using standard tools, insufficient time, and inadequate tools, which indicate that Thailand's special education units desire a specific standardized tool for practical use.

The International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) defines 'activity' as the execution of a task or action by an individual. The Activities and Participation chapters of the ICF-CY comprised the following nine chapters: Learning and Applying Knowledge; General Tasks and Demands; Communication; Mobility; Self-care; Domestic Life; Interpersonal Interactions and Relationships; Major Life Areas; and Community, Social and Civic Life.[17] The results of the survey show the most applicable chapters in schools for children with CP are the Mobility and

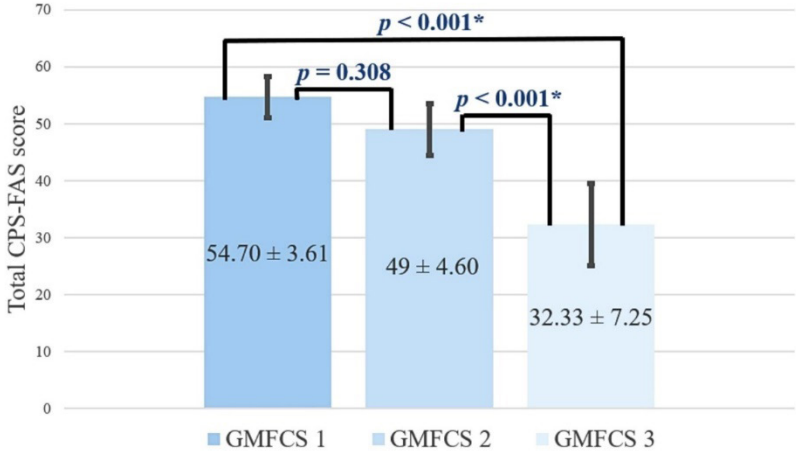

Fig 2. The mean differences between the total CPS-FAS scores at the three GMFCS levels; *mean significant difference at the 0.05 level; GMFCS mean Gross Motor Function Classifications System; CPS-FAS mean cerebral palsy screening of functional abilities in school.

TABLE 2. The demographics of children with cerebral palsy.

Variable	Level of GMFCS			Kruskal-Wallis Test (p-value)
	Level 1 (n=10)	Level 2 (n=5)	Level 3 (n=15)	
Gender (n;%)[b]				
Boy	5 (50%)	2 (40%)	7 (46.7%)	0.937
Girl	5 (50%)	3 (60%)	8 (53.3%)	
Ages (year)[a]	13.4 ± 0.53 (9 – 18)	14.8 ± 2.86 (11 – 18)	12.4 ± 3.16 (8 – 18)	0.345
Education level (n;%)[b]				
Primary	5 (50%)	2 (40%)	11 (73.3%)	0.242
Secondary	5 (50%)	3 (60%)	4 (26.7%)	
Diagnostic (n;%)[b]				
Hemiplegia	8 (80%)	0 (0%)	1 (6.7%)	0.003*
Diplegia	1 (10%)	2 (40%)	9 (60%)	
Triplegia	0 (0%)	1 (20%)	2 (13.3%)	
Ataxia	0 (0%)	1 (20%)	1 (6.7%)	
Athetoid	1 (10%)	1 (20%)	2 (13.3%)	
Gait aids (n;%)[b]				
Walker	0 (0%)	2 (6.7%)	7 (23.3%)	<0.001*
Wheelchair	0 (0%)	0 (60%)	8 (26.7%)	
No	10 (33.3%)	3 (10%)	0 (0%)	
CPS-FAS Score[a]	54.70 ± 3.61 (47 – 60)	49 ± 4.60 (42 – 55)	32.33 ± 7.25 (17 – 45)	<0.001*

Note: a mean ± standard deviation (min-max); b number (%); *mean significant difference at the 0.05 level; CPS-FAS mean cerebral palsy screening of functional abilities in school; GMFCS mean Gross Motor Function Classifications System.

TABLE 3. The differences between the total CPS-FAS scores at the three GMFCS levels.

Post-hoc test	Group	Comparing group	Mean difference (±S.E.)	p-value	95% Confidence interval
Bonferroni method	GMFCS level 1	GMFCS level 2	5.7 ± 3.37	0.308	-2.92– 14.32
		GMFCS level 3	22.37* ± 2.52	<0.001	15.95– 28.79
	GMFCS level 2	GMFCS level 3	16.67* ± 3.18	<0.001	8.54 – 24.79

Note: *mean significant difference at the 0.05 level; S.E. mean standard error; CPS-FAS mean cerebral palsy screening of functional abilities in school; GMFCS mean Gross Motor Function Classifications System.

Self-care chapters because the special education unit policy prescribes that students should have basic mobility and be able to perform self-care to guarantee that they can participate in school activities without obstacles. During the school day, children with CP have to do various activities both academic and nonacademic.[6,18,19] Accordingly, a PT in a special education unit has a role in helping to optimize children's academic and nonacademic functional tasks to support their education.[15,17]

CPS-FAS is concerned with the PT role in schools. The 21 items of the CPS-FAS tool represent elementary movement, such as sitting, standing, and locomotion with and without gait devices. Moreover, the CPS-FAS tool has test items on balance and limb co-ordination, which are important components in doing complex activities. Importantly, daily life activities, such as grooming, toileting, and eating, are covered to estimate children's dependence levels, which are very important for planning care plans and managing manpower in special education units.[18]

The CPS-FAS tool emphasizes mobility because it is often an important obstacle to doing activities. This is in accordance with a systematic review in 2019 which found that motor skills were related to school participation for children with CP, and if they had an attentive PT or school structure, it would support their school life.[20] The results of the internal consistency test showed the CPS-FAS tool had a Cronbach's alpha of 0.921 based on all items, and a Cronbach's alpha based on standardized items of 0.917, which means all 21 items had strong reliability and were related to the tool's objectives. All 21 items of the CPS-FAS tool were relevant, and it was not necessary to remove any items.[21]

The CPS-FAS tool had the ability to discriminate between the three GMFCS levels. The statistical testing confirmed the differences between GMFCS level 1 (very high function without gait device) and GMFCS level 3 (fair function with gait device), and between GMFCS level 2 (high function with or without gait device) and GMFCS level 3 (fair function with gait device). The study did not find a difference between GMFCS level 1 and 2, which might be due to the small number of children with CP at GMCFS level 2 (n=5).[21]

The previous studies found the gross motor skills development of children with CP had effects on school participation and quality of life.[22,23] Accordingly, the purpose of the CPS-FAS tool is to help PTs in special education units define gross motor functions and functional activity impairment because they affect children's health and quality of life. One purpose of parents who send their children with CP to school is to get PTs to improve their children's performance, reduce physical limitations and teach self-care activities. From the parents' perspective, it is important that teachers and multidisciplinary teams in schools are good facilitators who can improve their children's quality of life.[10,22,23]

The strengths of the study are the inclusion of children with varying CP types, age ranges and study grades. Moreover, the purposive sampling and simple incursion conditions of subjects generalize the result to a school-based population. A limitation is that the author focuses on studying children with CP at GFMCS levels 1-3.

CONCLUSION

The psychometric testing confirmed that the CPS-FAS tool had good validity and reliability. The CPS-FAS tool is simple to use in a school-based setting, with clear instructions, and it only takes a short time (10-15 minutes) to screen children with CP impairment using this tool before selecting more specific tools.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the assistance of Sri Sangvalya Khon Kaen School, Thailand, for the permission to collect data on their students and their support in providing the setting for the study.

Conflict of Interest

No potential conflict of interest was reported by the authors.

Author Contributions

JW, LW, and RB designed the study plan and developed the methodology. LW was investigated and collected the data. JW and LW were involved in the interpretation and analysis of data. LW and JW were involved in manuscript writing, review, and editing. All authors reviewed, edited, and approved the final version of the article.

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Nicotine Gum in Thai Smokers with Different CYP2A6 Enzymes: A Population Pharmacokinetic Analysis

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ABSTRACT

Objective: Despite the popularity of nicotine gum in Thailand, population pharmacokinetics of nicotine gum in the Thai population has not been investigated. This study aimed to develop a population pharmacokinetic (POPPK) model of nicotine and to quantify the effects of genetic and non-genetic factors to nicotine pharmacokinetics.

Materials and Methods: Secondary data collected from a previous clinical trial assessing cytochrome P450 2A6 (CYP2A6) genotypes in Thai smokers was investigated. Eighteen participants who had received a single dose of 2 mg nicotine gum were included. Blood samples were collected before, at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4.5 and 6 hours after nicotine administration. POPPK analysis was performed using nonlinear mixed effect modelling.

Results: One-compartment with 1st order elimination and absorption with 6 transit compartments best described the data. CYP2A6 enzyme activity was a significant covariate on the nicotine clearance. Apparent elimination clearance (CL/F) for a person with 100% CYP2A6 activity was 266.0 L/h. CL/F would be 36.0 L/h in a subject with 0% CYP2A6 activity. However, the impact of non-genetic factors (monthly alcohol consumption, Fagerstrom Test for Nicotine Dependence score and the number of cigarettes per day) on pharmacokinetics of nicotine were not found.

Conclusion: This first report on population pharmacokinetics of nicotine gum in Thai smokers provided the pharmacokinetic model and quantified CL/F for smokers with different CYP2A6 genotypes. A markedly lower exposure to nicotine in the Thai population compared to others highlights the need for more studies to ensure the efficacy of nicotine gum in the Thai population.

Keywords: Population pharmacokinetics; nicotine chewing gum; Cytochrome P-450 CYP2A6 (Siriraj Med J 2024; 76: 504-513)

INTRODUCTION

Tobacco related health problems are serious and rampant in the world today, especially in Thailand. According to a WHO report in 2018, tobacco related deaths accounted for 18% of all deaths in Thailand.[1] Quitting smoking has been shown to substantially reduce mortality rates.[2] Nicotine replacement therapy (NRT), the first-line pharmacotherapy for smoking cessation, is widely used to aid smoking cessation. NRT reduces cravings and relieves nicotine withdrawal symptoms. Without NRT, a successful quit rate of 11.34% was achieved following 6 months of cessation counseling with

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Received 4 February 2024 Revised 31 March 2024 Accepted 1 April 2024

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https://doi.org/10.33192/smj.v76i8.267636

or without sodium nitrate mouthwash.[3] Providing NRTs increased the successful quit rate by 50-60%.[4] Nicotine gum is one form of NRTs, and it is the most dispensed medicine for smoking cessation in Thai community pharmacies.[5]

Nicotine is a weak base, readily absorbed in basic pH, and widely distributed into body tissues.[6] Nicotine is mainly metabolized via hepatic metabolism mediated by the cytochrome P450 2A6(CYP2A6) enzyme. Substantial variations in plasma levels of nicotine after receiving multiple doses of 2-mg nicotine gum has been reported.[7,8] Several pharmacokinetic studies using a non-compartmental approach have been conducted with nicotine gum.[9-14] Considerable variation in pharmacokinetics of nicotine gum has been found in these literatures. The area under plasma concentration-time curve from initiation to infinity ($AUC_{0\text{-}inf}$) ranged from 11.2 to 36.6 ng*h/ml.[9-14] Apparent elimination clearance (CL/F) of nicotine gum was between 54.7 and 178.6 L/h[9-14], whereas elimination clearance of nicotine in intravenous studies was between 66.6 and 90.0 L/h.[6] Plasma elimination half-life of nicotine was between 2.0 and 7.4 hours.[6,9-14]

CYP2A6, a highly polymorphic gene with more than 40 variants, enzyme activity has been shown to influence the therapeutic efficacy of NRT.[15] CYP2A6 enzyme activity varies with different CYP2A6 genetic allele, which has been shown to affect the nicotine metabolism rate and the efficacy of NRTs. Variability in therapeutic responses to NRT was found in groups of different nicotine metabolizers. Providing personalized pharmacotherapy might increase the rate of successful smoking cessation and improve the efficacy of NRT.[16]

Population pharmacokinetic analysis is used to identify sources of variation in a population leading to individualized pharmacotherapy. Although some non-compartmental pharmacokinetic analyses of nicotine gum have been reported, there are limited population pharmacokinetic studies of nicotine following administration of different preparations of nicotine including nicotine gum.[17,18] However, that study did not investigate a Thai population. The objectives of this study were to develop a population pharmacokinetic model of nicotine in adult Thai smokers with different CYP2A6 enzyme activities after administration of nicotine gum and to quantify the effects of genetic and non-genetic factors on the pharmacokinetics of nicotine.

MATERIALS AND METHODS

Study design

This retrospective population pharmacokinetic analysis was performed on secondary data collected from a previous clinical trial investigating CYP2A6 genotypes in Thai smokers at King Chulalongkorn Memorial Hospital, Bangkok, Thailand in 2014-2016 (the trial has not been published, the registration link: https://www.thaiclinicaltrials.org/show/TCTR20161227002). All subjects provided written informed consents. This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (Approval number 085/58).

Study population

The previous clinical trial was divided into 2 parts: CYP2A6 genotyping and pharmacokinetics of nicotine. In the part of the pharmacokinetic study, eighteen participants were recruited. There were 18 adult Thai smokers (10 normal and 8 slow metabolizers) who smoked every day in the 5 months prior to the study with an average of approximately 10 cigarettes per day were selected to investigate the pharmacokinetic profile following single administration of 2-mg nicotine gum. Subjects who were consuming food or drugs that were CYP2A6 inducer or inhibitors, subjects who had a history of chewing disorders or abnormalities in jaw joints, subject with liver or kidney insufficiencies and pregnant and breast-feeding women were excluded.

Sampling schedule and nicotine bioanalysis

Subjects were directed to abstain from any form of nicotine for 12 hours prior to the study and to refrain from any sour juice for 30 minutes before the study. A 2-mg nicotine gum (Nicotinell®, Fertin Pharma A/S, Denmark) was administered orally and chewed as instructed for 30 minutes. Blood samples were collected before the administration of nicotine gum (pre-dose) at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4.5 and 6 hours after the start of nicotine administration.

Nicotine plasma concentrations were determined by a validated LC-MS/MS using liquid-liquid extraction from the previous clinical trial (the trial has not been published.) The calibration curve ranged from the lower limit of quantification (LLOQ) of 0.25 ng/ml to 50.00 ng/ml. The intra-day and inter-day accuracy and precision were carried out for low (0.75 ng/ml), medium (15.00 ng/ml) and high concentrations (30.00 ng/ml). The accuracy ranged from 92.80% to 103.20% and the precision (% CV) did not exceed 7.80%.

Pharmacokinetic modelling

The population pharmacokinetic model of nicotine was developed using non-linear mixed effect modelling approach as implemented in the NONMEM software,

version 7.3.0 (ICON Development Solutions, Ellicott city, MD, USA).[19] The NONMEM runs were executed by PDx-Pop version 5.2.1 (ICON Development Solutions, Ellicott city, MD, USA). Data checkout and model diagnostics were performed via the software Xpose (version 4).[20]

The first-order conditional estimation method with interaction (FOCE-I) was used throughout the model building process. One- and two- compartment linear models were explored to describe the distribution of nicotine. Various kinds of absorption models including zero-, first-, mixed zero- and first-order absorption, first-order absorption with fixed transit compartments and Weibull-type absorption model were tested to model the absorption of nicotine from buccal mucosal membrane. Pre-dose concentration of nicotine was measurable in 11 subjects and was modelled by a decreasing mono-exponential term as described in literature.[16] Different error models including additive, proportional, combined additive and proportional, and exponential models were tested for residual unexplained variability. Exponential function was used to model inter-individual variability (IIV). Base model was evaluated by examining the basic goodness-of-fit plots, precision of parameter estimates, objective function value (OFV), and akaike information criterion (AIC).

Covariate analysis was performed using a stepwise approach. In the forward addition step, a decrease in OFV of >3.84 ($\chi^2_{0.05}$) was considered significant. In the backward elimination step, an increase in OFV of >10.83 ($\chi^2_{0.001}$) was necessary to retain the covariate in the model. Depending on the relationship between pharmacokinetic parameters and covariates, linear, power, exponential and piece-wise covariate models were evaluated.

The effect of CYP2A6 genetic polymorphism on the clearance of nicotine were evaluated in two different ways; Groups of CYP2A6 phenotype (normal metabolizers and slow metabolizers) as a categorical covariate or activity of CYP2A6 genotype (%) as a continuous covariate which is defined as the following equation.

Activity of CYP2A6 genotype (%) = (AS of genotype/AS of full-function genotype) *100 … (*Equation 1*)

The activity score (AS) was assigned to each CYP2A6 genotype based on known enzymatic activity of CYP2A6 variants as described in previous literature.[21] We transformed AS of each genotype into a percentage value to facilitate the model estimation. Monthly alcohol consumption, Fagerstrom Test for Nicotine Dependence (FTND) score, and number of cigarettes per day were investigated as categorical covariates on clearance of nicotine. The impact of body weight and body mass index on volume of distribution of nicotine were also studied.

The final model was evaluated by bootstrap analysis and with a prediction-corrected visual predictive check.[22,23] Parameter precision was evaluated via bootstrap techniques using 1,000 replicate datasets produced from the final model to determine 95% confidence intervals (CI) of each parameter. Predictive performance of the model was evaluated with visual predictive checks. The magnitude of eta shrinkage (shrinkage in empirical Bayes estimates) and epsilon shrinkage (shrinkage in individual predictions) was investigated to evaluate the informative value of individual data.[22]

RESULTS

A summary of patient characteristics was presented in Table 1. All subjects were male with a median age of 33 years. Six different CYP2A6 genotypes were included in the study. Subjects with a full-function CYP2A6 genotype *1/*1were defined as normal metabolizers. The remaining CYP2A6 genotypes had decreased enzyme activity and therefore subjects with decreased enzymatic activity were defined as slow metabolizers. The enzymatic activity of CYP2A6 genotypes ranged from 0% to 100%. After exclusion of 8 concentrations below the limit of quantification (~4%, 7 concentrations were at time 0 and 1 concentration was at time 6), 172 concentrations were available to develop a population pharmacokinetic model.

Structural model

A two compartment model did not converge successfully and was not used. A one compartment model with 1st order elimination adequately described the observed data. First order absorption with 6 transit compartments was superior compared to all other investigated absorption models (ΔOFV= -35.9 and -10.3 in compared with 1st order absorption and zero-order absorption, respectively). The addition of more transit compartments did not improve the fit. Weibull, serial first-order, and mixed zero- and first-order absorption models did not converge successfully and were not used. Due to high variability during the absorption phase, the first-order absorption rate constant could not be appropriately estimated (the 95%CI for IIV contains zero) and was fixed to the estimated population value of 2.9 h^{-1}, based on model fit. The robustness of the fixed value was verified using a sensitivity analysis by varying the value from1.8 to 4.4 h^{-1}; the variance model parameter values indicated the chosen value of 2.9 to be appropriate. A proportional error model was chosen to describe the residual variability based on suitability or plausibility of parameter estimates.

TABLE 1. Patient characteristics.

Characteristics	Value (N = 18) Median (minimum-maximum)
Age (year)	33.0 (26.0-58.0)
Body weight (kg)	70.5 (57.0-112.0)
Body Mass Index (kg/m^2)	24.6 (19.7-37.9)
Years of smoking (year)	15.5 (8.0-34.0)
Enzymatic activity of CYP2A6 genotypes (%)	100.0 (0-100.0)
	No. (%) of patients
CYP2A6 genotypes	
*1/*1 (AS 2.0 or 100% enzyme activity)	10 (55.5%)
*1/*9 (AS 1.5 or 75% enzyme activity)	1 (5.6%)
*1/*4 (AS 1.0 or 50% enzyme activity)	2 (11.1%)
*9/*9 (AS 1.0 or 50% enzyme activity)	3 (16.7%)
*4/*9 (AS 0.5 or 25% enzyme activity)	1 (5.6%)
*4/*4 (AS 0 or 0% enzyme activity)	1 (5.6%)
Monthly alcohol consumption	
Yes	5 (27.8%)
No	13 (72.2%)
Number of cigarettes per day	
≤10	16 (88.9%)
11-20	2 (11.1%)
	No. (%) of patients
FTND score	
Very low (0-2)	9 (50.0%)
Low (3-4)	7 (38.9%)
Medium (5)	-
High (6-7)	2 (11.1%)
Very high (8-10)	-

Abbreviations: AS = activity score of CYP2A6 genotype, FTND = Fagerstrom Test for Nicotine Dependence score

Covariate model

Modelling clearance as a linear function of activity of CYP2A6 genotypes (%) improved the model fit significantly (ΔOFV= -17.2, p<0.001) and reduced IIV of apparent elimination clearance from 64.9% to 38.5%. Other tested covariates were found not significant. The final elimination clearance is described in equation 2.

CL/F (L/h) = 266.0 + 2.3*(Activity of CYP2A6 genotype (%) -100) … (*Equation 2*)

Model evaluation

Parameter estimates of the final model are presented in Table 2. Fixed effect parameters were estimated with high precision with relative standard errors (%RSEs)

TABLE 2. Population pharmacokinetic parameters of final model.

