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MONTHLY

ORIGINAL ARTICLE REVIEW ARTICLE

The Outcomes of Peripherally Inserted Central Catheter (PICC) Insertion in Pediatric Patients at Siriraj Hospital

Objective:

This study aims to demonstrate the outcomes of PICC insertion and management in pediatric patients by the **Anesthesia Line Service Team (ALiST) at Siriraj Hospital.**

Materials and Methods:

- IRB approval
- Retrospective chart review

124 pediatric patients

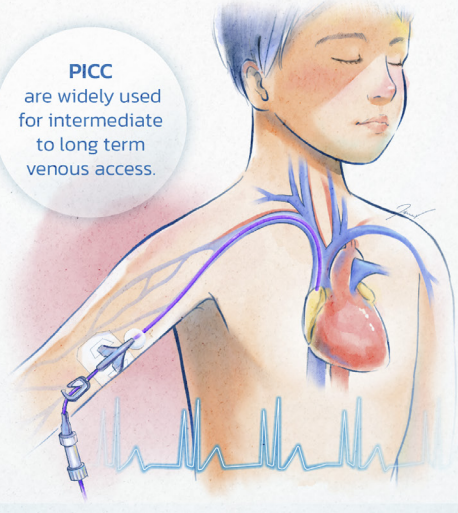
65 Girls 59 Boys

AGE 3 month – 15 years old

THE PRIMARY OUTCOME
- Success rate
- Acute complication rate

OTHER DATA
- Patient characteristics
- Type of catheter
- Reason for PICC removal and complications

PICC are widely used for intermediate to long term venous access.



Results:

96.92% Success rate

All use ultrasound guided technique

NO acute complications

39.5% under IV sedation

70.97% use PICC until no longer need

4.03% accidental removal

1.61% patient non-adherence

26.6% under general anesthesia

8.06% problems with catheter

8.06% catheter related infection

Conclusion:

Our research demonstrates a notably high rate of successful PICC placement among pediatric patients, with data indicating a minimal occurrence of complications and an extended duration of catheter usage.

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Sleep Habits and Behavioral Problems in Preschool-aged Children with ADHD

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ABSTRACT

Objective: This study aimed to investigate the relationship between sleep habits and behavioral problems in preschool-aged children with ADHD.

Materials and Methods: A cross-sectional study was conducted in a child developmental clinic at Siriraj Hospital between October and December 2023. Parents of children aged 4-6 years with ADHD completed the Children's Sleep Habits Questionnaire (CSHQ) and the Strengths and Difficulties Questionnaire (SDQ). Descriptive analysis, Pearson correlation, and multivariate linear regression analysis were used to examine the association between sleep habits and behavioral problems.

Results: This study recruited 80 preschoolers with ADHD and 75% were boys. The mean total CSHQ score was 43.76 ± 7.38 and 40% of the participants had sleep problems. 31.3 % had clinically significant behavioral problems. The most common behavioral problems were hyperactivity (33.8%), emotional problems (16.3%), and conduct behavior (10%). More sleep disturbances were highly correlated with all behavioral problems in SDQ, with a Pearson correlation between 0.78 and 0.90. After multivariate regression analysis, the total CSHQ score remained the strongest predictor of all domains of behavioral problems in preschool-aged children with ADHD ($p < 0.05$).

Conclusion: More than 1/3 of preschool children with ADHD were affected by sleep disturbances. Furthermore, sleep problems in these children can contribute to significant behavioral problems. Therefore, the treatment of ADHD in preschoolers should always include the management of sleep disturbances.

Keywords: ADHD; preschool children; behavioral problems; sleep disturbances (Siriraj Med J 2024; 76: 116-124)

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood. Its symptoms include inattention and/or hyperactivity-impulsiveness, among which these symptoms are more manifested than those of individuals with comparable development levels. ADHD symptoms cause behavioral problems, inappropriate social interaction, and academic difficulties in the long term.[1] According to the Fifth Edition Diagnostic and Statistical Manual (DSM-5), ADHD can be diagnosed from the preschool period.[2] In current pediatric practices, early detection of ADHD in preschool children is essential to provide early treatment to reduce the severity of symptoms and the negative consequences after entering primary school.[3] A study conducted by Addanki in 2023 found that the prevalence of ADHD among preschool children was approximately 8%, accounting for almost a quarter of children diagnosed with ADHD at all ages.[4]

Sleep problems were shown to be more common in children with ADHD (50%) than in children without ADHD (25%).[5] Poor sleep quality and delayed bedtime can lead

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to fatigue during the day and affect mood, concentration, behavior, and physical health. Many studies have reported an association between sleep problems and increased severity of ADHD symptoms or behavioral problems in school-aged children with ADHD.[6,7] For specific sleep problems in preschool children with ADHD, only a study by Stickley (2021)[8] found that the prevalence of sleep problems in these children was as high as 83.6%. The most common sleep problems in these children included awakening at night (59.6%), nightmares (29.9%), and snoring (22.6%).[8] However, there is no study to determine the relationship between sleep problems and behavior problems in preschool children with ADHD. Therefore, this study aims to identify the association between sleep habits and behavior in preschool children with ADHD to narrow the knowledge gap and increase awareness of the importance of quality sleep in these children.