Parameter	Parameter Description	Estimate [%RSE]	Bootstrap (n=991) Median	95%CI	Shrinkage (%)
Fixed effect					
Apparent elimination clearance (CL/F) = TVCL/F + θ_{CYP2A6} * (CYP2A6-100)					
TVCL/F (L/h)	CL/F for a typical male subject with 100% CYP2A6 enzyme activity	266.0 [10.7]	271.0	219.0 - 348.0	-
θ_{CYP2A6}	Proportional constant of median-normalized CYP2A6 enzyme activity	2.3 [12.6]	2.4	1.1 - 3.6	-
V/F (L)	Population apparent volume of distribution	851.0 [10.3]	863.0	703.0 - 1050.0	-
KA (h^{-1})	Population first-order absorption rate constant	2.9 *fix*	-	-	-
MTT (min)	Population mean transit time	7.2 [15.6]	7.2	4.8 - 10.2	-
C0 (ng/ml)	Population pre-dose concentration	0.6 [18.8]	0.6	0.4 - 0.9	-
Random effect (CV%)					
IIV of CL/F	Interindividual variability for CL/F	38.5 [43.3]	37.1	14.8 - 53.9	3.9
IIV of V/F	Interindividual variability for V/F	38.1 [29.7]	37.2	23.7 - 49.4	4.8
IIV of MTT	Interindividual variability for MTT	54.1 [34.0]	53.5	0.2 - 87.0	15.2
IIV of C0	Interindividual variability for C0	73.1 [22.6]	73.2	50.7 - 96.1	4.2
RUV	Residual unexplained variability	14.7 [26.3]	14.8	10.5 -18.4	18.2
Secondary parameters		**Median (minimum-maximum)**			
C_{max} (ng/ml)	Maximum plasma concentration	1.8 (1.1-4.5)			
t_{max} (h)	Time to reach C_{max}	1.5 (1.0-2.0)			
AUC_{0-6} (h*ng/ml)	Area under plasma concentration-time curve from initiation to last sampling time	6.6 (3.1-21.4)			
AUC_{0-inf} (h*ng/ml)	Area under plasma concentration-time curve from initiation to infinity	8.7 (3.3-57.2)			
$t_{½}$ (h)	Elimination half-life	2.9 (1.3-7.9)			

Coefficient of variation (CV%) of inter-individual variability and residual variability was calculated as $((\exp(\text{variance})-1)^{1/2}) * 100$. Relative standard errors (%RSE) were presented as 100*(standard deviation/mean). The 95% confidence interval (CI) was given as the 2.5th to 97.5th percentiles of bootstrap estimates.

between 10% and 20%. The goodness-of-fit plots did not show any obvious model misspecification (Supplementary Fig 1). However, a small deviation was found at higher concentrations, which was contributed by substantially higher plasma concentrations of subjects who had the complete lack of CYP2A6 enzyme activity. Final parameter estimates of the model were within the 95% confidence interval of the range of estimated obtained from 1,000 bootstrapped datasets, which indicated a stable and appropriate model (Table 2). Value of eta and epsilon shrinkage were within acceptable limits (3.9-18.2%).[22] Prediction- corrected visual predictive checks are presented in Figure1 showing a good predictive performance of the model.[23]

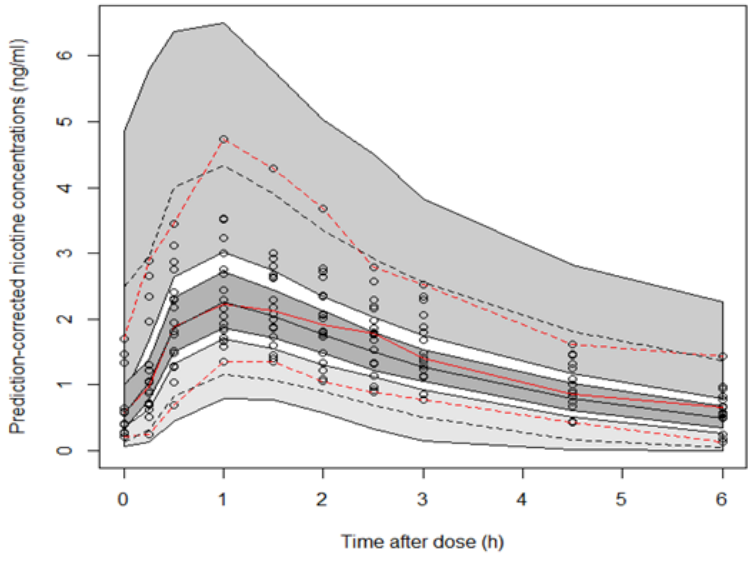

Fig 1. Prediction-corrected visual predictive check of the final model.

Open circles represent the prediction-corrected observed concentrations of nicotine. The black dashed line at the top, black solid line, and black dashed line at the bottom represent 97.5th, 50th and 2.5th predicted percentiles respectively. Observed 97.5th, 2.5th and 50th percentiles are presented as red dashed lines and red solid lines. Shaded areas represent 95% prediction intervals.

DISCUSSION

To date there are limited population pharmacokinetic studies of nicotine, which includes nicotine gum, published in literature.[17,18] It was difficult to directly compare the results of the present study with the previous studies because of differences in study designs. The previous studies developed a population pharmacokinetic model for nicotine following different NRTs (2-mg nicotine gum and 1-mg nicotine nasal spray) and tobacco products (tobacco heating system and cigarette) administration.[17,18]

In the present model, a first-order absorption with a transit compartment model best described the absorption characteristics of nicotine gum whereas a zero-order absorption model did well in the Marchand study[17] and first order absorption in Gisleskog study.[18] It should be noted that Marchand investigated only zero- and first- order absorption models and did not test a transit compartment model. Moreover, there were different formulations between studies (Nicotinell in this study and Nicorette in Marchand and Gisleskog study). These might be part of the reasons for the discrepancy in absorption model. Longer blood collection period (24 hours) in the Marchand study might contribute to the discrepancy in the number of distribution compartments between the two studies: one-compartment in the present study and two-compartments in Marchand study.[17]

Apparent volume of distribution (V/F) of nicotine in a Thai population was 851.0 L, which is higher compared to most values found in literature (V/F=322.0-833.0 L in non-compartmental pharmacokinetic analyses of 2-mg nicotine gum[9-14] and steady state V/F=241.0 L in Marchand study[17]). CL/F for a typical person who had 100% CYP2A6 enzyme activity was 266.0 L/h in the current study, which was approximately 7 times higher than that in the Marchand study[17] and approximately 4 times higher than the Gisleskog study[18], and was also higher than the most values found in the NCA studies of nicotine gum (CL/F=54.7-178.6 L/h). However, it is notable that none of the studies included data on CYP2A6 polymorphism. The elimination half-life of nicotine in the present study (2.2 h) is consistent with the value reported in literature. This suggests a lower bioavailability in Thai population compared with other population. It should be noted that different brands of 2-mg nicotine gum were used in this study and previous studies (Nicorette®).[9-14,17]

The CYP2A6 enzyme is major metabolizing enzyme of nicotine and the CYP2A6 polymorphism has a significant impact on metabolism of nicotine.[6,16] Different CYP2A6 genetic variants result in variation in CYP2A6 enzyme activity, which affects the nicotine metabolism rate. The influence of CYP2A6 polymorphism on CL/F of nicotine was investigated in two different ways; groups of CYP2A6 phenotype as a categorical covariate or activity of CYP2A6 genotype (%) as a continuous covariate. We found that the inclusion of activity of CYP2A6 genotype (%) significantly improved the model fit (ΔOFV= -17.2, $p<0.001$) and reduced IIV of CL/F from 64.9% to 38.5% which were better than the inclusion of groups of CYP2A6 phenotype (ΔOFV= -7.8, $p<0.05$; IIV of CL/F reduced from 64.9% to 51.5%). Therefore, CYP2A6 activity (%) was chosen as a significant covariate to explain the impact of CYP2A6 polymorphism on IIV of CL/F.

According to final model described in equation 2, if the CYP2A6 activity decreased 25.0%, the CL/F decreased by 57.5 L/h (or 21.6%). Positive relationship between CL/F of nicotine and CYP2A6 activity was consistent with previously reported data.[17] However, the results need to be interpreted with caution because different methods of CYP2A6 activity measurement might affect the results. Nicotine metabolite ratio (NMR) has been reported as a valid indicator of CYP2A6 activity.[24] Unfortunately, NMR data was not available and activity score system was used to predict CYP2A6 activity based on known enzymatic activity of CYP2A6 variants. However, it is worth noting that the activity score system is also a valid, easy-to-use tool to predict phenotype and is utilized to provide genotype-based dosing recommendation in clinical settings.[25,26]

It has been reported that smoking itself inhibited the metabolism of nicotine.[6] Therefore, we investigated the impact of the number of smoking years and the number of cigarettes per day on CL/F. None of these covariates were significant, consistent with findings in a previous study.[17] Further, Dermody et al[27] and Gubner et al[28] have reported that an association between alcohol consumption and rate of nicotine metabolism, but we did not find a significant effect of monthly alcohol consumption on CL/F. The reason could be that the previous two studies included chronic heavy drinkers diagnosed with alcohol dependent disorder, while only 5 out of 18 individuals in the current study consumed between 5 and 50 glasses of alcoholic beverages per month and alcohol dependent disorders were not present. A larger sample size, with various smoking and alcohol consumption history is needed to examine these associations.

Despite a 12-hour washout period, plasma concentrations of nicotine were measurable before dosing. This has also been seen in previous studies.[10,14,17] The presence of pre-dose concentrations could interfere with the estimation of the pharmacokinetic parameters of nicotine. Different approaches to handle the baseline data have been studied.[29] Among them, estimating the typical value and IIV of baseline concentrations provided the best performance, with less bias and less imprecision compared to other methods.[29] Therefore, typical value and IIV of pre-dose concentrations were estimated in this study. Then, pre-dose concentrations were modelled as mono-exponential decay as described in literature.[17] Addition of pre-dose model into the base model provided the better model fit in every aspect of absorption models and RUV models (Supplementary table 1).

There are some limitations in this study. First, this was a retrospective analysis performed on secondary data with a small sample size, the result validity may be distrustful, however, the study has demonstrated a crucial trend of CYP2A6 genotypes effects on drug elimination in Thai smokers. This study analyzed only Thai smokers' data, therefore the results from this study might not represent other populations. Second, all subjects were male. It has been reported that clearance of nicotine is higher in females than in males.[6,17] We could not investigate that factor in this study. However, it is worth noting that the prevalence of smoking is about 15-20 times higher among men than women in Thailand.[30] Third, due to the secondary data analysis, the details of collected data (monthly alcohol consumption, FTND score, and number of cigarettes per day) were not enough to analyze as continuous data, it might be one of the reasons why we have not found some significant relation between these covariates and pharmacokinetic parameters. Finally, the 6-hour sampling time was relatively short and might affect the characterization of the elimination phase.

Despite limitations, to the best of our knowledge, this is the first population pharmacokinetics of nicotine gum in a Thai population. Comparison of pharmacokinetic parameters of plasma nicotine from both compartmental and non-compartmental analysis of single-dose 2-mg nicotine gum in non-Thai population versus Thai population was shown in Table 3. Interestingly, exposure of nicotine after chewing nicotine gum is substantially lower in Thai population compared to non-Thai population. This observation might challenge the therapeutic efficacy of current dosage regimen of nicotine gum for Thai population. Therefore, the efficacy of current dosage regimen should be confirmed by further studies. Moreover, studies with a larger sample size and more frequent sampling design are recommended to better characterize the pharmacokinetics of nicotine gum.

CONCLUSION

The pharmacokinetics of nicotine in Thai population after nicotine gum administration was best described by a linear one-compartment disposition model with first-order absorption and 6 transit compartments describing the absorption phase. The enzymatic activity of different CYP2A6 genotypes influences the nicotine clearance. Providing personalized smoking cessation based on CYP2A6 genetic variation is important to optimize therapeutic efficacy of nicotine medications. However, the impact of non-genetic factors like monthly alcohol consumption, FTND score and number of cigarettes per day on pharmacokinetics of nicotine were not found in this study. Moreover, this study highlights a substantially lower exposure of nicotine in Thai population compared

TABLE 3. Comparison of pharmacokinetic parameters of plasma nicotine after administration of single dose 2-mg nicotine gum in non-Thai population versus Thai population.

NCA											**POP PK**
Author (year)	Choi (2003)[a]	Dautzenberg (2007)	Muneesh (2016)	Hansson (2017)[a]	Brossard (2017)[b]		Du (2018)	This study		Marchand (2017)[b]	This study
Population	USA	French	Indian	Swedish	Japanese		European	Thai		Japanese	Thai
N	23	9	43	44	18 (Tokyo)	18 (Saitama)	62	10 (Normal metabolizer)	8 (Slow metabolizer)	36	18
Blood sampling	14 samples over 12 h	11 samples over 8 h	19 samples over 24 h	19 samples over 12 h	16 samples over 24 h		13 samples over 12 h	10 samples over 6 h		16 samples over 24 h	10 samples over 6 h
C_{max} (ng/ml)	4.0 ± 1.5	2.9 ± 1.2	7.3 ± 2.1	5.9 ± 1.9	4.8	7.52	3.7 ± 1.3	2.53 ± 1.80	3.15 ± 0.47	5.7	1.8 (1.1-4.5)
T_{max} (h)	0.8 ± 0.2	0.8 ± 0.1	0.7 (0.3,3.0)	0.5[c]	0.6[d]	0.8[d]	0.8 (0.5, 1.5)	0.80 ± 0.13	1.50 ± 0.13	0.8	1.5 (1.0-2.0)
$AUC_{0\text{-last}}$ (h*ng/ml)	10.7 ± 6.6	10.6 ± 4.4	32.3 ± 11.5	15.1 ± 5.3	14.9	27.9	10.2 ± 3.78	8.30 ± 0.77	13.32 ± 2.45	21.3	6.6 (3.1-21.4)
$AUC_{0\text{-inf}}$ (h*ng/ml)	11.3 ± 7.6	13.8 ± 5.6	36.6 ± 13.4	17.1 ± 6.0	16.6	31.1	11.2 ± 4.0	11.23 ± 1.41	24.63 ± 7.03	27.0	8.7 (3.3-57.2)
$t_{1/2}$ (h)	2.5 ± 1.2	2.5 ± 1.0	7.4 ± 4.7	2.9[c]	4.8	3.5	2.0 (1.2, 4.2)	2.59 ± 0.30	4.22 ± 0.63	0.8*, 11.97	2.9 (1.3-7.9)

Values were expressed as Mean ± SD or Median (minimum, maximum). NCA = non-compartmental pharmacokinetic analysis;
POP PK = population pharmacokinetic analysis; C_{max} = maximum plasma concentration of nicotine; t_{max} = time to C_{max}; $AUC_{0\text{-last}}$ = area under plasma concentration-time curve from initiation to last sampling time; $AUC_{0\text{-inf}}$ = area under plasma concentration-time curve from initiation to infinity; $t_{1/2}$ = plasma elimination half-life; *distribution half-life. [a] Plasma concentrations of nicotine were reported as baseline-adjusted values because of measurable pre-dose concentrations. [b] Values were expressed as geometric means. [c] Value was expressed as mean. Standard deviation was not reported. [d] Value was expressed as median. Range was not reported.

to other populations, which emphasizes the need of more study to ensure the efficacy of nicotine gum in Thai population.

ACKNOWLEDGEMENTS

The equipment and software used in this study were provided by the Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University. We would like to express sincere gratitude to Chulalongkorn University which provided "Scholarship Program for ASEAN Countries". We also would like to thank Dr. Richard Hoglund for his valuable advice and suggestion to develop a population pharmacokinetic model.

Disclosures

The Authors declare that there is no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Prevalence of Abnormal Cerebroplacental Ratio in Uncomplicated Full-term Pregnancy and Correlation with Adverse Perinatal Outcomes

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ABSTRACT

Objective: To investigate the prevalence of abnormal cerebroplacental ratio (CPR) and predicting values for adverse perinatal outcomes in uncomplicated full-term pregnancies.

Materials and Methods: This prospective cross-sectional study was conducted at Bhumibol Adulyadej Hospital, Royal Thai Air Force, Thailand between July and December 2023. The study population comprised pregnant women between the ages 18 and 45 presenting uncomplicated full-term pregnancies. Transabdominal ultrasonography in Doppler color mode was performed on all participants. Umbilical artery pulsatility index (UAPI) and middle cerebral artery pulsatility index (MCAPI) were both measured. CPR was calculated by MCAPI divided by UAPI. A CPR value was considered low if it was less than 1.03. Obstetric and perinatal outcomes were recorded including route of delivery, gestational age (GA) at delivery, obstetric complications, Apgar score, neonatal birth weight, neonatal intensive care unit (NICU) admission, and fetal non-reassuring tracing (FNR).

Results: A total of 250 pregnant women were recruited. The mean maternal age and GA was 27.7 years, 39.6 weeks, respectively. Low CPR prevalence was recorded at 16.4 percent. There were 41 and 209 cases in low (<1.03) and normal (≥1.03) CPR groups, respectively. UAPI and MCAPI of the normal/low CPR group were 0.8/1.3 and 1.1/0.9 with statistical significance. CPR for predicted value of FNR (1.03) gave sensitivity, specificity, PPV, and NPV at 95.5, 91.2, 51.2 and 99.5 percent, respectively. This study presented no adverse perinatal outcomes.

Conclusion: Low CPR prevalence was 16.4 percent. Normal CPR values measured within a week before birth was a good indicator of normal perinatal outcomes.

Keywords: Umbilical artery; middle cerebral artery; cerebroplacental ratio (Siriraj Med J 2024; 76: 514-521)

INTRODUCTION

The umbilical artery (UA) is responsible for outflow in fetal circulation and carries deoxygenated blood to the placenta and can indicate placental vascular resistance.[1] The middle cerebral artery (MCA) of the fetus is one of the main fetal cerebral blood vessels. When the blood flow to the fetus is reduced, the resistance of MCA is lowered to divert blood flow to supply the fetal brain.[2] Resistance of MCA is generally used as an indicator of intrapartum fetal hypoxia (IFH).[3]

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Received 11 February 2024 Revised 27 March 2024 Accepted 29 March 2024
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https://doi.org/10.33192/smj.v76i8.267732

Cerebroplacental ratio (CPR) is a hemodynamic parameter measurement derived from dividing the MCA by the UA Doppler pulsatility index ratio.[4] CPR is a reflection of the arterial redistribution that occurs during preferential brain perfusion in response of fetal hypoxia.[5] A low CPR value demonstrates impaired fetal oxygenation and brain hypoxemia.[6] It is believed that a low CPR is associated with adverse perinatal outcomes such as low neonatal birth weight, low Apgar score, and fetal non-reassuring tracing (FNR).[7]

Currently, there is no recommendation for antenatal surveillance in uncomplicated full-term (39-40 weeks and 6 days) pregnancies according to ACOG guidelines.[8,9] Previous literatures reported correlation between low CPR and fetal non-reassuring among pregnant women with intrauterine fetal growth restriction.[10-12] It has been suggested that the use of Doppler ultrasound in pregnancies with normal-sized fetuses at term could potentially identify those at risk of subclinical placental impairment.[7] The aim of this study is to analyze the prevalence of low CPR in uncomplicated full-term pregnancies and establish correlation with adverse perinatal outcomes.

MATERIALS AND METHODS

This prospective cross-sectional study was conducted between July and December 2023. Pregnant women who attended antenatal care unit (ANC) at the Maternal and fetal medicine unit at Bhumibol Adulyadej Hospital (BAH) during the study period were recruited. The study was approved by the Bhumibol Adulyadej Institutional review board (BAIRB) (Registration number 33/66). The clinical trial registration number was TCTR20230602002. All participants were first comprehensively counseled regarding the study and its procedures before informed consent was established and signed for enrollment.

Pregnant women aged between 18 and 45 years old with gestational ages (GA) between 39 to 40 weeks and 6 days were recruited. Accurate GA was confirmed by the first day of the last menstrual period and first trimester ultrasound. For purposes of this study; an uncomplicated pregnancy was defined as pregnancy displaying an absence of maternal medical disorders such as diabetes mellitus, hypertension, renal disease, autoimmune diseases. Our exclusion criteria were maternal medical disorders and multiple gestations.

At a GA of 39 weeks, pregnant women were required to attend weekly antenatal care until delivery. Color Doppler ultrasonography was performed at 39 weeks and repeated weekly until delivery via transabdominal technique based on International Society of Ultrasound in Obstetrics and Gynecology 2021 guidelines.[5] Non-stress test and amniotic fluid index measurement (modified biophysical profiles) were also performed weekly to all participants until delivery.[13,14] Doppler ultrasound was performed within one week before delivery. Obstetrics and perinatal outcomes were followed up and data was collected at delivery date. A flow chart of the study is displayed in Fig 1.

Umbilical artery pulsatility index (UAPI) was measured by transabdominal ultrasonography in color Doppler mode by using an ultrasound machine (Voluson E10 model: GE healthcare, Zipf, Austria). Point of UAPI measurement was the free loop of the umbilical cord. The acceptable velocity waveform of UAPI was presented in Fig 2A. Middle cerebral artery pulsatility index (MCAPI) was measured at the axial section of the brain including the thalami and the sphenoid bone wings. The circle of Willis was identified by the color flow Doppler mode. Point of pulse wave measurement was placed at the proximal third of the MCA closing to its origin (internal carotid artery) as shown in Fig 2B. Acceptable Doppler waveform of MCA and the angle of insonation was adjusted to be at nearly zero degrees.[5] Each Doppler ultrasound was performed by a single operator. Three waveforms were selected for measurement of UAPI and MCAPI in autotrace mode. When a CPR value measured less than 1.03, it was classified as abnormal or low CPR.

When subjects approached the active phase of labor, routine intrapartum care was attended. Standard labor protocol including nothing by mouth, intravenous fluid infusion and continuous external fetal monitoring were applied. Labor progression, namely uterine contraction, cervical progression and vital sign were monitored by an on-duty expert obstetrician. Cesarean delivery was performed as needed as decided under obstetrics indication.

Obstetric and perinatal outcomes were recorded including route of delivery, GA, obstetric complications, Apgar score, neonatal birth weight, neonatal intensive care unit (NICU) admission, and FNR. FNR was classified in subjects who had intrapartum fetal heart rate monitoring with category two or three. The National Institute of Child Health and Human Development terminology (revised in 2008) classified continuous electronic fetal monitoring tracings into a three-tiered system.[15]

When Apgar score at 5 minutes was 7 or greater it was unlikely to indicate peripartum hypoxia.[16] Adverse perinatal outcomes being described as: Apgar score less than 7, low birth weight (lower than 2,500 gram) and NICU admission.[17]

A pilot study was conducted among ten subjects. Prevalence of low CPR was 10 percent. Precision of estimation was set as level of 0.04. Appropriate sample

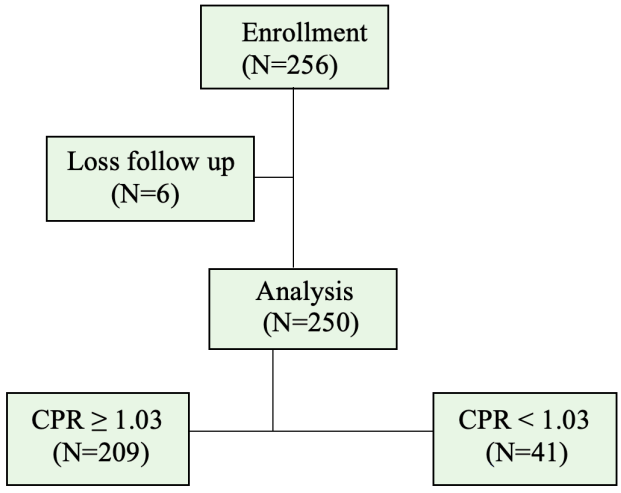

Fig 1. Flow chart of study.
Abbreviation: CPR: cerebroplacental ratio

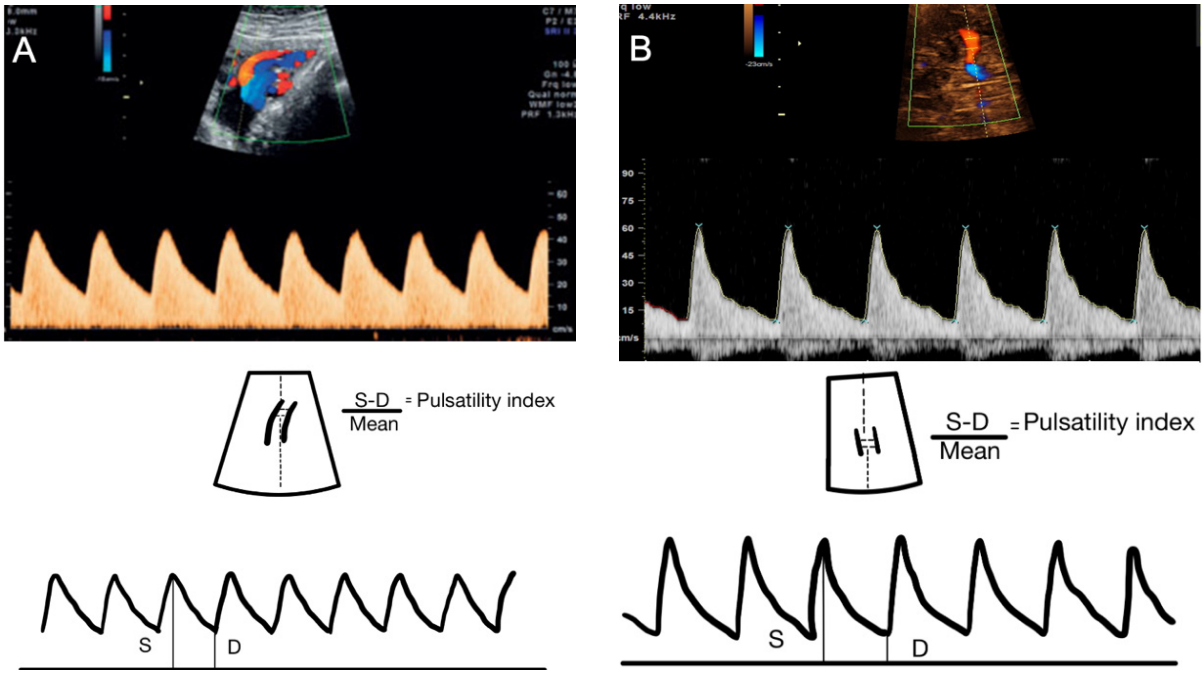

Fig 2. Ultrasonography image demonstrating the measurement of Umbilical artery and Middle cerebral artery.
Fig 2A: Umbilical artery Doppler, **Fig 2B:** Middle cerebral artery Doppler

size was at least 217 cases. Ten percent for data lost was added. The sample size in the current study was approximately 240 cases.

The commercial statistical package for social science version 22 program (IBM Inc., NY USA) was used for data analysis. Descriptive data was presented in percentages. Continuous and category variables between groups were presented as mean ± standard deviation and chi square or Fisher exact with appropriate application, respectively. Cut-off points for Doppler indices and FNR prediction were calculated using receiver operative curve (ROC) plotting. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of UA and MCA Doppler indices and CPR were evaluated. A *p*-value less than 0.05 was considered as statistical significance.

RESULTS

During the study period, 256 pregnant women were enrolled. A total of 250 pregnant women were recruited for the study as presented in Fig 1. The prevalence of low CPR in this study was 16.4 percent (41/250). Doppler ultrasound was performed within one week before delivery. The velocity waveform of UAPI and MCAPI was presented in Fig 2.

The participants' average age was 27.7 years old. Their average body mass index (BMI) was 27.8 kg/m^2 with a mean GA at delivery of 39.6 weeks. Two thirds of

subjects (155/250) were nulliparous. Low and normal CPR were defined as CPR < 1.03 and ≥ 1.03, respectively. There were 41 and 209 cases in the low and normal CPR groups, respectively. Subjects in the low CPR group were significantly older, with higher BMI, higher cesarean delivery (CS) rate, higher oligohydramnios and FNR (21 vs 1 cases) than those in normal CPR group. All subjects with FNR were evaluated for appropriate delivery according to obstetrics indication. One fourth (5/22) of FNR cases had vaginal delivery. Average neonatal birth weight from the low CPR group was significantly lower than those from the normal CPR group (3.1 vs 3.3 kg, respectively, $p = 0.01$). Average GA at delivery and parity of both groups were comparable as shown in Table 1. There was no newborn with low Apgar scores or any who required NICU admission among all subjects in this study.

The different cut-off values for predicting FNR including UAPI, MCAPI and CPR were presented in Fig 3. Receiver operative curve (ROC) was generated for appropriate cut-off value. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were shown in Table 2. CPR for predicted value of FNR (1.03) gave sensitivity, specificity, PPV, and NPV at 95.5, 91.2, 51.2 and 99.5 percent, respectively.

DISCUSSION

This prospective cohort study was to evaluate the use of Doppler indices for the prediction of abnormal intrapartum fetal tracing. FNR condition was recommended for the rapid fetus delivery to prevent IFH. CS was usually performed in FNR cases with slow cervical progression.[18]

The prevalence of low CPR in the current study was 16.4 percent. Previous studies from Italy and Turkiye reported incidence of low CPR were 15.7 and 19.3 percent, respectively.[19,20] While Mecke from Germany and Chinarong from Thailand reported incidence rates of 5.7 and 2.3 percent, respectively.[21,22] Study participants within Mecke and Chinarong's studies underwent Doppler ultrasound for CPR measurement at 22 and 37 weeks of pregnancy. Dall'Asta's study, Gunuy's, and the current study start Doppler ultrasound measurement at GA of 39 weeks. Increasing GA was a dominant factor for low CPR due to impairment of placental blood flow.[23] However, adverse perinatal outcomes fell short of statistical significance.

The CS rate of subjects in this study averaged approximately 20 percent (55/250). Half of subjects who had low CPR underwent CS (19/41). UAPI and MCAPI were Doppler indices used for predicting FNR.[18] High UAPI levels indicated that resistance of the umbilical

TABLE 1. Maternal characteristic, perinatal outcomes and Doppler indices of high CPR (n=209) and low CPR (n=41) total pregnant women (n= 250).

		CPR		
	Total*	**≥1.03***	**< 1.03 ***	***p*-value**
Age (year)	27.7±5.4	27.4 ±5.4	29.5±5.6	0.02
BMI (kg/m^2)	27.8±4.6	27.5±4.6	29.3±4.6	0.02
GA at delivery (weeks)	39.6±0.6	39.6±0.6	39.6±0.6	0.64
Nulliparity**	155 (62)	129 (61.7)	26(63.4)	0.84
Cesarean delivery**	55 (22)	36 (17.2)	19 (46.3)	<0.001
Oligohydramnios**	7 (2.8)	0 (0.0)	7 (17.1)	<0.001
EFW (kg)**	3.2±0.3	3.3±0.3	3.1±0.3	0.01
Fetal non-reassuring**	22 (8.80)	1 (0.48)	21 (51.2)	<0.001
UAPI	0.9±0.2	0.8±0.2	1.1±0.3	<0.001
MCAPI	1.2±0.3	1.3±0.3	0.9±0.2	<0.001
CPR ratio	1.5±0.4	1.6±0.4	0.9± 0.2	<0.001

* Mean ± standard deviation (SD), ** n (%)

Abbreviations: UAPI: umbilical artery pulsatility index, MCAPI: middle cerebral artery pulsatility index, CPR: Cerebroplacental ratio

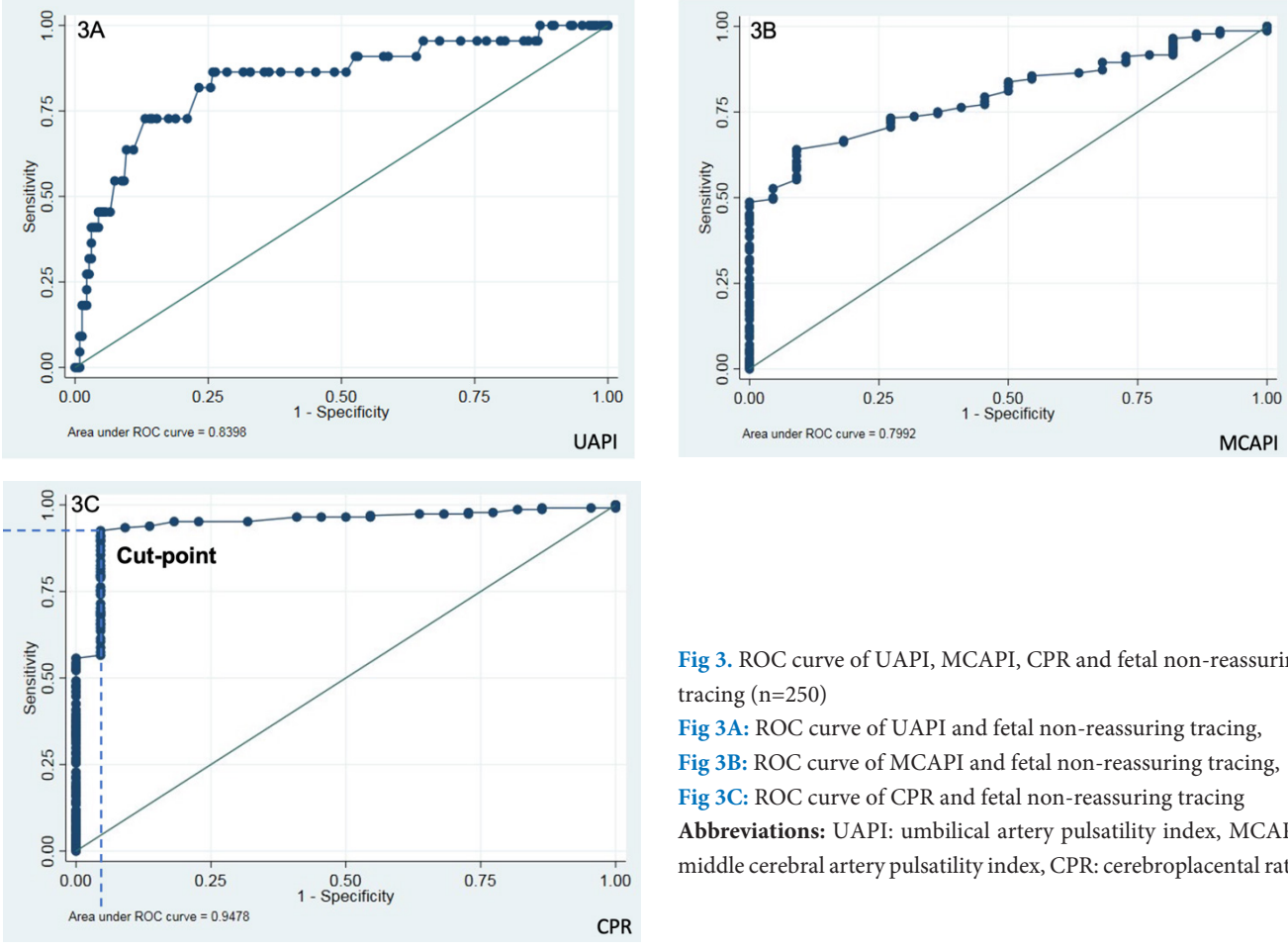

Fig 3. ROC curve of UAPI, MCAPI, CPR and fetal non-reassuring tracing (n=250)
Fig 3A: ROC curve of UAPI and fetal non-reassuring tracing,
Fig 3B: ROC curve of MCAPI and fetal non-reassuring tracing,
Fig 3C: ROC curve of CPR and fetal non-reassuring tracing
Abbreviations: UAPI: umbilical artery pulsatility index, MCAPI: middle cerebral artery pulsatility index, CPR: cerebroplacental ratio

TABLE 2. The performance of the different testing parameters.

	AUC	Cut off value	Sensitivity*	Specificity*	PPV*	NPV*
UAPI	0.80	1.05	72.7 (49.8-89.3)	86.8 (81.8-90.9)	34.8 (21.4-50.2)	97.1 (93.7-98.9)
MCAPI	0.77	1.13	90.9 (70.8-98.9)	64.0 (57.4-70.3)	19.6 (12.4-28.6)	98.6 (95.2-99.8)
CPR	0.93	1.03	95.5 (77.2-99.9)	91.2 (86.8-94.6)	51.2 (35.1-67.1)	99.5 (97.4-100)

* 95% confidence interval
Abbreviations: UAPI: umbilical artery pulsatility index, MCAPI: middle cerebral artery pulsatility index, CPR: cerebroplacental ratio, PPV: positive predictive value, NPV: negative predictive value

vessel was high. This implicated that placental vascular was higher resistance and dysfunction.[23]

In this study, FNR was classifed as fetal heart rate tracing in category two or three. Category two was defined as absent baseline variability and late or varibable decerelation of intrapartum fetal heart rate monitoring. While category two along with recurrent late or variable decerelations, bradycardia and sinusoidal pattern was classified as category three.[15] UAPI of more than 1.05 was proposed as allowing FNR prediction with sensitivity, specificity, PPV and NPV at a percentage of 72.7, 86.8, 34.8 and 97.1, respectively. When UAPI indicated a healthy fetus, the diagnosis accuracy was 97.1 percent. However, when UAPI indicated FNR, the diagnosis accuracy was only 34.8 percent. When UAPI was high, the unnecessary CS might be performed.

MCAPI indicated intracerebral resistance. In healthy fetuses, MCAPI was seen at high levels, indicating transport

of high oxygenation blood to peripheral and visceral organs.[24] When the fetus was FNR, the MCAPI appeared at low levels to shift blood flow to the brain to allow appropriate levels of oxygenation.[25] In this study, MCAPI lower than 1.13 could be used to predict FNR with sensitivity, specificity, PPV and NPV at a percentage of 90.9, 64.0, 19.6 and 98.6, respectively. When MCAPI indicated a healthy fetus, the correct diagnosis was comparable to the use of UAPI. The sensitivity of MCAPI was better than UAPI (90.9 and 72.7, respectively). However, the PPV of MCAPI was lower than UAPI (19.6 and 34.8). MCAPI alone was not a good validation of FNR when compared to the use of UAPI.

CPR was the ratio of MCA and UAPI. It was used for improving the predictive value of FNR and hence reducing unnecessary cesarean delivery.26 (26). From the current study, CPR of less than 1.03 could be used to predict FNR with sensitivity, specificity, PPV and NPV at the percentage of 95.5, 91.2, 51.2 and 99.5, respectively. Sensitivity for the detection of FNR by CPR was better than the sensitivity of MCA and UAPI (95.5, 90.9 and 72.7%). When CPR was used to ensure healthy fetus, it yielded a better result than the use of MCA and UAPI (99.5, 98.6 and 97.1%, respectively). When CPR was used to indicate FNR, the correct diagnosis of FNR was only 51.2 percent. CPR of less than 1.03 could be the appropriate Doppler index for prediction of FNR. The CPR cut-off point used in literature varied between 1.0 to 1.08 had been used as a predictor of FNR and applied for assessment of fetal well-being as summarized in Table 3.[19-22]

The cesarean delivery rate in Thailand, Turkiye, Germany, as of the current study were 46.1, 42.8, 36.9 and 22 percent, respectively.[19-22] However, the cesarean delivery rate of the Italian study was only 14.6 percent.[19] FNR prevalence in Thailand, Turkiye, Germany, Italy and the current study were 31.5, 16.7, 10.1, 6.6 and 8.8, respectively, see: Table 4.[19-22] FNR was shown not to be the indication for rapid delivery, but the CS rate seemed to be higher in the high prevalence of FNR cases.

TABLE 3. Comparison of Maternal characteristic, perinatal outcomes and Doppler indices.

	Gunay		Chainarong		Mecke		Dall'Asta		Present	
Year	2022		2018		2022		2019		2024	
Country	Turkiye		Thailand		Germany		Italy		Thailand	
CPR	≥1	< 1	≥ 1	< 1	≥ 1.08	< 1.08	≥ 10th	< 10th	≥ 1.03	< 1.03
Cases (n)	117	28	375	9	669	41	290	54	209	41
Prev**		19.3		2.3		5.7		15.7		16.4
Age (year)*	27.0	28.0	29.0		30.5	30.4	30.5	30.3	27.4	29.5
GA (weeks)*	39.4	38.1	39.3		39.4	38.9	39.6	39.1	39.6	39.6
BMI (kg/m^2) *	30.0	29.0	21.8			28.9	29.1	27.5	29.3	
Nulliparity**	57.0	15.0	72.0			57.1	51.9	61.7	63.4	
CS**	37.6	64.3	46.1		36.9		14.6		17.2	46.3
Oligo**	14.5	10.7	35	37.5					0	17
EFW (kg)*	3.4	3.2	3.1	3.0	3.4	3.0	3.4	3.2	3.3	3.1
FNR**	12.8	32.1	13.3	33.3	9.0	29.3	5.5	16.7	0.5	51.2
UAPI*	0.8	1.3					0.9		0.8	1.1
MCAPI*	1.4	1.2					1.3		1.3	0.9
CPR*	1.8	0.9			1.9	0.9	1.6		1.6	0.9

*Mean, **(%)

Abbreviations: Prev: prevalence of low CPR, UAPI: umbilical artery pulsatility index, MCAPI: middle cerebral artery pulsatility index, CPR: cerebroplacental ratio, GA: gestational age at delivery, BMI: body mass index, CS: cesarean delivery, Oligo: oligohydramnios, EFW: estimate fetal weight, FNR: fetal non-reassuring tracing

TABLE 4. Comparison of the performance of the different testing parameters.

Studies	Prev*	Cut off value	Sensitivity	Specificity	PPV	NPV
Gunay, Turkiye, 2022	16.7 (24/145)	< 1	37.5 (9/24)	84.3 (102/121)	32.4 (9/28)	87.0 (102/117)
Chinarong, Thailand, 2018	31.5 (121/384)	< 1	4.7 (6/121)	98.9 (260/263)	66.7 (6/9)	69.3 (260/375)
Mecke, Germany, 2022	10.1 (72/710)	< 1.08	16.7 (12/72)	95.5 (609/638)	29.3 (12/41)	91.0 (609/669)
Dall'Asta, Italy, 2019	6.6 (37/562)	< 10th	24.3 (9/37)	91.4 (480/525)	16.7 (9/54)	94.5 (480/508)
Present, Thailand, 2024	8.8 (22/250)	< 1.03	95.5 (21/22)	91.2 (208/228)	51.2 (21/41)	99.5 (208/209)

*%

Abbreviations: Prev: Prevalence of fetal non-reassuring tracing, PPV: Positive predictive value, NPV: Negative predictive value

NPV for detection of FNR in the current study, Dall'Asta', Mecke', Gunay' and Chainarong' studies were 99.5, 94.5, 91.0, 87.0 and 69.3 percent.[19-22] NPV from the current study was comparable to those from the mentioned studies. PPV in the current work, Chainarong', Gunay', Mecke' and Dall'Asta' studies were 51.2, 66.7, 34.4, 29.3 and 16.7 percent[19-22], respectively. PPV indicated high probability of FNR. When CPR predicts FNR, rapid delivery should be considered.

From the current finding, CPR of higher than 1.03 suggested the high probability of healthy fetus. When CPR was less than 1.03, the intrauterine surveillance and appropriate intervention should be performed. Immediate cesarean delivery among those who had CPR lower than 1.03 was not recommended. These fetuses should be treated as high-risk pregnancies and received close observation in intrapartum fetal monitoring.

Present study showed CPR as a method for antepartum fetal surveillance with high sensitivity (95.5%) to screen FNR. CPR of less than 1.03 was useful to encourage the attending obstetrician to closely survey the parturient. Low CPR (less than 1.03) was not an indication for cesarean delivery but was an indicator for intensive intrapartum monitoring. This could be used to potentially reduce rapid cesarean delivery with improved maternal perinatal outcomes.

CONCLUSION

Low CPR prevalence was presented at 16.4 percent. Normal CPR values measured within one week before delivery was a good predictor for normal perinatal outcome.

What is already known on this topic?

The umbilical artery (UA) is responsible for outflow in fetal circulation and carries deoxygenated blood to the placenta and can indicate placental vascular resistance. Resistance to MCA is generally used as an indicator of intrapartum fetal hypoxia. Cerebroplacental ratio (CPR) is a hemodynamic parameter derived by dividing the MCA by the UA Doppler pulsatility index ratio. A low CPR value demonstrates impaired fetal oxygenation.