MATERIALS AND METHODS

Study design and population

This was a questionnaire-based cross-sectional study among preschool children aged 4-6 years diagnosed with ADHD who received treatment at the child development clinic at Siriraj Hospital between October and December 2023. An estimate of the lowest correlation between sleep problems and behavioral problems was used in school-age children with ADHD[9] to calculate the number of participants in this study, and the type I error of 5% and the statistical power of 80% were determined. In this study, we calculated a sample size of 80 children. Participants who had co-occurring developmental conditions such as global developmental delay and autism spectrum disorder were excluded.

Data collection

This study protocol was approved by the Siriraj Institutional Review Board (COA no. Si 719/2023 (IRB3)). Caregivers of eligible participants were recruited and informed about this study. They completed paper questionnaires after giving their informed consent. In this study, the Children's Sleep Habit Questionnaire (CSHQ) and the Strengths and Difficulties Questionnaire (SDQ) were used.

Measurements

Demographic information form

Demographic and clinical data from the participants were recorded in this form. A review of the participant's medical record and the evaluation of his attending physician provided his information, including his sex, age, type and severity of ADHD, comorbidities, and treatment modalities he received. Sleep data collected from participants included bedtime, wake-up time, and total sleep duration, defined as nighttime sleep duration excluding the time spent waking up at night. Using the DSM-5 criteria, attending physicians classified the severity of ADHD symptoms as 'mild', 'moderate' or 'severe' based on behaviors associated with ADHD and its effects on social functioning and the learning process.[2]

The Children's Sleep Habit Questionnaire, Thai version (CSHQ-Thai)[10]

The CSHQ-Thai version was developed to assess the characteristics and problems of sleep in children aged 4-10 years. This questionnaire has 33 questions to examine sleep problems in 8 domains: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, parasomnias, sleep-disordered breathing, and daytime sleepiness. Caregivers were required to rate the frequency of their child's sleep habits on a 3-point Likert scale (ranging from 'often' (5-7 times per week) = 3, 'sometimes' (2-4 times per week) = 2, and 'rarely' (0-1 times per week) = 1). A total score greater than 41 points is considered to have sleep problems. This tool has strong internal consistency (Cronbach's alpha coefficients = 0.83).

Strengths and Difficulties Questionnaire, parent rating - Thai version (SDQ-parent rating)[11]

SDQ is a questionnaire to detect positive and negative behaviors in children and adolescents aged 4-16. This questionnaire, with a total of 25 items, is evaluated by caregivers and divides behaviors into five aspects: emotional symptoms, hyperactivity, conduct problems, peer relationship problems, and prosocial behaviors. Each behavior has five questions related to that behavior, answered on a 3-point Likert scale: 0 = 'not true', 1 = 'somewhat true', and 2 = 'definitely true'. The four behavioral domains of hyperactivity, emotional symptoms, conduct problems, and peer relationship problems were then used to calculate the overall difficulty score. Higher total difficulties scores indicate more emotional and behavioral problems. Our study used standard reference values developed by the Department of Mental Health, Ministry of Public Health, Thailand, which established cutoff scores to identify significant overall emotional/behavior difficulties and each problematic behavior. Children who have a total difficulty score greater than 16 are considered to have a clinically significant impairment of general emotional and behavioral problems. Children were considered to have problematic behaviors in each SDQ domain when they had an emotional problem score

greater than 5, a conduct problem score greater than 3, a hyperactivity score greater than 6, a peer relationship score greater than 3, and a prosocial behavioral score less than 5. SDQ had an overall Cronbach alpha internal consistency of 0.7, exhibiting a sensitivity and specificity of 0.63 and 0.95, respectively.

Statistical analyses

IBM SPSS version 25.0 (SPSS Inc., Chicago, USA) was performed for all analyzes. Descriptive statistics were used for the demographic characteristics of the participants, the prevalence of sleep disturbances, all CSHQ domain scores, the prevalence of behavioral problems, and all SDQ domain scores. The associations between the CSHQ score and the SDQ score were explored using Pearson's correlation. Multivariate linear regression analysis was used to analyze the relationship between sleep and behavioral problems by eliminating all potential confounder variables. Statistical significance was set at $p < 0.05$.

RESULTS

Demographic characteristics

As shown in Table 1, 80 preschool children with ADHD were recruited into this study. The average age of the participants was 5 ± 0.61 years and 75% were boys. More than two-thirds of the participants (67.5%) were of the hyperactive and impulsive type, and nearly one-third (32.5%) were of the combined type of ADHD symptoms. Half of the participants had mild ADHD symptoms and the other half had moderate to severe symptoms. In addition to the behavioral modification and parental management training received by all participants, 52.5% received concomitant pharmacotherapy, such as methylphenidate (25%) and risperidone (27.5%). None of the participants in this study had any other disease.