What does this study add?

CPR of higher than 1.03 suggested the high probability of healthy fetus. When CPR of less than 1.03 was useful to encourage the attending obstetrician to closely survey the parturient. Low CPR (less than 1.03) was not an indication for cesarean delivery but was an indicator for intensive intrapartum monitoring.

ACKNOWLEDGEMENT

This study was supported by Bhumibol Adulyadej Hospital.

Conflict of Interest

There was no conflict of interest.

Author Contributions

Study concept and designed (NO, WL), analysis and interpretation of data (NO, WL, NOr, MP, KP, SM, BP). Study supervision (KB, KS) provided critical revision and approved the final version of manuscript.

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Cost-effectiveness Analysis of Lercanidipine Compared to Amlodipine as an Addition to Renin-angiotensin System Blockers in Diabetic Hypertensive Patients with Albuminuria in Thailand

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ABSTRACT

Objective: Dihydropyridine calcium channel blocker (DHP-CCBs) is an appropriate add-on antihypertensive option for uncontrolled blood pressure diabetic hypertensive patients with albuminuria who are already taking renin-angiotensin system blockers (RASBs). Among DHP-CCBs, amlodipine is the first-line medication in combination with RASBs. However, new-generation DHP-CCBs like lercanidipine has demonstrated superior effectiveness and fewer side effects, although at a higher cost than amlodipine. This study aims to assess the cost-effectiveness of lercanidipine versus amlodipine when added to RASBs in diabetic hypertensive patients with albuminuria. The objective is to provide robust evidence guiding the selection of the most suitable and worthwhile treatment option in Thailand.

Materials and Methods: This study analyses the cost-effectiveness of lercanidipine versus amlodipine as an addition to RASBs in diabetic hypertensive patients with albuminuria. The analysis was conducted from a societal perspective using a Markov model.

Results: The total costs of lercanidipine and amlodipine treatments were 370,392.83 baht and 384,221.85 baht, respectively. The life years gained for lercanidipine and amlodipine treatments were 11.33 years and 10.96 years respectively. Additionally, the quality-adjusted life years (QALYs) of lercanidipine and amlodipine treatments were 8.06 years and 7.51 years respectively. The calculated ICER was negative, indicating treatment with lercanidipine as a dominant strategy.

Conclusion: Due to lercanidipine's noticeable cost-effectiveness, lower costs, and longer QALYs. Adding lercanidipine has proven to be more cost-effective than amlodipine for diabetic hypertensive patients with albuminuria who have been unable to achieve their blood pressure goals with RASBs alone. Therefore, lercanidipine should be the preferred choice as an add-on to RASBs in Thailand. These results could significantly aid policymakers in making informed decisions.

Keywords: Albuminuria; amlodipine; cost-effectiveness analysis; diabetes; hypertension; lercanidipine; renin-angiotensin system blockers (Siriraj Med J 2024; 76: 522-533)

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Received 14 February 2024 Revised 6 March 2024 Accepted 16 March 2024
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https://doi.org/10.33192/smj.v76i8.267782

INTRODUCTION

Hypertension (HT) poses a significant global public health challenge due to its association with adverse health outcomes and substantial healthcare costs.[1,2] Over the last three decades, the number of adults aged 30-79 years diagnosed with hypertension has surged from 650 million to 1.28 billion, with a majority (approximately 82 percent) residing in low- and middle-income countries.[3] This overall increase in hypertensive patients is expected to expedite the progression of renal diseases, potentially leading to end-stage renal disease (ESRD).[4,5]

The coexistence of hypertension and diabetes is a common occurrence among a substantial portion of the patient population.[4,6] Individuals with both conditions often share common risk factors, including family history, ethnicity, dyslipidemia, and lifestyle choices. Previous studies have highlighted that hypertensive patients with diabetes are more prone to elevated blood pressure levels compared to those without diabetes, significantly increasing their risk of developing nephropathy, a microvascular complication.[7-9] Furthermore, this combination accelerates the progression and mortality rates associated with kidney disease.[1,2,4,9]

Prolonged, uncontrolled hypertension leads to increased intraglomerular pressure, impairing glomerular filtration. Consequently, this damages the glomeruli, causing abnormally high protein levels in the urine, a condition commonly known as albuminuria or proteinuria.[4,5] The association between hypertension and elevated urinary albumin excretion levels is well-established in both diabetic and non-diabetic patients.[10-13]

Albuminuria is a condition characterized by elevated urine albumin excretion, leading to kidney damage or a reduced glomerular filtration rate (GFR).[4] It serves as an early indicator of hypertensive renal damage. It acts as a precursor to renal insufficiency, particularly in diabetic and non-diabetic hypertensive patients with chronically uncontrolled blood pressure (BP).[4] The prevalence of albuminuria varies significantly among different studies, ranging from 10% to 40% in hypertensive patients.[14-16] This prevalence increases with age and the duration and severity of hypertension.[14-16] Effective BP control is associated with reducing urine albumin content and can delay or prevent the progression of renal degeneration. Therefore, expanding kidney replacement programs becomes crucial to prevent straining healthcare resources and ensure cost savings.[4,5]

Numerous guidelines[1,2,4,17] for hypertension management recommend the first-line use of renin-angiotensin system blockers (RASBs), such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), in patients with or without diabetes who have albuminuria. The purpose is to control blood pressure, aiming for a target of less than 130/80 mmHg or even an intensive blood pressure target (SBP 120 mmHg) if feasible.[4] If a patient cannot tolerate either class of medications or if the BP goal cannot be achieved (i.e., at least 20 mmHg above the target)[4], the alternative class should be considered. However, combinations of ACEIs and ARBs should be avoided. It is essential to note that not all antihypertensive medications have a similar effect on renal function. This factor should be taken into account when adding another antihypertensive medication, as the goal is to protect organ function.

When combined with RASBs, calcium channel blockers (CCBs) emerge as a suitable antihypertensive drug.[2,18] This combination proves especially beneficial for diabetic hypertensive patients with albuminuria, outperforming other antihypertensive classes based on current evidence, which indicates its potent antihypertensive and reno-protective benefits.[19-21] Studies have demonstrated that the combination of RASBs and a dihydropyridine (DHP) CCB is superior to a single-agent approach, reducing proteinuria and slowing down the progression of kidney degeneration in diabetic hypertensive patients with albuminuria.[19-21]

However, it is worth noting that CCBs come with common adverse effects, including peripheral edema, particularly in the lower limbs, and headaches.[22-24] The incidence of peripheral edema caused by CCBs ranges from 5% to 60%, often leading to treatment discontinuation.[24] In Thailand's National List of Essential Medicines (NLEM), amlodipine besylate is the recommended first-line DHP-CCB medication to be added to RASBs. In cases where patients cannot tolerate amlodipine's side effects, especially peripheral edema, new-generation DHP-CCBs like lercanidipine hydrochloride are suggested as a second treatment option.[17]

The effect of amlodipine, when used in combination with RASBs, is comparable to that of lercanidipine hydrochloride, a new generation DHP-CCB, in hypertensive patients with albuminuria.[25,26] However, previous randomized trials have shown that patients receiving lercanidipine in combination with RASBs experienced significant benefits, including reduced albuminuria and slowed progression of renal degeneration.[25-27] In the RED LEVEL study, which directly compared the efficacy of lercanidipine and amlodipine in combination with enalapril to protect renal function by reducing albuminuria in patients with mild-to-moderate hypertension, the findings revealed a significant decrease in albuminuria in the lercanidipine group at 3, 6, and 12 months compared to patients in

the amlodipine group.[25] Additionally, the ZAFRA study suggested that lercanidipine hydrochloride has a significantly lower rate of peripheral edema than amlodipine.[26] While lercanidipine appears to be more effective than amlodipine, it is three times more expensive when administered at equivalent dosages, according to the Drug and Medical Supply Information Center (DMSIC) and the Ministry of Public Health in Thailand.[28-30]

Amlodipine is currently considered the primary DHP-CCB to be used in conjunction with RASBs in patients with diabetic hypertension who also have albuminuria. Although lercanidipine has been demonstrated to be more effective and to have fewer side effects than amlodipine, its cost-effectiveness in Thailand and other countries has yet to be established. Therefore, this study aims to demonstrate the cost-effectiveness of lercanidipine compared to amlodipine when added to RASBs in diabetic hypertensive patients with albuminuria. The objective is to provide reliable evidence for decision-making regarding the most suitable and worthwhile treatment option in Thailand.

MATERIALS AND METHODS

Study design

The study was a cost-utility analysis (CUA) applying a Markov model analysis to simulate cost-effective treatments between amlodipine and lercanidipine as an adjunct to RASBs in diabetic hypertensive patients with albuminuria. Incremental cost-effectiveness ratio (ICER) was estimated by dividing the difference in cost in baht by the difference in quality-adjusted life years (QALYs) between treatments. Lifetime horizon was applied with a societal perspective. The study's protocol was reviewed and approved by the Human Research Ethics Committee of Silpakorn University (COE 66.0313-011).

Interventions of interest

This study compared 5 mg per day of amlodipine versus 10 mg per day of lercanidipine[28-31] in diabetic hypertensive patients with albuminuria who have been unable to achieve their blood pressure target[4] with RASBs (i.e., angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)) for at least six months.

Model structure

A five-stage Markov model was constructed based on clinical practice guidelines and previous published studies[1,4,6], see in Fig 1. The model and assumptions were validated by two nephrologists and one cardiologist for the clinical sequence to ensure its suitability for managing diabetic hypertensive patients with albuminuria. Microsoft Excel 2022 was used to perform decision analysis of a Markov model.

The model simulated patients over their lifetime, incorporating five clinical health states: normoalbuminuria, microalbuminuria, macroalbuminuria, end-stage renal disease (ESRD), and death. Chronic kidney disease (CKD) stages G1 to G4 were included as subclinical states within the normoalbuminuria, microalbuminuria, and macroalbuminuria states. Patients treated with RASBs alone initially entered the model with normoalbuminuria and blood pressure less than 150/80 mmHg, regardless of their CKD stage for hypertension treatment. During each three-month Markov cycle, patients could either stay in the same state or transition to other states if they could not achieve their blood pressure goal (i.e., at least 20 mmHg above the target or equal to or more than 150/80 mmHg[4]) despite being treated with RASBs alone for at least six months. Amlodipine or lercanidipine would be added for patients whose hypertension did not improve

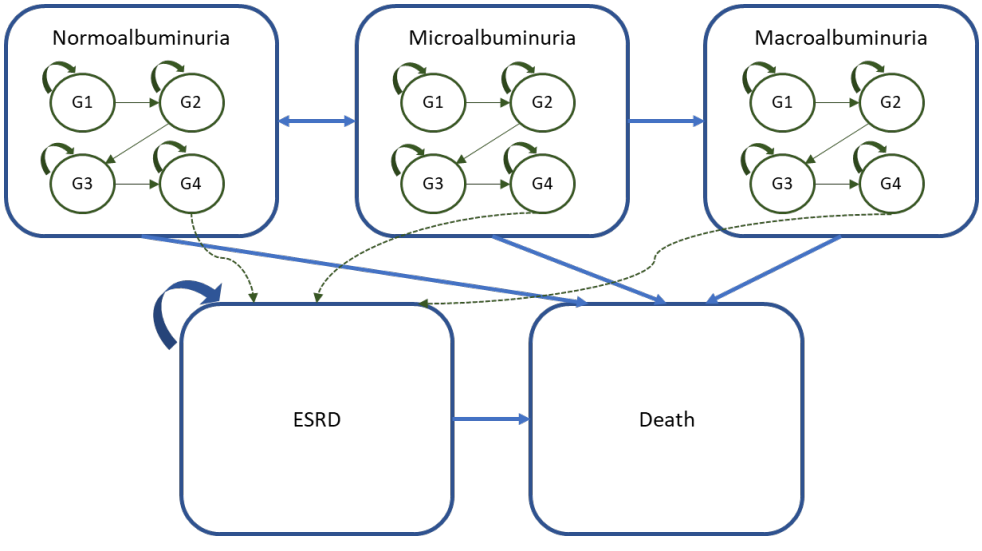

Fig 1. Markov model structure of diabetic hypertensive patients with albuminuria.

with RASBs to slow down renal degeneration. At the end of each cycle, transition probabilities for clinical status, adverse events (such as peripheral edema and headache), and mortality rates were assessed for each treatment group. Patients in the microalbuminuria state could regress to the normoalbuminuria condition. However, patients in the macroalbuminuria and ESRD states could not revert to previous states. The model continued until all patients met the criteria for the absorbing state, which was death, with an annual discount rate of 3%.

Assumptions of the model

1. The interested population in both add-on with amlodipine and lercanidipine arms is diabetic hypertensive patients who received RASBs for at least six months for hypertension and did not receive any other antihypertensive as well as other co-interventions.

2. According to a previous study in Thailand[32], the model's target population had an average age starting of 59 years and mean eGFR levels of 100 mL/min/1.73 m^2.

3. All patients used metformin as monotherapy for CKD stages G1 to G3 or eGFR ≥ 30 mL/min/1.73 m^2 or insulin for CKD stages G4/ESRD or eGFR < 30 mL/min/1.73 m^2. All had HbA1C levels between 7% and 9% and received no additional antidiabetic medications or co-interventions.

4. Patients with normoalbuminuria states have BP that is less than 150/80 mmHg and are treated with RASBs alone for hypertension.

5. Patients with microalbuminuria and macroalbuminuria states have BP that cannot be controlled or that are unable to achieve their BP goal (i.e., or more than or equal to 150/80 mmHg) while using RASBs alone for at least six months. 5 mg of amlodipine or 10 mg of lercanidipine daily would be combined to reduce BP and slow down albuminuria.

6. According to clinical practice guidelines[4], a BP of 150/80 mmHg is considered the upper limit of tolerable blood pressure, or at least 20 mmHg over the target of 130/80 mmHg. It requires the addition of other antihypertensive medications.

7. Patients with ESRD states are those who undergo continuous ambulatory peritoneal dialysis (CAPD) after being diagnosed with end-stage renal disease or increased plasma creatinine > 175 mol/L.

8. Peripheral edema and headaches were common adverse effects in all patients who added on with CCB, either amlodipine or lercanidipine.

9. Patients who experienced peripheral edema were switched from amlodipine or lercanidipine to 25 mg of hydralazine four times per day and then continued this medication to control hypertension. Patients who received hydralazine had no side effects.

10. Patients who experienced headaches were treated with paracetamol 500 mg 4 times daily.

11. Patients in microalbuminuria states of health could be transferred to normoalbuminuria conditions. Patients with macroalbuminuria and ESRD health conditions were unable to return to their previous state.

Time Horizon

A Markov model was developed to imitate the treatment of adult Thai hypertensive patients over a lifetime period from the mean age[32] of 59 until death with a life expectancy of not more than 75 years.[33,34] A three-month cycle was considered appropriate to determine the clinical efficacy of treatment in each health state from a survey of treatment in Thailand.

Probability of clinical outcomes

A systematic search for clinical parameters was conducted in Medline and Cochrane databases. The keywords were amlodipine "AND" lercanidipine". Two reviewers (KR and JL) independently reviewed abstracts and articles sequentially to select studies for data abstraction based on the study eligibility criteria. All searched literature was evaluated for the quality of studies according to the revised Cochrane risk of bias tool (RoB 2.0) for randomized trials and the STROBE statement for observational studies. All probabilities were converted into risks over three months because of the cycle length. All clinical parameters used in the Markov model were approved by the clinical experts and are shown in Table 1.

Studies were identified as eligible for inclusion if they were published as full papers in English. All transition probabilities were obtained from studies involving diabetic hypertensive patients with albuminuria who had been using RASBs for at least six months and added either amlodipine or lercanidipine to their treatments, according to the health transitions in the Markov model. The utility of health states was obtained from studies involving Thai diabetic hypertensive patients using amlodipine and lercanidipine and had the health state according to the Markov model with or without adverse effects. If search results were inconclusive, the study proceeded as follows:

(i) involving diabetic hypertensive patients with albuminuria with controlled hypertension by antihypertensive drug or BP less than 150/80 mmHg and whether they had adverse effects, or (ii) other patients who had utility

TABLE 1. All parameters used in the Markov model.

Parameters	Distribution	Mean ± SE	References
Clinical parameters:			
Transition probabilities			
Normoalbuminuria to Microalbuminuria	Beta	0.01748 ± 0.00121	39
Probability of eGFR reduction (G1 to G4)	Beta	0.00619 ± 0.00018	40
Normoalbuminuria (G4) to ESRD	Beta	0.04292 ± 0.01397	41
Microalbuminuria (G4) to ESRD	Beta	0.04292 ± 0.01397	41
Macroalbuminuria (G4) to ESRD	Beta	0.11100 ± 0.00385	42
Normoalbuminuria to Death	Beta	0.00352 ± 0.00014	43
Microalbuminuria to Death	Beta	0.00759 ± 0.00051	43
Macroalbuminuria to Death	Beta	0.01170 ± 0.00137	43
ESRD to Death	Beta	0.05190 ± 0.00665	43
Lercanidipine			
Microalbuminuria to Normoalbuminuria	Beta	0.26279 ± 0.02631	44
Microalbuminuria to Macroalbuminuria	Beta	0.00000 ± 0.00000	44
Peripheral edema	Beta	0.00473 ± 0.00222	25, 45, 46
Headache	Beta	0.01826 ± 0.00511	45, 47
Amlodipine			
Microalbuminuria to Normoalbuminuria	Beta	0.04083 ± 0.02508	48
Microalbuminuria to Macroalbuminuria	Beta	0.04083 ± 0.02508	48
Peripheral edema	Beta	0.25763 ± 0.04508	49
Headache	Beta	0.14455 ± 0.17583	49, 50
Hydralazine			
Microalbuminuria to Normoalbuminuria	Beta	0.00639 ± 0.00622	51
Microalbuminuria to Macroalbuminuria	Beta	0.06186 ± 0.01439	51
Humanistic parameters: *Utility*			
Normoalbuminuria state	Beta	0.720 ± 0.024	52
Microalbuminuria state	Beta	0.720 ± 0.024	52
Macroalbuminuria state	Beta	0.590 ± 0.041	52
ESRD state	Beta	0.550 ± 0.035	52
CKD stage G1-G2	Beta	0.85 (0.76, 0.94)	53
CKD stage G3-G4	Beta	0.72 (0.57, 0.87)	53
Reduction on utility of peripheral edema	Beta	0.033 ± 0.005	54
Reduction on utility of headache	Beta	0.115 ± 0.014	55

TABLE 1. All parameters used in the Markov model. (Continue)

Parameters	Distribution	Mean ± SE	References
Economic parameters (Baht):			
Direct medical cost			
(Normoalbuminuria, Microalbuminuria and Macroalbuminuria state)			
Medical costs			
Enalapril 20 mg (per tablet)	Gamma	0.5500 ± 0.0550	36
Lercanidipine 20 mg (per tablet)	Gamma	3.0000 ± 0.3000	36
Amlodipine 10 mg (per tablet)	Gamma	0.9000 ± 0.0900	36
Hydralazine 25 mg (per tablet)	Gamma	1.5000 ± 0.1500	36
Metformin 500 mg (per tablet)	Gamma	0.4000 ± 0.0400	36
Insulin NPH injection 100 IU/3 ml	Gamma	78.1100 ± 7.8110	36
Paracetamol 500mg (per tablet)	Gamma	0.4500 ± 0.0450	36
Laboratory costs			
Albumin test (per unit)	Gamma	33.6300 ± 3.3634	37
BUN test (per unit)	Gamma	83.4600 ± 8.3462	37
Creatinine test (per unit)	Gamma	83.4600 ± 8.3462	37
Urine protein test (per unit)	Gamma	150.7300 ± 15.0730	37
OPD treatment (per visit)	Gamma	83.4619 ± 8.3462	37
Pharmaceutical care service (per visit)	Gamma	84.6300 ± 8.4633	37
Direct medical cost *(ESRD state)*			
Erythropoietin	Gamma	2,794.84 ± 279.48	38
Palliative care (per month)	Gamma	23,454.01 ± 2345.40	38
Laboratory for ESRD (per 2 months)	Gamma	1,031.43 ± 103.14	38
Peritoneal dialysis catheter placement (per life)	Gamma	62,107.94 ± 6,210.79	38
Dialysis solution	Gamma	2,603.19 ± 260.32	38
Cleaning set	Gamma	111.79 ± 11.179	38
Direct non-medical cost			
(Normoalbuminuria, Microalbuminuria and Macroalbuminuria state)			
Travel (per visit)	Gamma	177.570 ± 17.757	37
Food (per visit)	Gamma	65.4100 ± 6.5411	37
Direct non-medical cost *(ESRD state)*			
Travel, food, and accommodation for CAPD (patients and caregivers)	Gamma	6402.84 ± 640.28	38

of health state and adverse effects, or (iii) utility was retrieved from international published studies if there was a scarcity of data in Thailand. Articles were excluded from the review if they met any of the following criteria: (i) non-full text papers, (ii) editorials and opinions, letters, research protocols, conference abstracts, duplicate reports of the same study, and notes and books.

Utility values

Utility values of clinical health states were obtained from previously published studies, see Table 1. QALYs were used as humanistic outcomes measurements in the ICER denominator. Humanistic outcomes were calculated by estimating the life years (LY) remaining of patients and weighted with utility values in different health states, ranging from 0 (death) to 1 (perfect health). Utility weights were multiplied by life expectancies to generate QALYs.