Sleep habits and sleep disturbances

More than half of the study participants (53.8%) went to bed between 7 and 8 pm, and 5% went after 10 pm, while most of the children (62.5%) woke between 7

TABLE 1. Demographic characteristics and sleep practices of preschool-age children with ADHD

Demographic characteristics	Descriptive results
Sex, boy (%)	60 (75)
Age[a], years	5 (0.61)
ADHD type, n (%)	
Hyperactive type	54 (67.5)
Combined type	26 (32.5)
Severity of ADHD, n (%)	
Mild	40 (50)
Moderate to severe	40 (50)
Pharmacological therapy, n (%)	
Methylphenidate	20 (25)
Risperidone	22 (27.5)
Sleep practices	
Bedtime, n (%)	
7:00 – 8:00 PM	43 (53.8)
8:01 – 9:00 PM	12 (15)
9:01 – 10:00 PM	21 (26.3)
10:01 – 11:00 PM	4 (5)
Wake-up time, n (%)	
6:00 – 7:00 AM	30 (37.5)
7:01 – 8.00 AM	50 (62.5)
Total sleep duration[a]	11.04 (1.57)

Data presented as number (percentage), [a]Data presented as mean (SD).
Abbreviations: ADHD = attention deficit/hyperactivity disorder, PM = Post Meridiem, AM = Ante Meridiem

and 8 pm. The mean duration of sleep was 11.04 ± 1.57 hours. The average overall CSHQ score was 43.76 ± 7.38, and 40% of the participants had clinically significant sleep problems. The CSHQ scores categorized by each sleep problem domain are shown in Table 2.

Emotional and behavioral problems

The median overall difficulty score of our participants was 13.4 (IQR = 8, 20.75). According to the standard reference values in the Thai context, 31.3% of the participants were indicated to have significant emotional/behavior problems. When considering all SDQ domains, compared to the standard reference value, 33.8% of the participants had clinically significant hyperactive symptoms and 16.3% had a problematic level of emotional difficulties. Meanwhile, 10% had significant conduct problems and 5% had substantial inappropriate peer relationships. However, only 2.5% of the participants had impairment in prosocial behavior (Table 3).

Association between sleep problems and emotional / behavior problems in preschool-age children with ADHD

According to Pearson's correlation analysis, the total CSHQ score was significantly correlated with the SDQ total difficulty score (r = 0.900, p < 0.001), and all domains of behavioral problems (all p < 0.001). As shown in Table 4, almost all types of sleep problems except parasomnias and sleep disorder breathing were also significantly associated with the total difficulty score and all domains of behavioral problems (all p < 0.05).

To adjust potential variables that may affect emotional and behavioral problems, sex, type of ADHD, severity symptoms of ADHD, treatment modalities, and total CSHQ scores were analyzed by multivariate linear regression (enter method). In Table 5, the total CSHQ scores remained significant predictors of the total difficulty score (β = 0.80, p < 0.05) and all domains of behavioral problems (β = 0.65-0.85, all p < 0.05). Girls had a negative correlation with the total SDQ difficulty score (β = -0.11), emotional

TABLE 2. The children's sleep habits questionnaire (CSHQ) subscale scores and total scores in preschool children with ADHD.

CSHQ Score	Mean (SD)
Bedtime resistance	9.05 (3.01)
Sleep onset delay	1.85 (0.66)
Sleep duration score	4.00 (0.97)
Sleep anxiety	4.41 (0.74)
Night waking	3.26 (0.44)
Parasomnias	7.78 (0.66)
Sleep disorder breathing	3.83 (0.91)
Daytime sleepiness	9.63 (2.55)
Total CSHQ score	43.76 (7.38)
Positive sleep problems, n (%)	32 (40)

TABLE 3. The strengths and difficulties questionnaire (SDQ) subscale scores and total difficulties scores.

SDQ domains	Results	Problematic behavior, n (%)
Emotional problems[a]	3.75 (2,6)	13 (16.3%)
Conduct problems[a]	3.58 (2,6)	8 (10%)
Hyperactivity[b]	4.54 (1.35)	27 (33.8%)
Peer problems[a]	1.54 (0,3)	4 (5%)
Prosocial behavior[b]	7.59 (1.37)	2 (2.5%)
Total difficulties score[a]	13.4 (8,20.8)	25 (31.3%)

[a]Data presented as median (IQR), [b]Data presented as mean (SD)

TABLE 4. Pearson's correlations between the CSHQ and SDQ domains.

CSHQ Domains	SDQ domains											
	Emotional problem		Conduct problem		Hyperactivity		Peer problem		Prosocial behavior		Total difficulties score	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Bedtime resistance	0.881	<0.001**	0.871	<0.001**	0.770	<0.001**	0.826	<0.001**	-0.781	<0.001**	0.905	<0.001**
Sleep onset delay	0.624	<0.001**	0.502	<0.001**	0.562	<0.001**	0.506	<0.001**	-0.577	<0.001**	0.590	<0.001**
Sleep duration	0.695	<0.001**	0.621	<0.001**	0.550	<0.001**	0.728	<0.001**	-0.728	<0.001**	0.702	<0.001**
Sleep anxiety	0.407	<0.001**	0.298	<0.001**	0.345	0.002**	0.220	0.049*	-0.367	0.001**	0.344	0.002**
Night waking	0.551	<0.001**	0.538	<0.001**	0.545	<0.001**	0.442	<0.001**	-0.363	0.001**	0.558	<0.001**
Parasomnias	0.207	0.065	0.115	0.308	0.196	0.082	0.235	0.053	-0.176	0.119	0.204	0.070
Sleep disorder breathing	0.155	0.169	0.189	0.094	0.108	0.339	0.189	0.093	-0.120	0.290	0.176	0.119
Daytime sleepiness	0.757	<0.001**	0.730	<0.001**	0.710	<0.001**	0.807	<0.001**	-0.691	<0.001**	0.806	<0.001**
Total CSHQ score	0.880	<0.001**	0.831	<0.001**	0.777	<0.001**	0.850	<0.001**	-0.800	<0.001**	0.900	<0.001**

*$p < 0.05$, **$p < 0.01$

TABLE 5. Multivariate linear regression analysis for association between potential demographic characteristics (including total CSHQ scores) and SDQ scores.

Demographic characteristics	SDQ domains											
	Emotional problem		Conduct problem		Hyperactivity		Peer problem		Prosocial behavior		Total difficulties score	
	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Categorical variable												
Sex												
Boy	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
Girl	-0.128*	-1.240, -0.044	-0.154*	-1.358, -0.104	-0.082	-0.764, 0.255	-0.015	-0.582, 0.465	-0.063	-0.639, 0.242	-0.107*	-3.359, -0.012
ADHD type												
Combine	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
Hyperactive	0.026	-0.446, 0.690	0.057	-0.347, 0.844	0.151	-0.053, 0.915	0.038	-0.358, 0.637	0.227*	0.240, 1.077	0.065	-0.648, 2.531
Severity of ADHD												
Mild	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
Moderate to Severe	0.207*	0.061, 1.745	0.362*	0.605, 2.371	0.139	-0.345, 1.090	-0.032	-0.848, 0.627	-0.119	-0.942, 0.298	0.195*	0.297, 5.008
Phamacological therapy												
No medication	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
Methylphenidate	0.037	-0.835, 1.204	-0.076	-1.429, -1.319	-0.042	-0.999, 0.739	0.346*	0.477, 2.264	0.002	-0.747, 0.756	0.068	-1.788, 3.920
Risperidone	-0.102	-1.284, 0.294	-0.107	-1.319, 0.336	-0.068	-0.877, 0.468	0.144	-0.136, 1.246	-0.130	-0.978, 0.185	-0.042	-2.845, 1.573
Continuous variable												
Sleep duration	0.084	-0.275, 0.740	0.024	-0.469, 0.596	-0.044	-0.508, 0.358	0.148	-0.123, 0.767	-0.710	-0.498, 0.251	0.063	-0.878, 1.965
Total CSHQ score	0.775*	0.180, 0.280	0.654*	0.130, 0.236	0.724*	0.090, 0.175	0.854*	0.156, 0.627	-0.784*	-0.182, -0.108	0.804*	0.605, 0.886

* $p < 0.05$

symptoms score (β = -0.13), and the conduct problem score (β = -0.15). The hyperactive / impulsive type had a positive correlation with prosocial behavior (β = 0.23). Moderate to severe ADHD symptoms were associated with emotional symptoms (β = 0.21), conduct problems (β = 0.36), and the total SDQ difficulty score (β = 0.20). Additionally, taking methylphenidate had a positive correlation with inappropriate peer relationships (β = 0.35).

DISCUSSION

Many previous studies have shown that children with ADHD are more likely to have sleep problems than healthy children.[12-14] However, our study found that the prevalence of sleep disturbances in preschool children with ADHD was 40%, similar to the findings of the study by Gultekin and Bayik-Temel (2020)[15], which found that the prevalence of sleep problems in healthy preschool children was 43.4%. This comparison is contradictory with previous studies[12-14] that found a higher prevalence of sleep problems in school-age children and adolescents with ADHD compared to those without ADHD. These inconsistent results may be explained by preschool children who are more likely to share the same room with their parents[16], thus better controlling good sleep practices compared to older children and adolescents.[17] In addition, children with ADHD tend to have poorer regulation of their sleep practices than normal children.[12-14] Therefore, compared to preschool children with ADHD, school-age children and adolescents with ADHD who had less parental involvement in sleep practices may have more sleep problems compared to those without ADHD.