Economic values (costs)

All costs are expressed in Thai baht (as shown in Table 1) and adjusted to 2022 values using the consumer price index from the Bureau of Trade and Economic Indices, Ministry of Commerce, Thailand.[35]

Medical costs (i.e., lercanidipine, amlodipine, enalapril, hydralazine, metformin, insulin NPH injection, paracetamol) were derived from the Drug and Medical Supply Information Center (DMSIC) and the Ministry of Public Health, Thailand.[36] All direct non-medical costs (i.e., costs of travel and foods), laboratory costs, which included test for urine protein, albumin, blood urea nitrogen (BUN), creatinine, cost for OPD treatment, and pharmaceutical care service were obtained from the mean cost per unit from the standard cost lists for health technology assessment in Thailand.[37] The costs of all health states include medical costs and direct non-medical costs. Total costs include all treatment-related costs per patient from the time patient receives the treatment until death. Costs of patients in ESRD health state undergoing CAPD, including direct medical or direct non-medical costs, were derived from the previous studies in Thailand.[38]

Cost-effectiveness analysis

The ICER assessed the analysis based on a societal perspective, which was estimated by dividing the difference in cost in baht by the difference of QALYs between lercanidipine and amlodipine arms. Future costs and QALYS were discounted at 3% per year.

One-way sensitivity and Probabilistic Sensitivity Analysis (PSA)

The sensitivity analysis was performed to examine the robustness of the results using Microsoft Excel 2020. The upper and lower bounds of the 95% confidence interval (CI) around each parameter were used in a one-way and probabilistic sensitivity analysis.

For one-way sensitivity analysis, the parameter values were changed individually and regularly to the lowest and highest values. The results of one-way sensitivity analyses were presented in a tornado diagram. PSA was applied by randomly running 1,000 iterations using Random Monte Carlo Simulation to examine how parameters affected the ICER. Beta distribution was used for transition probabilities and utility values, whereas gamma distribution was used for costs. The results are presented as an ICER plane between incremental costs and incremental QALYs.

RESULTS

Cost-effectiveness analysis

The cost-effectiveness analysis results in Table 2 revealed that the total costs of lercanidipine and amlodipine treatments were 370,392.83 baht and 384,221.85 baht; LYs were 11.33 years and 10.96 years, and QALYs were 8.06 years and 7.51 years, respectively. The ICER of the lercanidipine treatment compared with the amlodipine was -25,143.67 baht/QALY gained. Because of the noticeable

TABLE 2. Cost-effectiveness results.

	Total cost (Baht)	LYs (Years)	QALYs (Years)	ICER (Baht/QALY)
Lercanidipine	370,392.83	11.33	8.06	-25,143.67
Amlodipine	384,221.85	10.96	7.51	

cost-effectiveness of lercanidipine treatment, lower costs, and longer QALYs, lercanidipine treatment was the preferred option.

Sensitivity analyses

The one-way sensitivity analysis result is shown in a tornado diagram in Fig 2. Regarding the outcomes, the variable with the most significant impact on the ICER was the probability of changes in health state in stage 4 CKD patients with normoalbuminuria to ESRD, followed by the probability of headaches of amlodipine. The probabilistic sensitivity analysis result is shown in Fig 3 as a cost-effectiveness plane between the incremental cost and the incremental QALYs of lercanidipine treatment compared with amlodipine treatment. Each variable was randomized 1,000 times in the Monte Carlo simulations. The yellow dot stands for the base-case ICER. Almost 88.6% of the ICER from randomization was dropped in quadrant 4, implying that lercanidipine had lower costs and longer QALYs.

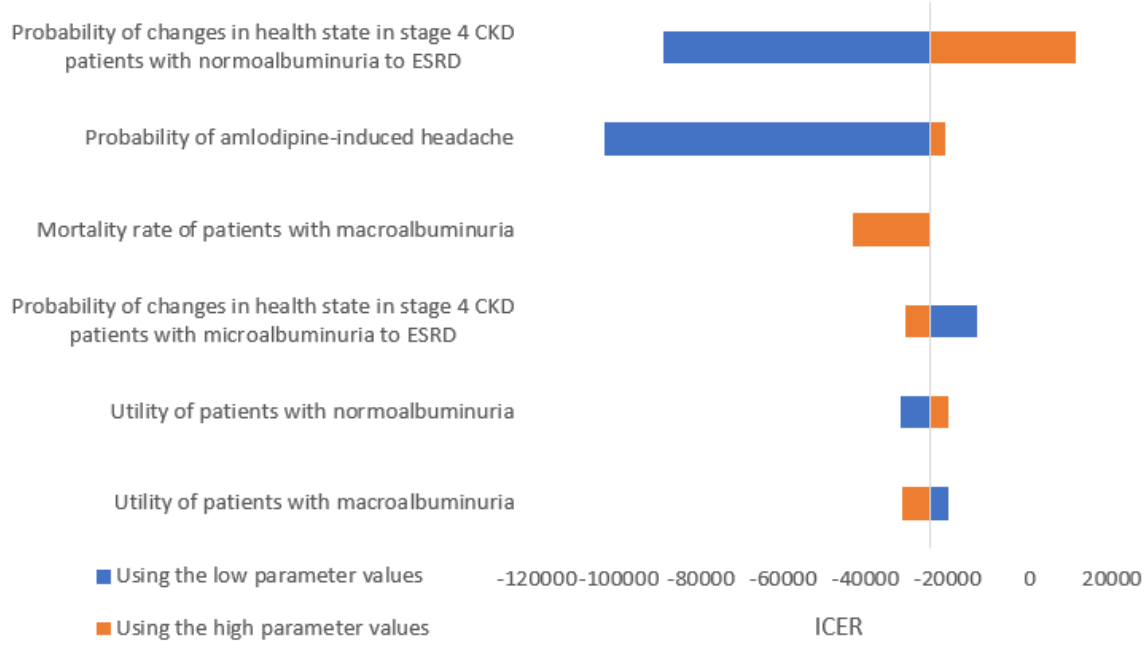

Fig 2. The tornado diagram depicts the results of a one-way sensitivity analysis.

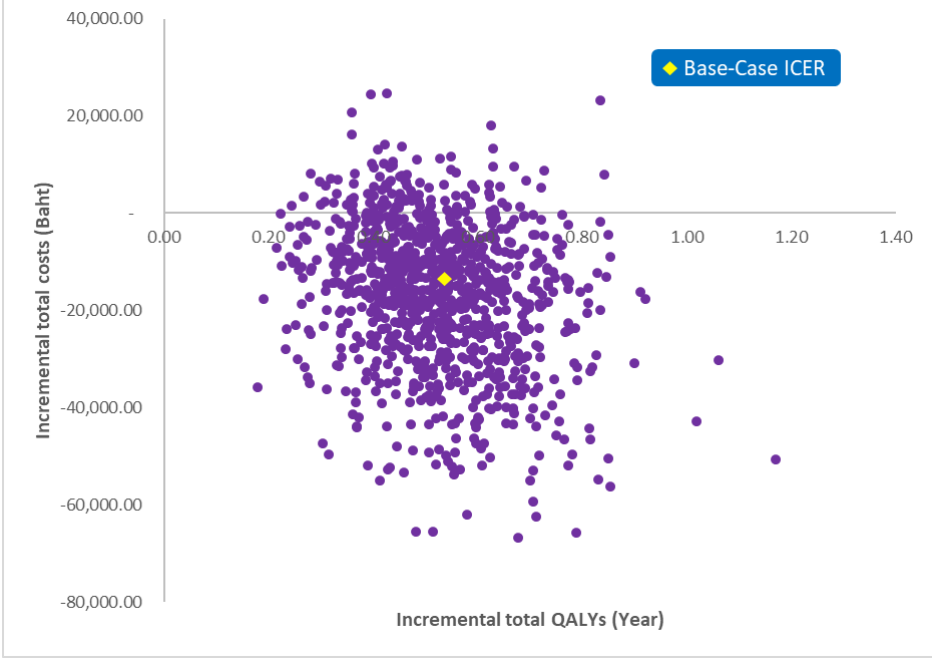

Fig 3. The cost-effectiveness plane of treatment with lercanidipine compared with amlodipine.

DISCUSSION

This is the first cost-effectiveness study to evaluate the addition of lercanidipine compared to amlodipine in diabetic hypertensive patients with albuminuria who are unable to achieve their BP target with only RASBs in Thailand. Even lercanidipine is three times more expensive compared with amlodipine. The results of this study revealed that an add-on with lercanidipine to RASBs is more cost-effective than amlodipine in the treatment of diabetic hypertensive patients with albuminuria from a societal perspective. As a result, lercanidipine has been associated with improved outcomes in terms of both LYs and QALYs gained, reducing total health expenditures. Treatments with lercanidipine demonstrate slower ESRD progression and lower adverse drug reactions, which will save on the cost of dialysis and treatments, resulting in significant cost savings. Therefore, the results indicated the ICER value is negative (i.e., -25,143.67 baht/QALY gained.), which is unquestionably lower than the GNI per capita with a ceiling threshold in Thailand of 160,000 baht per QALY. The results were also validated using one-way and probabilistic sensitivity analysis. They were consistent with the ICER-based results, which unambiguously demonstrated that adding lercanidipine was a cost-effective strategy as it reduced health expenditures for each QALY gained.

Previous clinical studies evaluating the efficacy and safety of lercanidipine and other CCBs have demonstrated its superior therapeutic efficacy in reducing albuminuria and minimizing adverse effects associated with vasodilation, particularly peripheral edema and therapy discontinuation. According to meta-analyses[31,56], lercanidipine and amlodipine (as a first-generation CCB) showed no significant differences in their long-term blood pressure-lowering effects.[31,56] However, lercanidipine was notably linked to a substantial reduction in peripheral edema and treatment discontinuation due to adverse events, in contrast to amlodipine.[31] Interestingly, lercanidipine's unique effects on renal hemodynamics, dilating both afferent and efferent glomerular arteries, contribute to preserving renal function even when used as a single medication. This is unlike amlodipine, which exhibits renal protection only when paired with RASBs.[57,58] The DIAL Study[58] demonstrated a reduction of more than 50% in microalbuminuria with lercanidipine treatment, although there was no statistically significant difference when compared to the use of RASBs alone.

Additionally, lercanidipine and RASBs have a synergic effect in reducing microalbuminuria in patients with proteinuria renal disease, which significantly reduces proteinuria by 20% to 35%.[27,45,59] Previous studies[25,44] suggested that enalapril combined with lercanidipine more reduced albuminuria than those combined with amlodipine. Lercanidipine had a higher rate of reversion to normoalbuminuria in microalbuminuria patients. In contrast, amlodipine had a greater progression from the microalbuminuria to the macroalbuminuria, the macroalbuminuria state to ESRD, and ESRD to death than lercanidipine.[44] Due to the higher likelihood of progression of renal disease and related complications, patients using amlodipine may experience higher health expenditures and less cost-effective treatment options. Our one-way sensitivity analysis revealed that the probability of changes in CKD stage 4 with normoalbuminuria to ESRD was the most sensitive parameter for the cost-effectiveness of lercanidipine versus amlodipine, indicating that the ICER values decreased when this parameter was reduced. Patients with CKD stage 4 with normoalbuminuria were less likely to develop to ESRD than those with albuminuria, according to the progression of the renal disease, which is in accordance with the previous evidence that lercanidipine can lower albuminuria to acceptable levels. Even when this parameter is raised, the ICER value increases, but the results are unchanged and remain below the Thailand ceiling threshold. These findings have substantial implications regarding optimizing the beneficial effects of controlling urinary albumin excretion to normoalbuminuria of lercanidipine.

Nevertheless, our study had several limitations due to the following factors: first, there were few studies[25,44] that directly compared the efficacy and adverse drug reactions of add-on lercanidipine and amlodipine to RASBs, and no previous studies were conducted in Thailand. Sensitivity analysis was performed utilizing ranges from all parameters to ensure the robustness of our results and reduce uncertainty influenced by confounding factors. Second, the available evidence is insufficient to distinguish macroalbuminuria from microalbuminuria in the lercanidipine arm (i.e., none would develop into macroalbuminuria), which might impact the final results of the analysis. However, we performed the worst-case scenario using the transition probability from microalbuminuria to macroalbuminuria of lercanidipine to be equal to amlodipine. The results are consistent that lercanidipine was still a dominant option (data not shown). Third, only CAPD was taken into account for the ESRD health state; we did not consider other modalities, such as hemodialysis, automated peritoneal dialysis, and kidney transplantation, which are used for kidney replacement therapy. Because CAPD was the first modality used to treat ESRD patients in Thailand, we assumed macroalbuminuria could not be

moved backward to the previous state or fully forestalled. Because albuminuria is a surrogate marker for chronic kidney disease progression.[4] Furthermore, only peripheral edema and headaches were considered adverse effects of CCB. Because these effects related to the mechanism, which were the most frequently reported from previous evidence and affect the patient's quality of life and lead to the discontinuation of treatment.[22,24,31,60]

Further economic evaluation studies require real-practice data across the country to perform a cost-effectiveness analysis for Thai diabetic hypertensive patients to provide a more accurate and reliable evaluation.

CONCLUSION

Adding lercanidipine hydrochloride, a new generation DHP-CCB, is more cost-effective than using amlodipine for diabetic hypertensive patients with albuminuria who cannot achieve their blood pressure goal with RASBs alone for at least six months. Lercanidipine not only leads to better outcomes in terms of Quality-Adjusted Life Years (QALYs) but is also more economical than amlodipine. Therefore, lercanidipine should be the preferred choice as an add-on to RASBs. This information is valuable for clinicians and policymakers as it guides future decisions regarding medical selection and reimbursement policies for diabetic hypertensive patients with albuminuria.

ACKNOWLEDGEMENTS

This study received a specific grant from Abbott Laboratories Limited. However, the funding source had no role in the design of this study and no influence on the literature review, developing model, data analysis, interpretation of the data, or decision to submit results.

We would like to thank Mr. Anthony Arthit Phonpituck, Faculty of Pharmacy, Silpakorn University, for proofreading the article.

Author Contributions

KR performed a systematic review, developed the model, and prepared the data for analysis. WT developed the economic methodology and conceptual framework of this study and the model and prepared the data for analysis. PU developed the model and prepared the data for analysis. JL performed a systematic review, developed the model, analyzed the cost-effectiveness result, and analyzed one-way and probabilistic sensitivity. All authors interpreted the results and participated in manuscript preparation.

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Conversion Therapy for Gastric Cancer with Peritoneal Metastasis

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ABSTRACT

Peritoneal metastasis in gastric cancer has a poor prognosis and is increasing in prevalence. Neoadjuvant chemotherapy is used for advanced tumors; however, surgery is generally not considered for metastatic and unresectable diseases. Recently, conversion surgery, a treatment which aims for an R0 resection following chemotherapy, has become a novel therapeutic option with better survival rates. In addition to surgery, hyperthermic intraperitoneal chemotherapy (HIPEC) leads to significant tumor reduction, but it is limited by its morbidity. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) delivers high concentrations of chemotherapy, but does not remove the tumor, making it useful mostly in palliative settings. Intraperitoneal (IP) therapy, known for its minimally invasive nature and repeatability, shows promise but requires further research. Ultimately, an integrated approach involving systemic chemotherapy, radical gastrectomy, HIPEC, PIPAC and IP chemotherapy can be used to optimize treatment outcomes of gastric cancer patients with peritoneal metastasis.

Keywords: Gastric cancer; conversion surgery; HIPEC; peritoneal metastasis (Siriraj Med J 2024; 76: 534-540)

INTRODUCTION

Peritoneal metastasis from gastric cancer is associated with an extremely poor prognosis. In recent years, there has been a notable increase in the prevalence of peritoneal metastasis, with *Koemans* reporting that the incidence rate rose from 18% in 2008 to 27% in 2017. Furthermore, the median survival duration has remained unchanged at 9.4 months over this period.[1] According to a study by *Ikoma*, among the 488 patients with gastric cancer who underwent curative gastrectomy, peritoneal metastasis was the most prevalent site of recurrence (49%).[2] Furthermore, peritoneal metastasis in gastric cancer patients was associated with lower survival rates compared to liver metastasis.[3] In Thailand, despite the fact that the majority of gastric cancers are diagnosed at advanced stages, radical gastrectomy can still yield favorable survival results, with acceptable rates of postoperative complications, particularly when an enhanced recovery after surgery protocol is followed.[4] However, once peritoneal metastasis develops, surgery cannot be performed, and a patient's prognosis significantly worsens.

Patients with gastric cancer typically undergo gastroscopy and a computerized tomography scan to determine disease stage. Diagnostic laparoscopy is particularly valuable in identifying peritoneal metastases in cases of advanced gastric cancer. According to a

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https://doi.org/10.33192/smj.v76i8.268224

meta-analysis, diagnostic laparoscopy has a sensitivity of 84.6% and specificity of 100%.[5] It has been able to alter therapeutic approaches in 8.5%–59.6% of patients and prevented unnecessary surgery in 8.5%-43.8% of cases.[6] To get the best results, diagnostic laparoscopy must be performed thoroughly and systematically, including examining the anterior abdominal wall, pelvic cavity, mesentery, small intestine, stomach, and omental bursa.[7] Diagnostic laparoscopy is particularly recommended for patients with a Borrmann type 3 or 4 tumor or when there is the presence of bulky lymph nodes.[8] Diagnostic laparoscopy also plays a crucial role in determining the appropriate chemotherapy regimen. The presence of a peritoneal nodule warrants the use of the FLOT regimen, which consists of fluorouracil, leucovorin, oxaliplatin, and docetaxel.[9] In the absence of peritoneal metastasis, a combination of fluorouracil and oxaliplatin is recommended.

Conversion therapy

The REGATTA study, a large-scale clinical trial involving patients with stage IV gastric cancer, evaluated the outcomes of combining gastrectomy and chemotherapy versus chemotherapy alone. The study included a diverse sample of patients, each with a single, incurable factor (liver, peritoneal, or paraaortic lymph node involvement). The findings revealed that combination treatment did not significantly improve survival rates compared to chemotherapy alone. As a result, palliative chemotherapy is now considered the standard of care approach for patients with stage IV gastric cancer.[10,11] However, despite this, the median survival time achieved with palliative care remains unsatisfactory.

In 1977, *Nakajima* introduced the concept of conversion surgery at Japan's Cancer Institute Hospital for patients with stage IV gastric cancer who demonstrated a complete clinical response, a partial response, or stable disease after receiving palliative care. These patients underwent gastrectomy, lymphadenectomy, and metastasectomy, resulting in a longer median survival time and an increased likelihood of achieving complete tumor removal (R0 resection).[12] Thus, conversion surgery is defined as a surgical technique designed to achieve an R0 resection following chemotherapy. It is used in cases of stage IV gastric cancer that were initially deemed unresectable or only marginally resectable due to technical or oncological challenges. This strategy presents a potentially viable option for patients with tumors that were previously considered unresectable or marginally resectable. By aiming to achieve R0 resection following chemotherapy, conversion surgery aims to improve patient outcomes and potentially increase survival rates. However, it is important to note that conversion surgery may not be suitable for all patients, as its success rate varies depending on factors such as the extent of peritoneal metastasis and a patient's response to chemotherapy.

Conversion therapy can be performed in one or more of the following methods:

- Systemic chemotherapy
- Hyperthermic intraperitoneal chemotherapy (HIPEC)
- Pressurized intraperitoneal aerosol chemotherapy (PIPAC)
- Intraperitoneal (IP) chemotherapy

Yoshida et al. identified four types of conversion therapy based on incurable factors, such as T4b lesions, non-regional lymph node metastasis, hepatic metastasis, and peritoneal metastasis.[13] He initially categorized stage IV gastric cancer patients into two groups based on the presence or absence of macroscopic peritoneal spread. Categories 1 and 2 comprised patients without macroscopic peritoneal dissemination, while categories 3 and 4 included the presence of macroscopic peritoneal dispersion. Patients with liver metastasis, distant organ metastasis or paraaortic lymph node metastasis, but without visible macroscopic peritoneal metastasis (categories 2), were categorized as marginally resectable gastric cancer. In contrast, those with visible macroscopic peritoneal metastasis (categories 3 and 4) were classified as unresectable gastric cancer. After chemotherapy, conversion surgery has shown about a 70% success rate in tumor removal in categories 1–3, but only 50% in category 4. Furthermore, the overall survival rate in all categories sees an improvement if conversion surgery and R0 resection are successful, with five-year survival rate for each group ranging from 30% to 40%. Overall, category 2 has the highest survival rate.[14]

The 2018 Chicago consensus provides guidelines on the use of conversion surgery for gastric cancer patients with peritoneal metastasis.[15] It outlines the role of conversion surgery in cases where chemotherapy is the primary treatment choice. According to the consensus, conversion surgery, including cytoreduction surgery, gastrectomy, and intraperitoneal chemotherapy, is viable if a patient's condition is stable, and they have a low peritoneal carcinomatous index (PCI). The PCI score divides the abdomen into nine regions and the small bowel into four, with scores ranging from 0 to 3 in each area. This helps surgeons assess the extent of peritoneal metastases during surgery.[16] However, patients exhibiting a high PCI score following laparoscopic intraperitoneal chemotherapy or neoadjuvant intraperitoneal and systemic

treatment, gastrectomy alone is recommended. These recommendations help medical professionals make informed decisions about the use of conversion surgery based on an individual patient's characteristics and circumstances.