Compared to Thai school-age children with ADHD from the Chiraphadhanakul study[14] (2016), the mean total CSHQ sleep disturbance score of preschool-age children with ADHD in this study was apparently lower than that of school-age children with ADHD (52.92 ± 7.40). Additionally, when considering each domain of sleep problems, mean scores for all domains of sleep problems in preschoolers with ADHD were lower than those of older children with ADHD. Therefore, these comparisons confirm that preschool children with ADHD tend to have fewer sleep problems than school-age children with ADHD. In addition to less parental participation in sleep practices in school-age children[16,17], exposure to psychostimulants (such as methylphenidate) may be another reason for sleep problems in these children. Psychostimulants, which are the first-line treatment for school-age children with ADHD[3], result in insomnia.[18] Although giving ADHD patients the last dose of short-acting psychostimulants at noon is to avoid the possibility of drug-induced sleep difficulties, some of these patients also reported more sleep problems, including prolonged sleep latency and insomnia, than ADHD patients who did not receive these medications.[19] Therefore, the use of these drugs may be a significant cause of sleep disturbances in school-age children more than preschoolers with ADHD, who were treated primarily with behavioral modification.[3]

Furthermore, according to the recommendations of the American Academy of Sleep Medicine, the average duration of sleep of our participants is within the normal range of preschool age (10-13 hours) to promote optimal health.[20] Our participants' bedtime and wake-up time were similar to Mindell's survey, which collected data from 3-6 year old healthy preschool children 3-6 years of age of Asian origin.[21] Therefore, it can be tentatively concluded that the sleep habits and sleep problems of preschool children with ADHD are not different from those without ADHD.

Our study found that clinically significant emotional and behavioral problems in preschool children with ADHD are as high as 31.3%, higher than the prevalence of behavioral and emotional difficulties in typical preschool children according to Rescorla's study (2011), which found only 9%.[22] Taking into account each emotional and behavioral problem, hyperactivity (33.8%) is considered the most common symptom in preschool children with ADHD, followed by emotional problems (16.3%), and higher than those without ADHD, which found only 11% and 10% of hyperactivity and emotional problems, respectively.[22] These results emphasize the negative consequences of ADHD caused by abnormal brain structure and function[23], as well as parent-child interaction.[1] Compared to healthy children, thinning of the prefrontal cortex and its poorer function in children with ADHD leads to impairment of behavioral inhibition and decrease in coping ability of the emotional state.[23] Furthermore, children with ADHD and their caregivers have a poor quality of communication[24], which can destabilize their emotion and aggravate externalizing behaviors.

When analyzing Pearson's correlation between sleep problems and significant emotional/behavioral problems in preschool-age children with ADHD, our study found that the total CSHQ sleep disturbance score had a robust correlation coefficient with the total SDQ difficulty score and all domains of emotional and behavioral problems. After multivariate linear regression analysis, the total CSHQ sleep disturbance score remained an essential factor that affected the total SDQ difficulty score and all domains of emotional and behavioral difficulties in these children.

Although the preschool age group has not been studied, our results are consistent with the study by Lucas and Mulraney (2017), which found a moderate correlation between sleep quality and emotional and behavioral problems in school age children with ADHD (β = 0.39 - 0.47).[25] Our results support previous studies that have found that good sleep quality is an essential factor in the development of the prefrontal cortex, which influences the ability to regulate behavior and manage emotions.[26,27] Compared to the study by Lucas and Mulraney, the effect of sleep quality in preschool children with ADHD on behavioral and emotional problems is greater than in older children and adolescents. This can be explained by the rapid rate of thickening of the prefrontal cortex during the preschool period, so sleep quality greatly influences the development of the prefrontal cortex in this period.[28] Therefore, improving sleep quality is an important measure to reduce emotional and behavioral problems in preschool children with ADHD.

Our study has some limitations. First, because our study collected data from a small sample size in only a single tertiary hospital, it affects the generalizability of the results. Large sample sizes and multicenter studies should be investigated. Second, our study does not have a healthy control group to compare the prevalence and types of sleep and emotional and behavioral problems directly. Therefore, further research should also collect data in the healthy control group. Finally, this cross-sectional study design cannot determine the causal relationship between sleep disturbances and behavioral problems. Therefore, longitudinal studies should be conducted in the future.

CONCLUSION

Preschool-aged children with ADHD are likely to experience sleep problems. Additionally, their sleep disturbances can affect their emotional and behavioral problems. Therefore, sleep habits and quality should be checked and emphasized in the treatment of ADHD.

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Conflict of interest

All authors declare no conflict of interest.

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Effects of N-Acetylcysteine Supplementation on Semen Analysis, Hormonal Profile and Spontaneous Pregnancy Rate in Idiopathic Infertile Men: Before and After Clinical Trial

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ABSTRACT

Objective: To compare sperm quality and quantity, hormonal profiles and spontaneous pregnancy rates before and after administering a 3 months course of N-Acetylcysteine (NAC).

Material and Methods: This prospective clinical trial was conducted at the Infertility Unit of the Obstetrics and Gynecology Department at Bhumibol Adulyadej Hospital, Thailand. The study period was from June 1, 2023 to September 30, 2023. Subjects were idiopathic infertile males aged between 20 and 50 years old. All subjects received 600 mg of NAC orally per day. Semen analysis (SA) and male hormonal profiles (MHP; testosterone, LH, FSH and prolactin) were performed before and three months after NAC administration. Demographic, clinical characters and laboratory change were recorded.