Systemic chemotherapy

Systemic chemotherapy serves as an initial treatment for metastatic gastric cancer, as it can help reduce tumor size and slow down disease progression. A critical component of this treatment is identifying tumor biomarkers, which inform treatment decisions and pinpoint the most effective medication to use. Key biomarkers include Human Epidermal Growth Factor Receptor 2 (HER2), overexpression and Programmed Death-Ligand 1 (PD-L1), with a Combined Positive Score greater than five (CPS >5), and microsatellite instability (MSI).[17] The CPS method assesses biomarker expression, such as PD-L1 in cancer tissue, by combining the expression levels from both tumor cells and immune cells, which aids treatment decisions, particularly for immunotherapy.[18] These biomarkers play a crucial role in guiding targeted therapies for metastatic gastric cancer. For example, HER2-positive tumors may respond well to HER2-targeted therapies such as trastuzumab, while tumors with high PD-L1 combined positive score may benefit from immunotherapies such as pembrolizumab. Additionally, microsatellite instability (MSI) can indicate the potential efficacy of immune checkpoint inhibitors such as pembrolizumab. The anticipated inclusion of claudin 18.2 as a biomarker will further refine treatment decisions and enable personalized approaches for patients with metastatic gastric cancer. Platinum and fluoropyrimidine-based chemotherapy remain the primary systemic chemotherapy options for metastatic gastric cancer. HER2-positive patients may also receive trastuzumab. After four sessions of systemic chemotherapy, patient eligibility for conversion therapy is reassessed using diagnostic laparoscopy and computed tomography. If peritoneal metastasis persists, patients should be considered for second-line treatments: MSI-high patients are given pembrolizumab, whereas those without MSI-high status are given paclitaxel and ramucirumab. Following an additional four courses, patients are reevaluated. If carcinomatosis continues, a third line of treatment will be administered. However, if reevaluation reveals support for conversion surgery, patients may proceed with cytoreductive surgery complemented by HIPEC.

Kano reported on conversion surgery in 79 stage IV gastric cancer patients, achieving an R0 resection rate of 79.7% with a 3-year survival rate of 44.5%,[19] whereas *Beom's* study found an R0 resection rate of 56.4% among patients, with a median survival time of 26 months.[20] Recent data indicates that the efficacy of conversion treatment can achieve an R0 gastrectomy that ranges between 34.4%-75%, with a median survival time of 19.2-62 months in those who achieve R0 resection.

Hyperthermic intraperitoneal chemotherapy (HIPEC)

This technique involves administering heated chemotherapy directly into the abdominal cavity after removing visible tumors during surgery (Fig 1). The elevated temperature enhances the chemotherapy's effectiveness through increased drug activity and deeper tissue penetration. However, HIPEC's effectiveness is limited to nodules not exceeding 2.5 mm in size. HIPEC is contraindicated in patients with distant metastases, high PCI scores, or those unfit for surgery. According to a German study,[20] cytoreductive surgery combined with HIPEC can increase survival by 17%. Moreover, neither HIPEC nor cytoreductive surgery should be used in isolation; the two should be combined. *Yonemura* suggested this combined approach for patients with PCI scores less than 6.[21] The GYMMSA trial,[22] which compared chemotherapy to HIPEC surgery, observed median survival increase from 4.3 months to 11.3 months in the HIPEC group. Moreover, HIPEC surgery plays an important role in complete cytoreduction as found by Glehan in a study that showed an extension of median survival to 15 months, with an overall median survival of 9.2 months, 61% survival at one year, and 23% at 5 years.[23] A meta-analysis of 23 studies and 1,892 patients, demonstrated that HIPEC surgery led to higher survival rates at 1 year, 2 years, and 3 years compared to systemic chemotherapy, and increased median survival time by 4.67 months in the HIPEC group.[24]

At Siriraj Hospital's Department of Surgery, we treated 20 patients with gastric cancer and peritoneal metastasis from April 2013 to March 2020. HIPEC was administered using an open technique with cisplatin and mitomycin-C as chemotherapeutic agents at 42°C for 60 minutes. After one year, the overall survival rate was 73.90%, and after three years, it was 9.60%. This demonstrates that HIPEC can significantly enhance survival rates with manageable complications. However, due to prolonged duration and potential risks of the procedure, careful patient selection is imperative.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC)

Chemotherapeutic drugs delivered through PIPAC utilize pressured aerosols to enhance penetration into

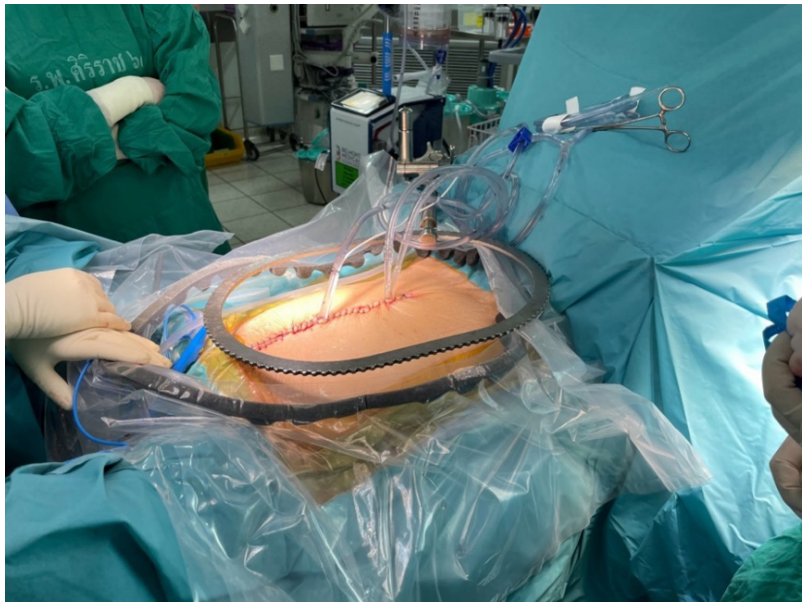

Fig 1. A demonstration of the inflow and outflow catheters connecting to the HIPEC machine.

cancer cells and optimize distribution. After laparoscopy, a specialized nebulizer device is connected to a high-pressure injector and then inserted into the peritoneal cavity via a trocar (Fig 2). Aerosols of cisplatin and doxorubicin aerosols are applied under pressure and maintained for 30 minutes. This method has been deemed safe during the procedure,[25] and its effectiveness in treating peritoneal metastases has been demonstrated with observed regression of peritoneal nodules.[26] In a systematic review by Case involving 751 patients with gastric cancer and peritoneal metastases treated with PIPAC, the median survival time ranged from 8-19.1 months, with a 1-year survival rate between 49.8-77.9%.[27] Complete response rates varied from 0% to 35%, and grade 3 and 4 toxicities ranged between 0.7% to 25% and 0%-4.1%, respectively. The advantage of PIPAC is that it enables repeated dosing and improves quality of life with minimal complications since no invasive surgery is required.

Intraperitoneal (IP) therapy

Intraperitoneal (IP) therapy involves administering drugs directly into the peritoneal cavity using a peritoneal implantable port system (Fig 3). This delivery method enables higher drug concentrations in the peritoneal fluid, leading to improved local disease control. The ability to administer repeated doses directly to the peritoneal cavity may improve the quality of life of patients with stomach cancer and peritoneal metastases. IP therapy can be used simultaneously with or after systemic chemotherapy if HIPEC surgery is not possible due to a PCI score of more than six. A high PCI score indicates significant cancer spread within the peritoneal cavity and complicates HIPEC surgery. However, IP therapy remains a viable treatment option for these patients.

Paclitaxel is often included in the IP therapy regimen due to its prolonged intraperitoneal retention, combined with intravenous paclitaxel and oral S-1. Typically, three

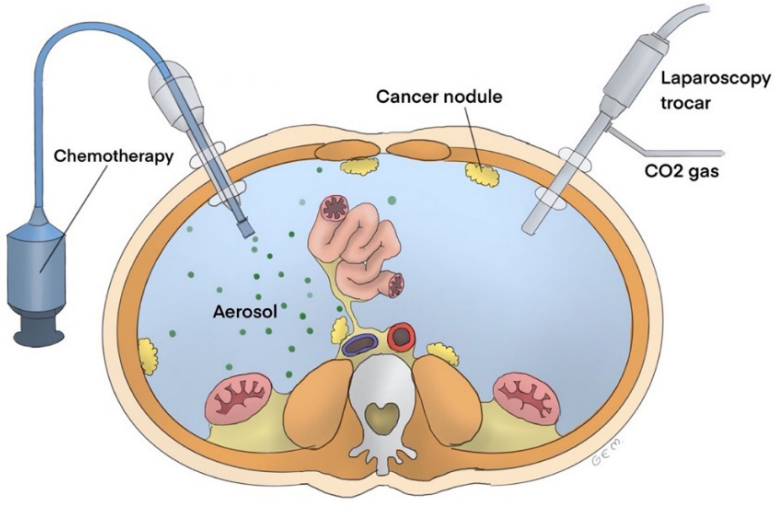

Fig 2. Schematic representation of the Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) procedure. This schematic illustrates the process of delivering chemotherapy directly into the peritoneal cavity using pressurized aerosolization.

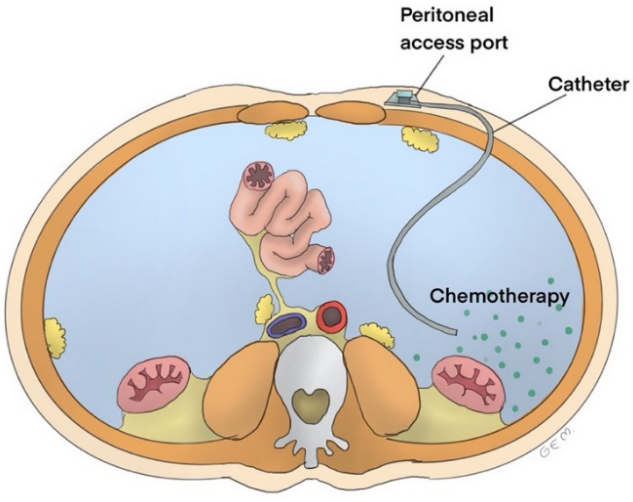

Fig 3. Illustration of catheter placement for intraperitoneal (IP) chemotherapy administration.

sessions of IP therapy precede diagnostic laparoscopy to assess peritoneal nodules. According to Ishigami's study,[28] 64% of patients who received IP therapy were able to undergo gastrectomy with an R0 resection rate of 69%, and a median survival time of 30.5 months. Additional research highlights IP therapy's effectiveness, showing a cytology negative conversion rate of 71%-97%, a median survival time of 15.1-24.6 months, and 1-year overall survival rate of 70.4%-78%.

Ishigami's Phoenix gastric cancer trial in 2018 compared the effectiveness of intraperitoneal and systemic chemotherapy for P1 gastric cancer with peritoneal metastasis.[29] The study compared intraperitoneal and intravenous paclitaxel and S-1 with intravenous paclitaxel and S-1, or S-1 and cisplatin. Despite prolonging the median survival time by 2.5 months and a reported hazard ratio of 0.72, the trial failed to show statistical significance. Future research may be able to demonstrate the statistical significance of this treatment strategy and provide better treatment options for patients with advanced gastric cancer.

The management protocol in gastric cancer with peritoneal metastasis

Each therapy has its own characteristics. HIPEC can achieve maximum elimination of cancer cells in the abdomen by delivering a high concentration of intraperitoneal drug which facilitates excellent drug penetration into the cancer cells. However, it is a one-time procedure and is linked with significant complications. It is recommended for patients with minimal peritoneal metastasis (PCI<6). PIPAC offers a high concentration of intraperitoneal drug and the advantage of being repeatable. Nonetheless, PIPAC does not eliminate gross tumor mass, and therefore, its main role is in a palliative care setting. Moreover, the procedure involves high-pressure injection of chemotherapeutic drugs, which requires a well-trained and certified PIPAC team. IP therapy allows for prolonged exposure to chemotherapeutic drugs and is repeatable. It can be used for tumor downstaging in conversion therapy or for palliative care, however, these roles have to be determined in future studies.

These methods are combined to optimize tumor reduction in gastric cancer with peritoneal metastases. The treatment flow protocol for gastric cancer with peritoneal metastasis is depicted in Fig 4. The process begins with diagnostic laparoscopy to confirm the presence of peritoneal metastases, followed by the initiation of systemic chemotherapy. A subsequent diagnostic laparoscopy assesses PCI and if it is less than 6, the patient may undergo radical gastrectomy combined with peritonectomy and HIPEC. If PCI exceeds 6, systemic treatment is maintained with a combination of PIPAC and IP chemotherapy. IP chemotherapy can also be used alongside systemic chemotherapy to enhance disease control.

CONCLUSION

Overall, the treatment for gastric cancer with peritoneal metastasis is multifaceted and depends on a patient's condition and response to different therapies. Although surgery can offer benefits to some patients, it is not the only solution. HIPEC provides substantial tumor reduction but it has limitations due to its non-repeatable nature and potential complications. PIPAC delivers a high concentration of medication directly to the peritoneum, but it does not remove the tumor. IP therapy has a longer drug exposure and can be repeated, but further research is still required to establish its role in the treatment. Ultimately, conversion surgery, utilizing a combination of systemic chemotherapy, radical gastrectomy, HIPEC, PIPAC and IP chemotherapy can be used to optimize treatment outcomes of gastric cancer patients with peritoneal metastasis.

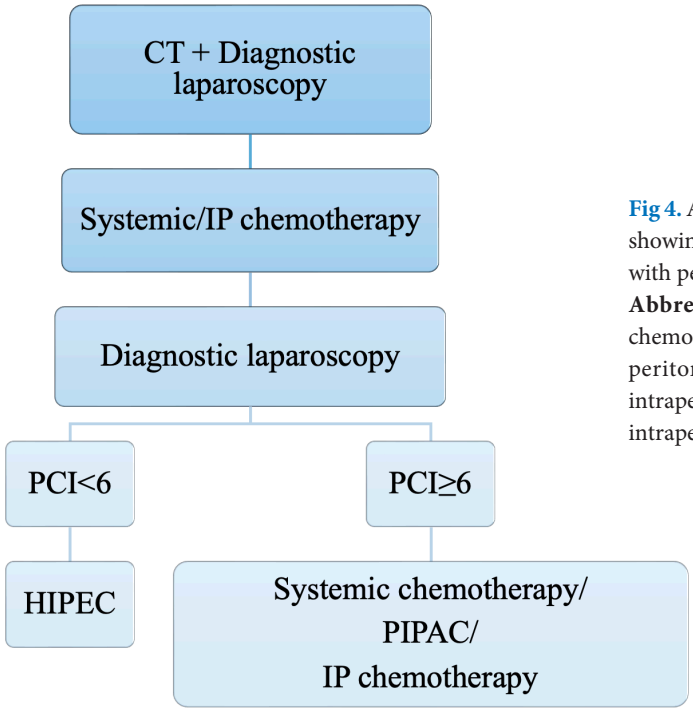

Fig 4. A flowchart based on the author's conclusions, showing the sequence of treatment for gastric cancer with peritoneal metastasis
Abbreviations: CT, computed tomography; IP chemotherapy, Intraperitoneal chemotherapy; PCI, peritoneal cancer index; HIPEC, Hyperthermic intraperitoneal chemotherapy; PIPAC, Pressurized intraperitoneal aerosol chemotherapy

ACKNOWLEDGMENTS

We would like to extend our sincere appreciation to Assistant Professor Weeraput Chadbunchachai from the Department of Surgery, Faculty of Medicine, Khon Kaen University, for his invaluable contribution to drawing Figs 2 and 3.

Author Contributions

Conceptualization: TI, AM; Data curation: TI, AM, CN; Investigation: TI, AM, TP; Methodology: TI, AM; Supervision: AM, TA, VC; Validation: TI, AM, AT; Visualization: JS, AT, CP, VT; Writing– original draft: TI, AM; Writing– review & editing: all authors.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that might have influenced the work presented in this paper.

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Effective Epidural Analgesia during Labor: A Feasible Method to Decrease Unnecessary Cesarean Deliveries in Thailand

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ABSTRACT

Thailand has reported a high rate of cesarean delivery (45%–55%), prompting global concern about an increase in cesarean delivery rates. Fear of labor pains is one of the most common reasons pregnant women opt for cesarean delivery. Labor pain is associated with cervix dilation and fetal descent into the birth canal, which is exacerbated by ischemic pain caused by uterine contraction. Modern medical and non-medical techniques have demonstrated efficacy in reducing pain and ensuring safety during labor and delivery. Neuraxial labor analgesia is a highly effective medical pain relief method but has no effect on the rate of cesarean or assisted vaginal delivery. Medication administration for pain relief during labor, using a combination of a local anesthetic and an opioid, was observed to be transmitted across the placenta to the fetus, but had no significant effects on fetal outcomes in mothers who chose epidural analgesia. There are several techniques for administering neuraxial labor analgesia that can be customized for each pregnant woman. To achieve the most wonderful feasible labor and delivery experience, effective epidural labor analgesia is a crucial technique for reducing anxiety and suffering about labor pain. It is safe, widely used world-wide, and effective. Implementing a policy to increase public and medical providers awareness and acceptance of labor pain relief, as well as establishing a safe obstetric anesthesia service provided by obstetric anesthesiologists, could improve maternal and neonatal safety while significantly lowering the rate of unnecessary cesarean deliveries.

Keywords: Cesarean delivery; labor pain; neuraxial labor analgesia; obstetric anesthesiologists (Siriraj Med J 2024; 76: 541-549)

INTRODUCTION

The global rise in the cesarean delivery rate is currently a significant concern.[1] Although the World Health Organization (WHO) does not specify an optimal cesarean delivery rate, reported cesarean delivery rates of more than 10% at the population level do not contribute to reductions in maternal and newborn mortality.[2] Thailand has reported a high rate of cesarean delivery, approximately 45%–55%.[3,4] Higher rates of cesarean deliveries are associated with an increase in adverse maternal and perinatal outcomes.[5] The Royal Thai College of Obstetricians and Gynecologists has declared that addressing this issue is a foremost concern, and they are actively advocating for policies to reduce the incidence of cesarean deliveries in Thailand.[6] Several studies conducted in Thailand[6-8] aimed to investigate the factors influencing

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https://doi.org/10.33192/smj.v76i8.268247

the preference of Thai pregnant women for cesarean delivery over natural vaginal delivery. These factors include the fear of childbirth, particularly the pain associated with labor and the uncertainty that arises during the waiting period for delivery. This preference is also influenced by safety concerns, such as underlying medical disease or advanced age, which can make vaginal delivery unsafe. Negative previous birth experiences and the belief that cesarean delivery is safer for babies, despite evidence to the contrary, may contribute to this preference. Finally, it is desirable to schedule a delivery date and time that is mutually convenient for both the healthcare professionals and the pregnant woman, rather than one related to the superstitious belief in auspicious birth dates and times.[6,7] Insufficient knowledge about the mode of delivery among Thai pregnant women may facilitate the decision to support their selection of cesarean delivery.[8]

One of the common reasons pregnant women opt for cesarean deliveries is a fear of labor pains. Historically, childbirth has been a painful experience for pregnant women. Modern medical and non-medical techniques, such as massage, controlled breathing, water immersion, focused guided imagery, and skilled labor support personnel, have proven effective in reducing pain and ensuring safety during the labor and delivery process.[9] It is thus unnecessary to endure pain indefinitely.

Labor epidural analgesia is one of the most effective medical pain relief methods recommended by ACOG (The American College of Obstetricians and Gynecologists) to support better maternal and neonatal outcomes.[10,11] The encouragement of sustainable increases in vaginal delivery rates by increasing access to safe labor epidural analgesia, supported by the establishment of the nongovernmental No Pain Labor & Delivery (NPLD) global health initiative in China, resulted in a decrease in the cesarean delivery rate and postpartum complications, such as episiotomy, postpartum blood transfusion, and newborn NICU admission.[12,13] In this article, we provide basic knowledge regarding labor epidural analgesia, also known as painless labor analgesia, to ensure that pregnant women and healthcare professionals have a greater understanding of this valuable resource.

Essential basic knowledge of labor pain[14]

There are three phases to labor: the dilation of the cervix in the first stage, the birth delivery in the second stage, and the placenta delivery in the third stage. The first and second stages of pain will manifest as distinct types of pain.

The pain experienced during the first stage of labor is visceral pain and is associated with the dilation of the cervix and fetal descent into the birth canal. This pain is characterized by various types of referred pain and cannot be specifically localized to a certain area. Sensitization of the central and peripheral pain-signal pathways is most likely the cause of its gradual amplification during labor progression. Pain sensation arising from stretching and distension in the lower uterine segment and cervix is transmitted through visceral afferent nerve fibers from the paracervical region, hypogastric nerve, and lumbar sympathetic chain and enters cell bodies located in the thoracolumbar dorsal root ganglia (DRG) at the T10-L1 level. In the late phase of this first stage, the innervation of the surface of the cervix is also transmitted to cell bodies in the sacral DRG at the S2-S4 level. The adjuvant pain is intensified by the inflammation process that arises from uterine contractions, leading to myometrial ischemia and the release of various inflammatory substances, such as potassium, bradykinin, histamine, and serotonin, which may stimulate pain.[15]

During the second stage of labor, the pain persists and is transmitted through the same activated afferent pathway. Additionally, somatic pain comes along, which is transmitted through the pudendal nerve in the vagina and perineum to enter to the spinal cord at the S2 to S4 segments. In this particular type of pain, the parturient may experience localized discomfort in a specific area (Fig 1).

Pregnant women with high levels of estrogen and progesterone hormones may experience a reduced analgesic response to opioids.[14] This phenomenon is caused by the influence of estrogen, specifically the estrogen-dependent suppression of supraspinal analgesia. However, this exclusively impacts the supraspinal μ-opioid receptor. Opioid receptors are crucial in the management of intense pain. According to the theory of opioid receptors, the μ-opioid receptor is only found in the central nervous system (spinal and supraspinal region) and is not present in peripheral nerves. For this reason, we do not combine opioids with a local anesthetic medication when doing a local infiltration. Furthermore, the k-opioid receptor is present in visceral organs. Medications that act as k-opioid receptor agonists can alleviate visceral pain. Thus, the utilization of intrathecal opioids is successful in the first stage of labor but could be less effective in the second stage.[16] This is due to their inability to effectively mitigate somatic pain, which is particularly pronounced during this stage.