Results: The 92 participants were recruited. The mean age of couples was 34.5 years old. The average duration of infertility was 3.6 years. Increase of semen volume (2.1 vs 2.4 ml, $p < 0.001$), semen concentration (30.5 vs 43.1 x 10^6/mL, $p < 0.001$), total motility (59.57 vs 72.38 %, $p < 0.001$), progressive motility (59 vs 69.8 %, $p < 0.001$), normozoospermia (60 vs 83 %, $p < 0.001$), testosterone (452.8 vs 479.0 ng/dL, $p = 0.038$), LH (4.6 vs 5.3 mIU/mL, $p = 0.004$) and FSH (4.4 vs 4.6 mIU/mL, $p = 0.009$) were observed after three months of NAC administration. No changes in sperm morphology and prolactin level. One-third (27/92) of each participant's spouse conceived spontaneously.

Conclusion: NAC potentially enhances male hormonal profiles, sperm quality and quantity with an impressive spontaneous pregnancy rate.

Keywords: Infertile; male; semen analysis; N-Acetylcysteine; pregnancy (Siriraj Med J 2024; 76: 125-134)

INTRODUCTION

Infertility is defined as one year of regular unprotected intercourse without conception.[1] Eighty percent of normal couples conceive within the first 6 months of unprotected sexual intercourse among couples living in the same residence.[2] It is estimated that 30 million men are infertile worldwide, with highest rates in Africa and Eastern Europe.[3] Male factors ranged from 20 to 73 percent in different regions worldwide. Among Asian regions, 37 percent was reported.[3] The male factor made up half of infertility issues.[4,5]

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Semen analysis (SA) is a basic laboratory test used for male factor evaluation. SA consists of semen volume, sperm concentration, motility, and morphology.[6] Acceptable values for SA are a semen volume of 1.4 mL, sperm concentration of 16 million per mL, total sperm motility of 42 percent, normal sperm morphology of at least 4 percent and WBC concentration less than one million per mL.[6] The past 16 years of data reported motile sperm count trends declining at approximately ten percent.[7] Sperm quality identified a declining tendency from 2015-2021 with increased male age.[8]

Based on well-established data, sperm concentration of less than one million sperm per mL (severe oligozoospermia) typically resulted in failed impregnation.[9] Male infertility was a result of abnormal function of testes, hypothalamic pituitary axis and other unexplained causes. Half of male infertility is still unexplained.[10]

Depletion of GSH pool is a consequence of oxidative stress and inflammatory processes.[11] Unexplained male infertility has been associated with oxidative stress.[12] Highly reactive oxygen species (ROS) are described to be responsible for the oxidative damage to nucleic acids, namely DNA and RNA. Oxidative stress is maintained in homeostasis by antioxidants.[13] This results from various factors, such as exercise, altered immune system, and antioxidant deficiencies.[14] This condition can cause pathological disorders, namely aging, neurodegenerative diseases, and cancers.[13,15,16]

Appropriate ROS levels affect sperm acrosome reaction, capacitation, and motility according to multiple studies via improving the efficacy of sperm binding to zona pellucida of the oocyte.[4,17-19] Excess antioxidants could alter sperm function and maturation, especially the function of superoxide dismutase.[4] Infertile men were reported to have oxidation imbalances when compared to healthy individuals, with findings suggesting sperm dysfunction in concentration, volume, and motility.[18,20]

There are multiple modalities to treat infertile males.[5] Medical treatment using antioxidant food supplements had been studied. Works demonstrated an association of zinc and folic acid with improved sperm morphology and concentration. There has yet to be conclusive evidence in the use of N-acetylcysteine (NAC) for such a cause.[5]

NAC is a derivative of amino acid L-cysteine agent. It is widely available over the counter and administered for upper viral infection of respiratory tract enterally.[21] Clinical usage of NAC is for mucolytic, antioxidant and anti-inflammatory properties.[22] NAC has an anti-oxidation effect by restoring the depleted pool of glutathione (GSH) synthesis.[23]

Previous literatures reported the effect of NAC in improving sperm concentration and acrosome reaction by reducing oxidative stress of sperm DNA.[11,24] There were some suggestions of NAC increasing SA quality.[25-28] Still, there remains controversy regarding effects on hormonal analysis.

This study aimed to investigate the improving effect of NAC on sperm quality, hormonal profile and spontaneous pregnancy rate.

MATERIALS AND METHODS

This study was conducted as a prospective clinical trial. Idiopathic infertile males between 20 and 50 years who came to the Infertility Unit of Obstetrics and Gynecology Department at Bhumibol Adulyadej Hospital (BAH), Bangkok, Thailand from June 1, 2023 to September 30, 2023 were enrolled. This study was approved by the Ethics Committee of BAH Institutional Review Board (IRB 47/65). Registration number obtained on the Thai Clinical Trial website (www.thaiclinicaltrials.org) was TCTR20230510002. All individuals gave written informed consent prior to their participation in the study. Inclusion criteria included primary infertile men with regular sexual intercourse (at least every two days of sexual intercourse) with partners. Stopping all medical treatments for at least three months before participating in the study was also a requirement for all participants.