Neuraxial labor analgesia

Neuraxial labor analgesia is now recognized as the most effective approach to relieve labor pain during

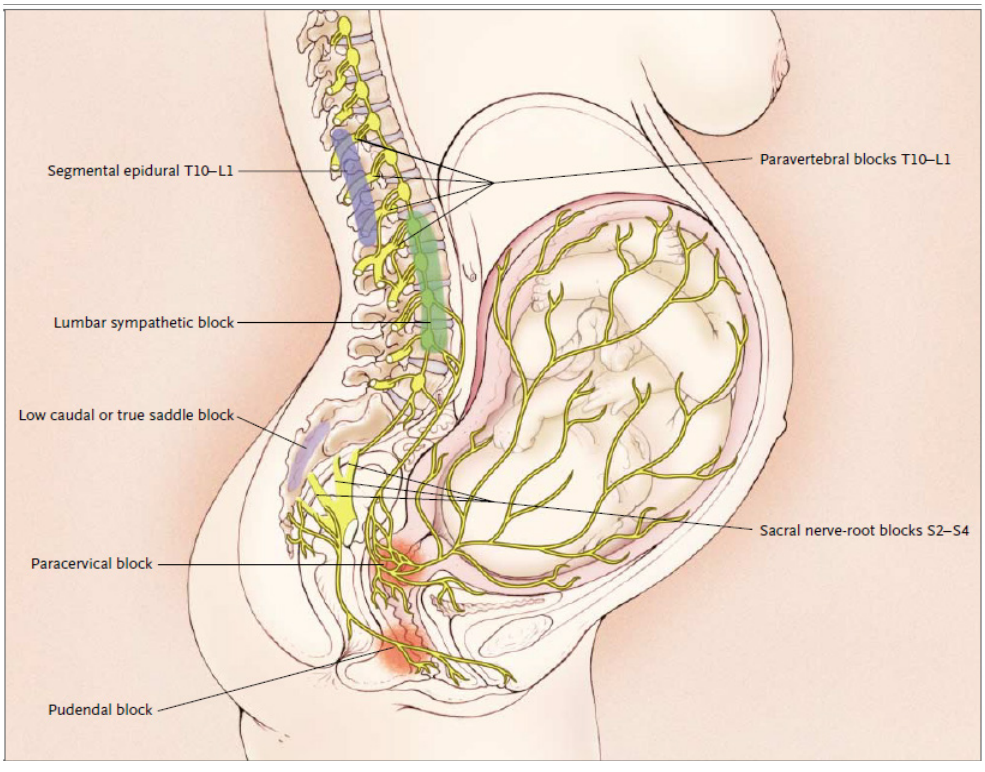

Fig 1. Pathway of labor pain. These pathways could be mapped successfully by a demonstration that blockade at different levels along this path (sacral nerve-root blocks S2 through S4, pudendal block, paracervical block, low caudal or true saddle block, lumbar sympathetic block, segmental epidural blocks T10 through L1, and paravertebral blocks T10 through L1) can alleviate the visceral component of labor pain. **Source:** Figure reprinted with permission From Eltzschig HK, Lieberman ES, Camann WR. Regional anesthesia and analgesia for labor and delivery. N Engl J Med 2003; 348:319-32.[15]

childbirth.[17] There is evidence suggesting that the utilization of neuraxial labor analgesia can significantly reduce maternal plasma catecholamine levels.[18] This decrease is a result of reduced sympathetic activity elicited by painful stimuli. Catecholamines exert effects on both alpha- and beta-adrenergic receptors, leading to a decrease in uteroplacental perfusion, and adverse effects on fetal well-being. Regarding the benefits of neuraxial labor analgesia, women typically request it to alleviate pain. Neuraxial analgesia is the ability of local anesthetic agents to block voltage-gated Na+ channels, suppressing action potentials in excitable tissues and preventing pain signals from reaching the spinal cord. Complete analgesia can be obtained by covering the levels T10 to L1 in the first stage of labor and S2 to S4 in the second stage. There are a variety of techniques for administering neuraxial labor analgesia, which can be adjusted for each individual pregnant woman (Fig 2).[19] Table 1 depicts the points to consider for each technique.

Epidural analgesia

The epidural space is a tiny cavity that can expand with the addition of fluid. It is situated outside the dural sac and contains loose connective tissue, adipose tissue, lymphatics, spinal nerve roots, and the internal vertebral venous plexus. For many previous decades, the widely used method for labor analgesia was lumbar epidural analgesia. Epidural analgesia (EPL) is a technique that involves inserting an epidural needle (Touhy epidural needle) into the lumbar epidural space using a loss-of-resistance technique, followed by threading an epidural catheter into the epidural space.[15] The purpose of this procedure is to administer pain medications, generally through intermittent bolus injections or continuous infusions of a local anesthetic drug, often combined with a lipid-soluble opioid. Lipid-soluble opioids and local anesthetics are used together to minimize unwanted side effects by enabling the use of lower doses of each agent.[18,20] Furthermore, the adjunctive containing lipid-soluble opioid contributes to the improvement of the analgesia quality by reducing latency and extending analgesic duration. Epidural analgesia is achieved approximately 15–30 minutes after injecting a bolus dose of a local anesthetic drug into the epidural space, which then spreads in both upward (cephalad) and downward (caudad) directions, affecting the nerve tissues in that area. After that, maintenance epidural analgesia is used to manage pain until delivery. In current labor

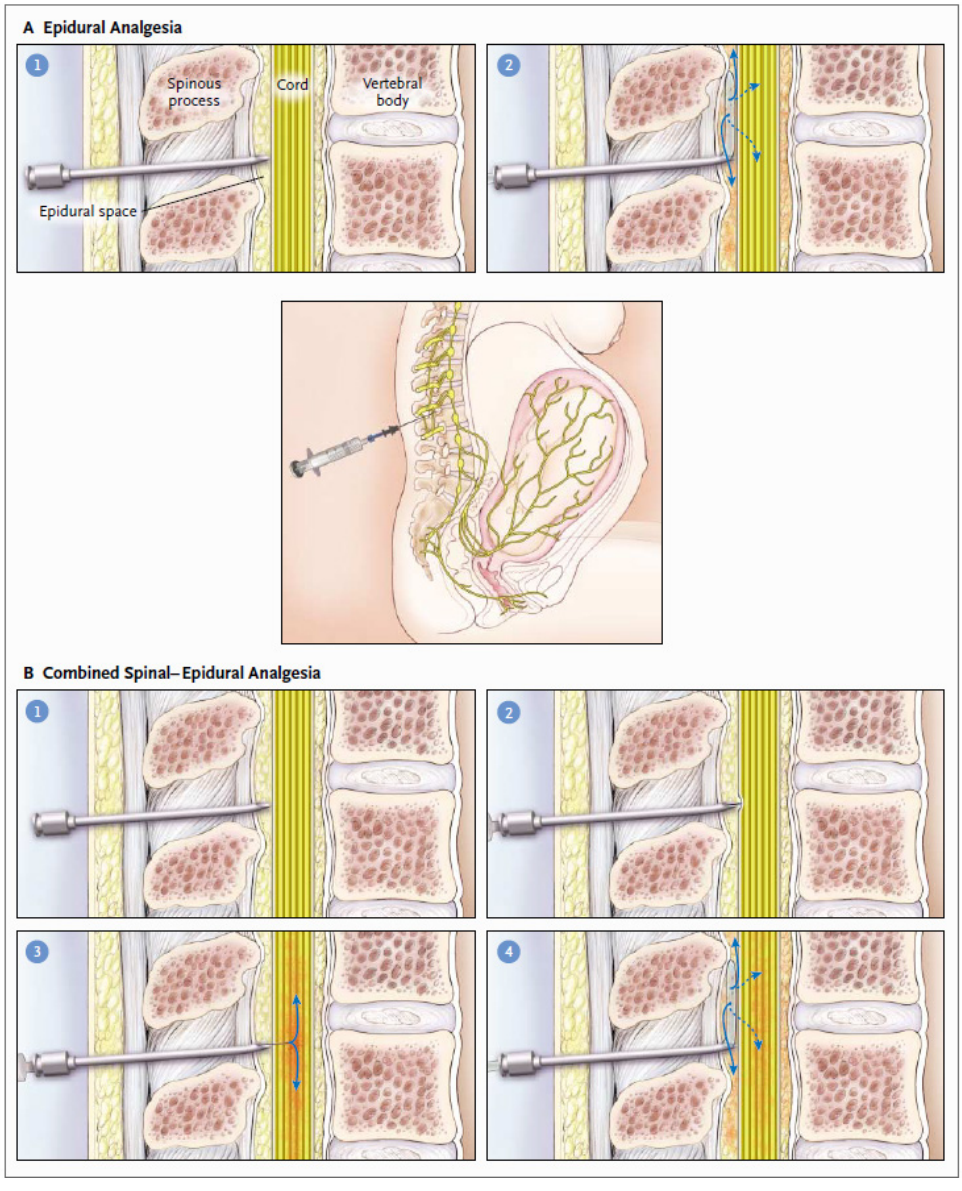

Fig 2. Techniques of epidural analgesia and combined spinal–epidural analgesia.
Panel A: Epidural analgesia; 1: An epidural needle is placed in the epidural space; 2: An epidural catheter is advanced into the space, and solutions of a local anesthetic, opioids, or a combination of the two can then be administered through the catheter.
Panel B: Combined spinal–epidural analgesia; 1: The lumbar epidural space is identified with an epidural needle; 2: A spinal needle is introduced through the epidural needle into the subarachnoid space, 3: Correct placement can be confirmed by the free flow of cerebrospinal fluid. A single bolus of a local anesthetic, opioid, or a combination of the two is injected through this needle into the subarachnoid space; 4: Subsequently, the needle is removed, and a catheter is advanced into the epidural space through the epidural needle. When the single-shot spinal analgesic wears off, the epidural catheter can be used for the continuation of pain relief.
Source: Figure reprinted with permission From Eltzschig HK, Lieberman ES, Camann WR. Regional anesthesia and analgesia for labor and delivery. N Engl J Med 2003; 348:319-32.15

analgesia, the continuous infusion of low-dose local anesthesia and opioid solutions results in more stable analgesia and reduced side effects. For breakthrough pain that the patient can treat with self-administered boluses (PCEA, or patient-controlled epidural analgesia), instead of continuing with continuous epidural infusion, programmed intermittent epidural boluses (PIEBs) with rescue pain and PCEA are becoming increasingly popular.[21,22] In certain cases, especially when using a vacuum or forceps to assist with delivery, pain can be intensified. However, an epidural catheter can be used to administer additional medication to alleviate pain during instrumental vaginal delivery.[23]

Combined spinal–epidural analgesia

The process of conducting combined spinal–epidural analgesia (CSE) seems similar to performing an epidural technique. It involves puncturing the dura mater using

TABLE 1. Key implementation aspects of commonly used neuraxial labor analgesia.

Type	Key points	Recommendation: common drugs and dosage
EPL	It will take around 15 to 30 min to feel pain relief. Sacral blockade is often unreliable. Typically, sensory rather than motor blockade. Risk of hypotension with bolus dose. May result in a slightly prolonged second stage of labor. No impact on the rate of cesarean delivery or assisted vaginal delivery.	**Mode of delivery system** PIEB + PCEA **Local anesthetic drug and opioid use** bupivacaine (0.0625%–0.125%) ± fentanyl (1.5–3 μg/mL) **Initial bolus dose** 10–15 ml of low-dose local anesthesia and opioid solutions **Maintenance of epidural analgesia** *Regimen 1* PIEB: 9 mL every 45 min (first bolus 30 min) + PCEA: 10 mL, 10 min lockout *Regimen 2* PIEB: 8 mL every 45 min (first bolus 15 min) + PCEA: 6 mL, 10 min lockout
CSE	Rapid onset of analgesia within 5–10 min. May be related with fetal heart bradycardia. Uterine hypertonus is a rarely reported condition that occurs after CSE. Risk of pruritus is higher than with EPL. Catheter placement cannot be confirmed until the effects of the spinal component have subsided. May result in a slightly prolonged second stage of labor. No impact on the rate of cesarean delivery or assisted vaginal delivery.	**Intrathecal dose** Bupivacaine 1–2.5 mg + fentanyl 10–25 μg **Maintenance of epidural analgesia** Start PIEB + PCEA without initial bolus dose
DPE	Pain relief starts more quickly than with EPL, but it starts more slowly than with CSE. Less bupivacaine is needed to achieve effective initial analgesia compared to EPL. Better sacral spread and bilateral coverage compared to EPL or CSE. Reduced incidence of maternal hypotension compared to CSE. Risk of pruritus is higher than with EPL.	Same dose as with EPL

Abbreviations: CSE: Combined spinal–epidural; DPE: Dural puncture epidural; EPL: Epidural analgesia; min lockout: A minute after a demand dose, a patient cannot press the button to receive a dose; PIEB: Programmed intermittent epidural bolus; PCEA: Patient-controlled epidural analgesia.

Source: Modified from Chau A, Tsen L. Neuraxial labor analgesia: Initiation techniques. Best Pract Res Clin Anaesthesiol. 2022;36(1):3-15.[19], Smith A, Laflamme E, Komanecky C. Pain Management in Labor. Am Fam Physician. 2021;103(6):355-64.[49], Carvalho B, George RB, Cobb B, McKenzie C, Riley ET. Implementation of Programmed Intermittent Epidural Bolus for the Maintenance of Labor Analgesia. Anesth Analg. 2016;123(4):965-71.[22]

a spinal needle inserted through an epidural needle. This allows for the administration of an opioid or a combination of an opioid and a local anesthetic into the subarachnoid space, followed by the insertion of an epidural catheter.[15] This technique was introduced to enhance the prompt onset of analgesia in comparison to epidural analgesia.[17,24] Intrathecal opioids can effectively relieve visceral pain in the first stage of labor. For somatic pain in the late first and second stages, a combination of local anesthetics is typically required. Women who present in the late active first stage with severe labor pain and need immediate pain relief can benefit from the rapid onset of CSE. Some studies have suggested a correlation between CSE and fetal heart bradycardia, which often leads to the requirement for an emergency cesarean delivery.[19,25,26] Ultimately, it is crucial to carefully evaluate the potential risks and benefits and determine the appropriate dosage for implementing this technique.

Dural puncture epidural analgesia

The dural puncture epidural (DPE) technique is a slight modification of both the standard epidural procedure and CSE, and involves puncturing the dura with a spinal needle, but without the administration of intrathecal drugs. The objective is to accurately locate the epidural space and enhance the delivery of epidural medications by puncturing the dura, allowing medications to reach the intrathecal space. This will result in a faster onset of pain relief and improve the effectiveness of the analgesia by a better sacral spread.[19,27-30] The DPE technique is particularly useful when there is a requirement for rapid-onset pain relief but a desire to avoid any potential negative effects associated with CSE.

Effect of neuraxial analgesia on the mode of delivery

Previously, obstetricians, anesthesiologists, and midwives who were unfamiliar with neuraxial labor analgesia held the belief that it increased the likelihood of cesarean delivery. This belief served as a barrier to the widespread application of effective pain relief to many women. However, numerous studies have demonstrated there is no significant difference in the incidence of cesarean delivery among women who received labor epidural analgesia compared to other methods of analgesia.[31,32] This finding was also supported by a recent study, which showed that the incidence of cesarean delivery was slightly lower in mothers who received labor epidural analgesia.[33,34] The primary determinant of the increased incidence of cesarean delivery associated with epidural analgesia is the extent of motor block achieved during the procedure, which can lead to a prolonged second stage of labor and ineffective maternal expulsive efforts.[35] For this reason, current standard practice is to use low concentrations of local anesthetics to prevent motor block while still achieving effective pain relief. Moreover, a previous belief held that the early administration of epidural analgesia during labor could lead to an increase in the incidence of cesarean delivery. According to more recent evidence and current standard practice, the timing of neuraxial labor placement can be carried out whenever the expectant mother requests it or if there is a medical indication, even if she is in early labor with cervical dilation of less than 4 cm. This will not raise the incidence of cesarean delivery.[36,37] Thus, current evidence supports that there is no increased incidence of cesarean delivery caused by neuraxial labor analgesia. The evidence regarding the heightened probabilities of instrumental delivery remains inconclusive. Several studies have suggested that using epidural analgesia with a low concentration of local anesthetic drug might result in a greater probability of instrumental vaginal delivery, consequently prolonging the second stage of labor.[31,32,38] However, other studies have found no evidence of an increased risk.[39,40]

Effect of neuraxial analgesia on fetal outcome

Medication administration for achieving pain relief during labor through a combination of a local anesthetic and an opioid has been observed to be transmitted across the placenta to the fetus, as evidenced by reports of these drugs in umbilical cord blood tests.[41] The impact of depression, particularly in relation to opioid use, was assessed using the Apgar score. However, the results did not show any significant effects on the babies of mothers who opted for epidural analgesia.[33,40] In contrast, the use of parenteral opioids for labor analgesia may result in maternal and fetal opioid-related side effects, such as lowered Apgar scores, feeding difficulties, altered thermoregulation, and possibly the requirement for naloxone administration. The babies of mothers who received epidural analgesia rarely, if ever, require naloxone administration,[42] because the small amount of opioid used during typical labor epidural analgesia results in minimal opioid transfer to the neonate. Maternal fever is associated with neonatal outcomes such as a low Apgar score and the need for immediate resuscitation. There is evidence indicating that the occurrence of maternal fever is associated with the use of epidural analgesia during labor, although the exact mechanism of this relationship remains unknown. The imbalance of body temperature that may occur with an epidural is unlikely to be caused by an infection. However, when a clinician detects maternal fever, they should investigate the source

of the infection, such as chorioamnionitis, in order to make any necessary appropriate clinical adjustment.[15,21,43]

Complication of neuraxial labor analgesia

Neuraxial labor analgesia provided by an experienced obstetric anesthesiologist is extremely safe. The incidence of severe complications is unlikely.[44] Occasionally, there may be minor and temporary side effects, such as pruritus, nausea, and vomiting, related with intrathecal opioid administration. Postdural puncture headache (PDPH) is the most common complication associated with epidural labor analgesia.[15,45] This headache is characterized by pain in both the frontal and occipital regions of the head, which worsens when sitting up and improves when lying down. It is accompanied by symptoms such as nausea, dizziness, neck pain, changes in vision, and occasionally ringing in the ears, hearing loss, or pain radiating down the arms. The condition is caused by a decrease in the volume of cerebrospinal fluid due to a leak at the site where the dura was punctured. The documented occurrence of PDPH was estimated to be approximately 0.7%–1%, with an even higher probability of developing PDPH, approximately 52%–60%, in cases involving an unintentional dural puncture occurring during the insertion of an epidural needle, rather than with a spinal needle.[45] Initial symptom management involves the use of basic pain relievers, either taken orally or administered intravenously, along with adequate hydration. It is also important to avoid sitting upright. These symptoms can be resolved spontaneously within a period of one to two weeks. Often, symptoms are intense and enduring, necessitating intervention using an epidural blood patch.

Serious complications of neuraxial anesthesia do occur but are rare. In a large survey in USA sponsored by the Society for Obstetric Anesthesia and Perinatology (SOAP) evaluating over 257,000 anesthetics, the most serious complications were high neuraxial block, respiratory arrest, and unrecognized spinal catheter migration. Incidences of these complications ranged from 1:3,000 to 1:25,000 anesthetics.[44] The majority of these complications occurred in patients with risk factors, such as obesity or replacement of epidural after a previous failed epidural. Efforts to reduce these complications include clinician education, enhanced monitoring, lower and more dilute concentrations of local anesthetics, fractionation of doses and appropriate test-dose protocols. Additional complications such as epidural abscess or hematoma were too infrequent to provide reliable estimates of incidence. Additional data can be obtained by large nationwide database or registry analysis. This is being established in USA by the American Society of Anesthesiologists (ASA). A similar effort in Thailand would add great perspective on the incidence of these complications.

Current status of access to labor epidural in Thailand

Neuraxial labor analgesia is crucial for effectively managing pain during labor and can also serve as an important motivation for pregnant women to opt for vaginal delivery. Neuraxial labor analgesia is additionally beneficially utilized to facilitate a transition to cesarean delivery, if required, during labor.[46] It has been found that countries with a high frequency of vaginal deliveries also tend to have a greater prevalence of neuraxial labor analgesia.[34] Meanwhile in Thailand, there is a high rate of performing cesarean deliveries under general anesthesia. This is mainly due to the fact that anesthetic services in Thailand are primarily provided by nurse anesthetists, who are not authorized to administer regional anesthesia. Consequently, the rate of performing neuraxial labor analgesia is quite extremely low.[46] Neuraxial labor analgesia is exclusively provided in Thailand's medical hospitals that are affiliated with universities. For demonstration, Siriraj Hospital, the largest medical institution in Thailand, has an annual neuraxial labor analgesia rate of merely 2.5%–3.4% and solely for educational purposes.[47] Which consistent with the declining trend of vaginal deliveries and the growing rate of cesarean deliveries at Siriraj Hospital.[48] The negative attitudes of obstetricians toward neuraxial labor analgesia during labor, the attitudes, fears and lack of education of patients, together with the scarcity of obstetric anesthesiologists pose significant barriers to the implementation of epidural analgesia services in Thailand.

The situation in China was previously similar to that of today in Thailand. Rates of neuraxial pain relief were low, and rates of cesarean delivery were high, although there were and still exist pockets of individual variation in these rates within each country. The reasons for these practice patterns in China were similar to the issues facing Thailand today. Namely, fear and lack of education of the potential side effects, both to mother and baby, of neuraxial analgesia, among both patients and physicians alike. In addition, lack of physician manpower resources to provide neuraxial analgesia. In response to this, an educational effort was begun in China called "No Pain Labor and Delivery" (NPLD).[12] This was a large effort to provide education to both patients and clinicians regarding the safety of neuraxial analgesia. NPLD efforts included institution of written protocols for neuraxial analgesic techniques, goal-oriented and evidence-based educational programs, and institution

of appropriate safety checklists. The NPLD program has resulted in favorable results in China with regard to both maternal and neonatal outcomes.[13] Rates of neuraxial analgesia have increased, and this has been associated with a decrease in cesarean deliveries as well as fewer NICU admissions for the babies.

CONCLUSION

The implementation of centralization in large hospitals with sufficient human resources is an essential goal in ensuring the provision of safe care to women during pregnancy and childbirth. This concept plays a significant role in establishing obstetric anesthesia services to promote patient comfort, facilitate vaginal delivery, and minimize the occurrence of unnecessary cesarean deliveries. Multidisciplinary teams, consisting of obstetricians, anesthesiologists, and nurses, should collaborate to make this goal a reality. Many women find that the relief of pain is the best way to increase their enjoyment of childbirth. To achieve the most wonderful feasible labor and delivery experience, effective epidural labor analgesia is a crucial technique for reducing anxiety and suffering from labor pain. It is safe, widely used world-wide, and effective. Implementing a policy to raise public and medical providers awareness and acceptance of labor pain relief and establishing a safe obstetric anesthesia service provided by obstetric anesthesiologists can enhance maternal and neonatal safety and effectively reduce the rate of unnecessary cesarean deliveries.

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A Reciprocal Relationship between Oxidative Stress, Antioxidants, and Cancer: A Review

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ABSTRACT

Oxidative stress is a defense mechanism that occurs when there is an imbalance between the production of reactive metabolites and free radicals and the antioxidants' ability to eliminate them. Reactive metabolites are free radicals referred to as oxidants or reactive oxygen species (ROS). Cells are harmed by this imbalance, which may influence the entire body. When the intra- and extracellular environmental circumstances in cells change, ROS is essential for stimulating the corresponding signaling pathways. All aspects of carcinogenesis, including prevention and treatment, are tightly associated with reactive species, particularly ROS. Numerous tumor suppressor genes and proto-oncogenes are deregulated by ROS, which also modify several cellular signaling pathways. However, most chemotherapy drugs and even radiation therapy dramatically raise the ROS concentrations in the tumor microenvironment. Antioxidants cause programmed cell death, which is used in cancer treatment; yet people receiving chemotherapy benefit from antioxidants. Nevertheless, the exact processes underlying this anticancer action remain unclear. Many studies carried out in laboratories and on animals revealed high concentrations of exogenic antioxidants, that inhibit the forms of free radical injury linked with the formation of cancer. There haven't been many human clinical trials looking into the potential of dietary supplementation to reduce the risk of cancer development or death. Since there have been studies on the advantages and downsides of antioxidants in the treatment of cancer, several considerations need to be deemed before administering antioxidant supplements. In conclusion, little is known about the mechanism underlying antioxidant effect in cancer treatment.

Keywords: Nutritional supplements; antioxidants; anticancer agents; oxidative stress; ROS (Siriraj Med J 2024; 76: 550-556)

INTRODUCTION

A class of chemicals known as reactive species are produced as byproducts of several metabolic events that occur in eukaryotes. They are known to control the expression of numerous genes and signal transduction pathways. Oxidative stress is a persistent threat to cells, resulting from several endogenous and exogenous sources.[1] On the other hand, persistent inflammation brought on by high levels of oxidative stress can develop into several diseases, including cancer, diabetes, neurological problems, and cardiovascular diseases. Because cancer cells proliferate and have higher metabolic rates, they require a higher redox level. By encouraging the transition from epithelial to mesenchymal tissue, invasion, proliferation, and angiogenesis, a moderate increase in ROS expression is linked to cancer stemness. Human volunteers were used to explore the effects of zinc, beta carotene, selenium, alpha tocopherol, tocopherol, and vitamin C as dietary antioxidant supplements. These investigations have produced a range of results. Certain preclinical studies have demonstrated that antioxidants boost tumor progression and metastasis. The cancer-bearing mice's supplements improved the tumor cells' capacity to metastasize and disseminate.[2] Reactive oxygen

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Received 8 April 2024 Revised 22 April 2024 Accepted 25 April 2024
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https://doi.org/10.33192/smj.v76i8.268647

species (ROS) are produced by endogenous sources, including respiratory chain action products in inner mitochondrion and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase nitrogen oxides (NOX) enzymes on the plasma cell membrane.[3] The primary site of ROS in eukaryotic cells, where the majority of O2 generation occurs, are mitochondria. Therefore, this review will go over how ROS affects how antioxidants work against cancer after being administered in previous research. A tiny number of electrons from the electron transport chain escape during oxidative phosphorylation, creating superoxide radical (O2-).[4] By facilitating the production of internal and extracellular O2-from O2 and NADPH, NOX enzymes serve as an additional source of O2.[5] The NOXs family, which consists of Duox1/2 and Nox1–Nox5, is typically composed of seven members, each of whom is an expert in generating a specific type of ROS. Nox-1, Nox-2, Nox-3, and Nox-5 only generate O2, but Nox-4 and Duoxes specifically produce H2O2 (hydrogen peroxide) (Fig 1).[6]

Origin of ROS and Its Function

Exogenous sources such heavy metals, cigarette smoke, ozone, ionizing radiation, and medicines can create reactive oxygen species (ROS). Reactive oxygen species can be created by cigarette smoke because it contains a lot of organic particles like superoxide and nitric oxide that are considered as oxidants or free radicals. Two impacts of ozone exposure are fatty peroxidation and the recruitment of neutrophils into the pseudo stratified epithelial tissue of the airways.[7] One of the carcinogens that is present at every stage of the carcinogenesis process is ionizing radiation. the generation of ROS from water radiolysis, which damages deoxyribonucleic acid (DNA) and causes gene mutations and cancer. Antineoplastic medications are examples of therapeutic medicines that can produce ROS. ROS are produced in large quantities by some drugs, including cisplatin and adriamycin, which harm DNA and kill cells.[8] There was also an exogenous ROS generated by the heavy metal transition (Cd, Hg, Pb, Fe, As). These drugs enter the body through a number of different channels, where they metabolize or break down to produce free radicals.[9] ROS can function as either beneficial or harmful species. Due to their involvement in a variety of biological processes in living things, they are an essential component. They contribute to preserving homeostasis by acting as messengers in cell signaling at a low level. On the other hand, excessive ROS production and accumulation in cells results in detrimental effects known as oxidative stress.[10] Oxidative stress is a condition in which one side produces too many reactive oxygen species (ROS) while the other side lacks antioxidants. The balance status of prooxidant to antioxidant activities in eukaryotes is disrupted by this imbalance. Overexposure to ROS can cause oxidative damage to proteins, lipids, DNA, and cell membranes, which can hinder the proper functioning of these constituents.[11] Lipid peroxidation, a process that damages cell membranes and lipoproteins, is brought on by an excess of hydroxyl radicals and peroxynitrite. As a result of this reaction,

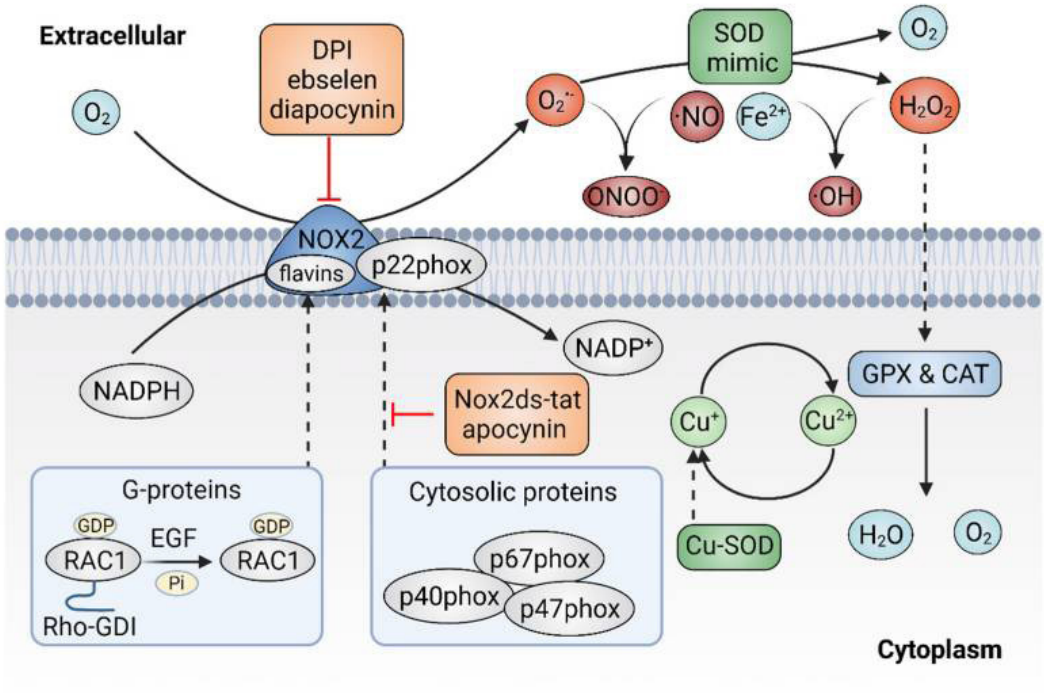

Fig 1. Targeting ROS using enzymatic antioxidants. Superoxide (O2•–) generation can be inhibited by inhibitors of plasma membrane NADPH oxidase 2 (NOX2), and O2•– may be dismutated into hydrogen peroxide by mimicking superoxide dismutase (SOD) (H2O2).[6]

cytotoxic and mutagenic conjugated diene molecules and malondialdehyde (MDA) are produced. Furthermore, structural alterations and a decrease in enzyme function are caused by damage to the proteins. Oxidative damage to DNA can result in a variety of oxidative DNA lesions.[12] Thus, emphysema, hemochromatosis, organ transplantation, acquired immunodeficiency syndrome, peptic ulcers, hypertension, pre-eclampsia, and neurological diseases have all been associated with oxidative stress. Moreover, lupus erythematous, heart disease, stroke, and adult respiratory illnesses syndrome are examples of ischemia diseases.[13]

ROS and Carcinogenesis

A normal cell can become a malignant neoplastic cell through a series of cellular and molecular alterations caused by both endogenous and exogenous stimuli during the multistage process of cancer. ROS are regarded as carcinogenic since they have been linked to the development, spread, and metastasis of cancer. Redox imbalance in cells is a typical occurrence in cancer cells as opposed to normal cells, and ROS can lead to this imbalance. It is widely acknowledged that oxidative DNA damage is the root cause of cancer growth.[12] In this case, ROS can directly damage DNA during carcinogenic transformation. For example, they can catalyze the mutation of the altered DNA base 8-hydroxy-2' -deoxyguanosine (8-OHdG), which results in the development of tumors.[14] Elevated ROS levels cause oxidative DNA damage, which can result in replication mistakes, base modification, base oxidation, single or double strand breaks, DNA cross-linking, and ultimately, cell malfunction and death. As a result, the altered DNA will cause genomic instability and, ultimately, cancer if it is not corrected. Increased reactive oxygen species (ROS) can alter several signaling paths and activate transcription aspects, such as nuclear kappa B factor (NF-kB) and nuclear factor erythroid 2-related factor 2 (Nrf2). This may result in altered gene expression patterns that promote the spread of cancer.[15]

Can Antioxidants Outcompete Cancer Cells?

Antioxidants:

Chemicals known as antioxidants interact with free radicals and neutralize them to stop them from doing harm. Another name for antioxidants is "free radical scavengers". The natural antioxidant defense system of the human body helps to both avoid and counteract oxidative stress. Antioxidants can mitigate the harmful effects of oxidants by dissolving them before their contact with biological targets. This stops highly reactive chemicals from releasing oxygen or starting chain reactions.[16] When a material is easily absorbed by the body, inhibits or suppresses the generation of free radicals, or chelates metals, it is considered optimally antioxidant. It should also function in the membrane and aqueous domains and positively affect gene expression.[17]

Antioxidant Classifications:

Different classes of antioxidants are known:

§ Enzymatic and non-enzymatic antioxidant systems are two categories into which antioxidants can be divided. Superoxide dismutase (SOD), catalase, and glutathione-dependent enzymes are examples of enzymatic antioxidants.[13] Non-enzymatic antioxidants can be further classified into nutritional and metabolic antioxidants. The body produces endogenous metabolic antioxidants, which include bilirubin, lipoic acid, coenzyme Q10, melatonin, Glutathione (GSH), arginine, and uric acid. Sources of nutritional antioxidants include exogenous dietary supplements and dietary consumption of nutrients like vitamin C, E, and polyphenols.[18] Although consuming these substances may increase endogenous activity, they do not counteract free radicals. Endogenous antioxidants play a crucial role in preserving the best possible functioning of cells. However, the endogenous antioxidants are insufficient under some circumstances that encourage oxidative stress. Therefore, exogenous antioxidants must be provided to sustain good cellular activities.[19]

§ Antioxidants can also be grouped based on their molecule size. The small-molecule antioxidants like glutathione (GSH), vitamin E, vitamin C, and carotenoids neutralize and eliminate ROS through a radical scavenging process. Large-molecule antioxidants such as Catalase (CAT), Superoxide dismutases (SOD), and glutathione peroxidase (GSH-Px), as well as sacrificial proteins like albumin, most probable scavenge ROS and block them from harming other fundamental proteins.[20]

§ Antioxidants can also be categorized according to how soluble they are in lipids or water. Lipid-soluble antioxidants and water-soluble antioxidants are the two groups into which they are divided. Water-soluble antioxidants, like vitamin C, are in fluids inside the cell like the cytoplasmic matrix, while lipid-soluble antioxidants, including carotenoids, vitamin E, and lipoic acid, are basically located in plasma cell membranes.[21]

Numerous studies have provided more and more evidence that flavonoids, including daidzein, flavanone hesperetin, and many others, have anticancer properties. These properties include modulating the activities of ROS-scavenging enzymes, cell cycle arrest, inducing apoptosis, autophagy, and suppressing the proliferation and invasiveness of cancer cells.[22] In the hepatocellular

cancer cell line HCCSK-HEP-1, for example, daifzein induced apoptosis by upregulating and downregulating anti-apoptotic proteins Bcl-2 homologous antagonist killer (Bak). As a result, cytochrome c was released from the mitochondria, and caspases 3 and 9 were involved in the subsequent apoptotic cascade.[23] Furthermore, as the paths behind this antineoplastic effect are still not entirely known, more research is required. Furthermore, similar to gallic acid, phenolic compounds have a potent anticancer effect on cancer cells. Their capacity to bring cell cycle stoppage, decrease oncogenic signaling cascades that control angiogenesis, cell proliferation, and apoptosis, change ROS levels, enhance tumor suppressor proteins like p53, and boost the facility to differentiate and convert into normal cells are the primary causes of these.[24]

As a possible phenolic chemical combination to be employed with cisplatin, gallic acid was chosen. Also known as 3,4,5-trihydroxybenzoic acid, gallic acid is a polyhydroxy phenolic complex that is obtained from many natural substances such as green tea, bananas, strawberries, grapes, and numerous other fruits. It is a naturally occurring molecule.[25] It was discovered and extracted from plants for the first time in 1786 by Carl Wilhelm Scheele, a well-known Swedish chemist. Following his discovery, other researchers conducted additional investigations and reports on the molecule and its derivatives, which helped to clarify its features and mechanism. It has been observed that gallic acid exhibits anticancer properties in a variety of cancer cell types, including HeLa.[26-28] Additionally, there are many natural plant-based sources of gallic acid. As a result, it was selected as a potential treatment for HeLa cells in conjunction with cisplatin to enhance the chemotherapeutic action of the platinum substance used to treat cancer.[29,30]

Many previous works have discussed antineoplastic activity in a range of tumor cells, including those from the esophagus, stomach, colon, breast, prostate, lung, and utmost notably, cervical carcinoma.[10,31] Earlier studies have shown that treatment of tumor cells with gallic acid alone can induce a potent form of apoptosis, characterized by nuclear condensation, blebbing of the plasma membrane, release of cytochrome c from the mitochondria into the cytosol, and activation of caspase-3.[32] Most previous studies conducted in labs and on animals demonstrated high concentrations of exogenic antioxidants, which obstruct the types of free radical damage related to the development of tumor. Human experiments were then done to explore the potential benefit of dietary supplementation in lowering the risk of cancer development or mortality. Many studies, involving case-control and cohort studies and other observational research, have been conducted to investigate the possibility of a relationship between the use of dietary antioxidant supplements and a decreased risk of cancer in humans. Overall, these studies have shown contradictory results because biases that could affect study outcomes have not been well controlled for.[33] Since they may address the biases found in observational research, randomized controlled clinical trials are thought to give the best and most dependable evidence of the impacts and/or benefits of a health-correlated intervention. Human volunteers were used to study the effects of dietary antioxidant supplements containing zinc, beta carotene, selenium, alpha tocopherol, tocopherol, and vitamin C.[34-37]

Inclusive, the randomized controlled clinical trials yielded no clue supporting the use of dietary antioxidant supplements in the primary prevention of cancer[38] whether consuming antioxidant supplements during neoplastic therapy changes the usefulness or diminishes the toxicity of medications has been the subject of numerous randomized controlled trials, some of which have involved relatively small patient numbers.[39] Some studies revealed that patients receiving antioxidant supplements during cancer therapy had worse outcomes, particularly if they were smokers, even though the results of these trials were varied. Antioxidants have been shown in certain preclinical investigations to enhance the growth and metastasis of tumors in animals having tumors as well as the capacity of circulating tumor cells to spread.[40-42] Some researchers complain that the usage of antioxidants must be in preventive doses which give a more beneficial effect on ROS while usage in therapeutic doses may increase ROS as illustrated in (Fig 2).[14]

Since oxidative stress is a well-established feature of cancer, antioxidants should be able to significantly reduce the incidence and progression of cancer.[43] Even though several antioxidant therapy approaches have been investigated and some are currently in clinical trials, their effectiveness has not been determined. The following factors hinder antioxidants' ability to fight cancer:

- Although complicated in vivo settings may alter antioxidants, most studies use pharmaceutical dosages rather than dietary ones based on in vitro investigations.[44]
- Antioxidants may exhibit unequal distribution among distinct tissues, and in certain instances, their limited bioavailability and bio-accessibility may impede their efficaciousness.[45]
- Depending on their concentration and oxygen pressure, certain antioxidants might show either pro-oxidant or antioxidant characteristics.[46]

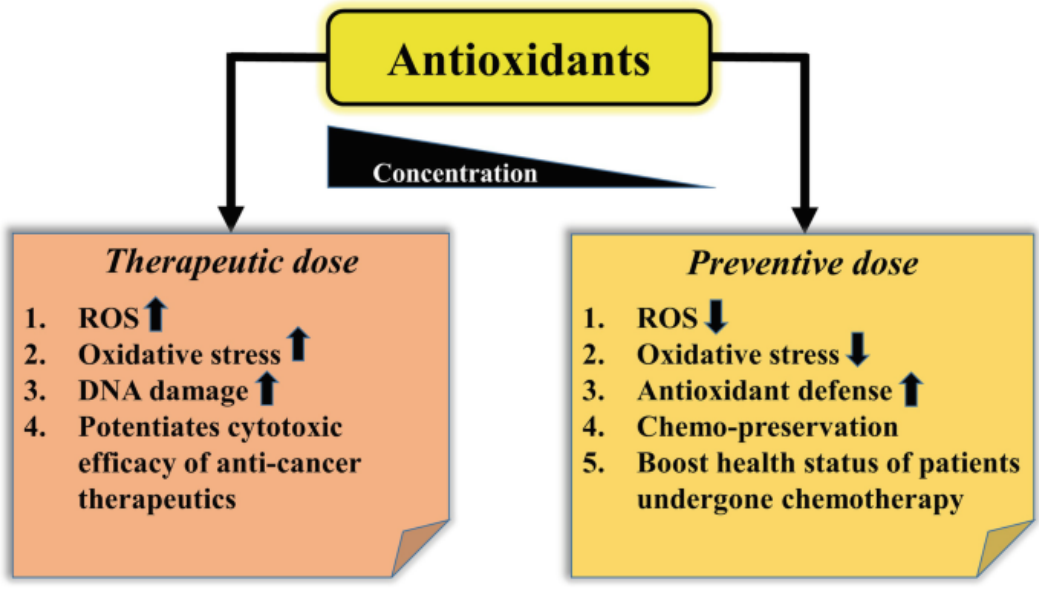

Fig 2. Comparison of therapeutic versus preventive dose effect of antioxidant in carcinogenesis.[14]

These variables dictate the specific effects of the additional antioxidants. Furthermore, most chemotherapeutic medications cause oxidative stress and produce significant quantities of ROS. Antioxidant therapy for cancer patients may potentially have the opposite effect on the cell death caused by chemotherapy drugs.[47]

As was previously mentioned, several antioxidants did not appear to work well in clinical situations. Since endogenous antioxidant enzymes or antioxidants account for the majority of antioxidant capacity, we propose that treating cancer patients with mild pro-oxidants to boost antioxidant activity may be a beneficial strategy. But further study is needed to fully understand the biochemical underpinnings of this, and long-term intervention monitoring is necessary. Developing new therapeutic drugs that may be useful in the prevention and treatment of cancer will be made easier by a better knowledge of these pathways. Thus, until further research can demonstrate the benefit of antioxidant supplements, cancer patients should take them with care.

CONCLUSION

Reactive oxygen species (ROS) excess can oxidatively damage proteins, lipids, DNA, and cell membranes, compromising their proper function. ROS overproduction during an antioxidant deficiency causes oxidative stress and upsets the equilibrium of prooxidant/antioxidant processes in living things. A small number of in vitro investigations using polyphenolic compounds produced encouraging findings about the antioxidant's ability to slow the growth of cancer cells. However, inconsistent outcomes were obtained in other animal and laboratory experiments. Preclinical experiments recorded similar observations. Studies have shown that the proliferation of cancer cells following antioxidant treatment varies depending on a few aspects, including the type of cancer and the drugs utilized.

Funding

None declared.

Conflict of interest

None declared.

Author Contributions

Concepts, Design, Definition of intellectual content, Literature search, Clinical studies, Experimental studies, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review and Guarantor were done by Khalida I. Noel.

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