Exclusion criteria were subjects who had well-known pathologic features, such as varicocele, leukocytospermia, hormonal abnormalities, and/or blockage that prevented sperm delivery, azoospermia, aspermia of semen analysis, the presence of cryptorchidism, vasectomy, history of testosterone and other exogenous hormone use, abnormal liver function, regular cigarette smoking, regular alcohol consumption, anatomical disorders, Klinefelter syndrome, cancer, and fever within 90 days prior to semen analysis. We defined the non, infrequent and regular smokers as non, one to six cigarettes and seven or more cigarettes per week, respectively.[29] Male who consumed more than 2 drinks per day were excluded from the study. One drink defined as 15 mL of pure ethanol.[30] All subjects' spouses were investigated by hysterosalpingography or laparoscopy and hormonal profiles namely luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), progesterone and prolactin (PRL). Healthy female in the current study was defined as subject with normal genital tract finding, normal ovulatory cycles, normal hormonal profiles and the absence of endometriosis.

Couple age and duration of infertility were recorded at the time of study. In addition, male height (m), weight (kg), body mass index (BMI, kg/m^2), underlying diseases, history of orchitis, sexually transmitted diseases (STDs),

history of regular smoking or alcohol intake, occupation, income and partners' age were recorded. Subjects were requested to consume 600 mg of NAC (Fluimucil A, Zambon, Switzerland) dissolving tablets in 120 mL in room temperature water orally once daily before sleep for three months. Safety of prolong NAC administration was reassured to subjects.[31]

Variables including SA, hormonal parameters namely LH, FSH, testosterone and PRL and successful pregnancy outcomes were measured before and after three months of orally administered NAC.

For effective communication between participants and the investigation team, an official group LINE chat (communication application on smartphone) account was created. All subjects and the investigation team were invited to participate in this application. Any problem and concern mentioned in the group forum were promptly responded to by members of the investigation team. Appointment reminders, regular NAC administration, and side effects were monitored via enquiry input in the LINE application, which is a code-encrypted program controlled by the investigator. Confirmation of NAC administration was checked daily via application by participants.

Semen samples were obtained through masturbation directly into the container without a condom, after 3-5 days of sexual abstinence. The collected sample was allowed to liquify at room temperature for one hour. Semen parameters (volume, sperm count, progressive and non-progressive motility and normal morphology) were evaluated according to 2021 WHO SA guidelines.[6] Standardized SA was assessed by one single trained laboratory technician at the at the Infertility Unit at BAH. Sperm count was evaluated by a sperm counting chamber under microscopy (10x, model CHS, Olympus, Japan) and expressed as million per milliliter. The spermatozoa's motility was classified as progressive, non-progressive, and immotile.[6] Spermatozoa's morphologies were investigated by Papanicolaou staining technique. Normal WHO 2021 criteria included a sperm concentration of 16 x 10^6 per ml or greater, 42 percent or greater motility with forward progression under light microscopy inspection. According to the Tygerberg Strict criteria, greater than four percent of normal form of spermatozoa was classified as normal morphology of spermatozoa.

A three milliliters peripheral blood sample was obtained from each participant in the morning and immediately centrifuged for 7 minutes at 3,500 rpm. Serum samples were collected then stored at (2-8 degree Celsius) for no more than one day for further evaluation and analysis. The serum levels of FSH (mIU/mL), LH (mIU/mL), PRL (ng/ml) and testosterone (ng/dL) in all samples were measured by using electrochemiluminescence immunoassay (ECLIA, Cobas 801, Roche, Thailand) for hormonal profile.

Sample size calculation was based on Jannatifar's study.[28] Mean difference, alpha error, and beta error were set at 0.44, 0.05 and 0.1, respectively. The minimal sample size needed was 92 cases. Categorized variables were expressed as percent (%). Continuous variables were expressed as mean ± standard deviation (SD). Normal distribution of data was assessed by Kolmogorov-Smirnov test. Data before and after NAC treatment were compared by the paired t-test, chi-square tests or Fischer exact tests when appropriate. Two-sided significance level of less than 0.05 was considered statistically significant. Analyses were performed using SPSS (Statistical Package for the Social Science for Window), version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, 92 participants were recruited as presented in Fig 1. Mean age of male and female participants was 35.1 ± 5.6 and 33.8 ± 4.2 years old, respectively (p-value < 0.001). Duration of infertility was 3.6 ± 3.2 years (p-value = 0.001). Average BMI of male participants was 26.4 ± 4.3 kg/m^2. Most participants (87/92: 94.6%) were government officers and employees as depicted in Table 1. Thirteen percent (12/92) of subjects had underlying diseases including hypertension, dyslipidemia, and diabetes mellitus. Among the participants, 17 individuals (18.5%) were smokers, and 42 individuals (45.7%) socially consumed alcohol. All subjects' education level was of bachelor's degree or higher. Two-thirds (65/72: 90.3%) of women had normal genital structure and function. The timing of pregnancy after NAC intervention was 2.63 ± 1.12 months (Table 1).

Quality of SA improvement after NAC administration is demonstrated in Fig 2 and Table 2. Regarding the semen analysis, an increase in normozoospermia was observed. There was a statistically significant increase of the semen volume, sperm concentration, and all attributes of motility, namely total, progressive and non-progressive motility. No change was observed with semen pH and sperm morphology. Hormonal profile revealed increases in testosterone, LH and FSH levels with statistical difference at p-value = .038, .004 and .009, respectively. PRL levels were not changed (Fig 2 and Table 2).

Spontaneous conception was observed among male participants aged younger than 31 years old regardless of their partner's age of whom featured no female anatomical

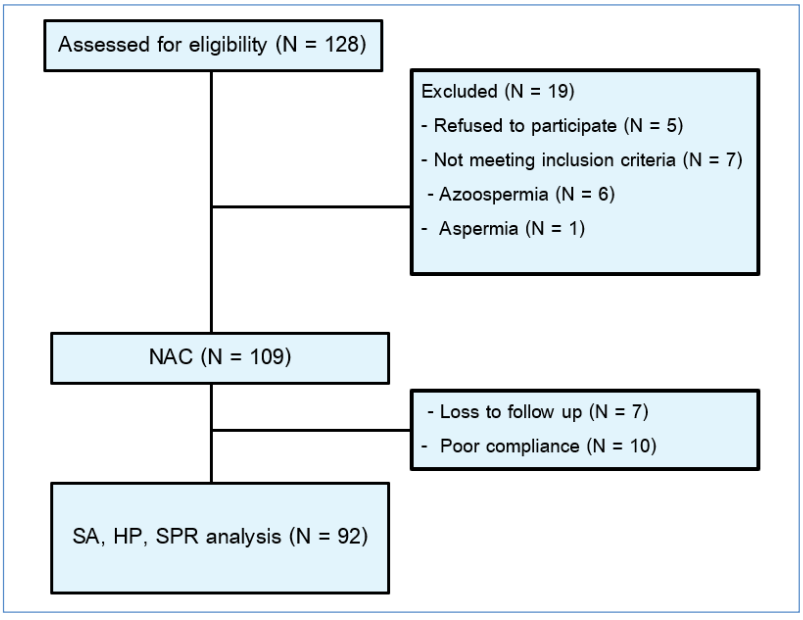

Fig 1. Flow chart of study. NAC = N-acetylcysteine supplement; SA = Semen Analysis; HP = Hormonal profile which includes: Testosterone (ng/dL); Luteinizing hormone (mIU/mL); Follicle stimulating hormone (mIU/mL); Prolactin (ng/ml); SPR = Spontaneous Pregnancy Rate.

TABLE 1. Demographic character of infertile couples who receive NAC before and after.

		Pregnancy		*p*-value
	Total (92)	**Yes (27)**	**No (65)**	
Age				
Female	33.8 ± 4.2	31.1 ± 2.8	35.0 ± 4.1	<.001*
Male	35.1 ± 5.6	31.7 ± 5.4	36.6 ± 5.1	<.001*
Duration (years)	3.4 ± 3.0	2.0 ± 1.9	3.9 ± 3.2	.001*
NAC (months)		2.6 ± 1.1	3.0	
NF	65 (70.7)	27 (100)	38 (58.5)	<.001*
PF	27 (29.3)	0 (0)	27 (41.5)	
Smoker	42 (45.7)	8 (29.6)	34 (52.3)	.047*
Non-smoker	50 (54.3)	19 (70.4)	31 (47.7)	
BMI	26.4 ± 4.3	26.3 ± 4.33	26.41 ± 4.37	.914
Underweight	1 (1.1)	0 (0)	1 (1.5)	.015*
Normal weight	19 (20.7)	9 (33.3)	10 (15.4)	
Overweight	22 (23.9)	1 (3.7)	21 (32.3)	
Obesity	50 (54.3)	17 (63)	33 (50.8)	
Occupation				
Government Officer	59 (64.1)	16 (59.3)	43 (66.2)	.638
Own Business	5 (5.4)	1 (3.7)	4 (6.2)	
Employee	28 (30.4)	10 (37)	18 (27.6)	
Income (Baht)				
< 20,000	4 (4.3)	0 (0)	4 (6.2)	.361
20,000 - 50,000	59 (64.1)	17 (63)	42 (64.6)	
>50,000	29 (31.5)	10 (37)	19 (29.2)	
UD	12 (13)	3 (11.1)	9 (13.8)	.723
Hypertension	8 (8.7)	0 (0)	8 (12.3)	
Dyslipidemia	3 (3.2)	3 (11.1)	0 (0)	
Diabetes mellitus	1 (1.1)	0 (0)	1 (1.5)	
Bachelor or more	92 (100)	27 (100)	65 (100)	

Note: Data are presented as mean (SD) for continuous variables, and as frequency (percentage) for categorical variables. NF = Normal female's factors; PF = Pathologic female's factors (diminished ovarian reserve (DOR); polycystic ovarian syndrome (PCOS); abnormal fallopian tube; abnormalities of the uterus; endometriosis; luteal phase defect); BMI = body mass index (kg/m^2); NAC = duration of N-Acetylcholine administration (months); Duration = duration of infertility before infertile clinic appointment (years); UD = underlying disease of participants namely hypertension, dyslipidemia, and diabetes mellitus.
*$p < .05$

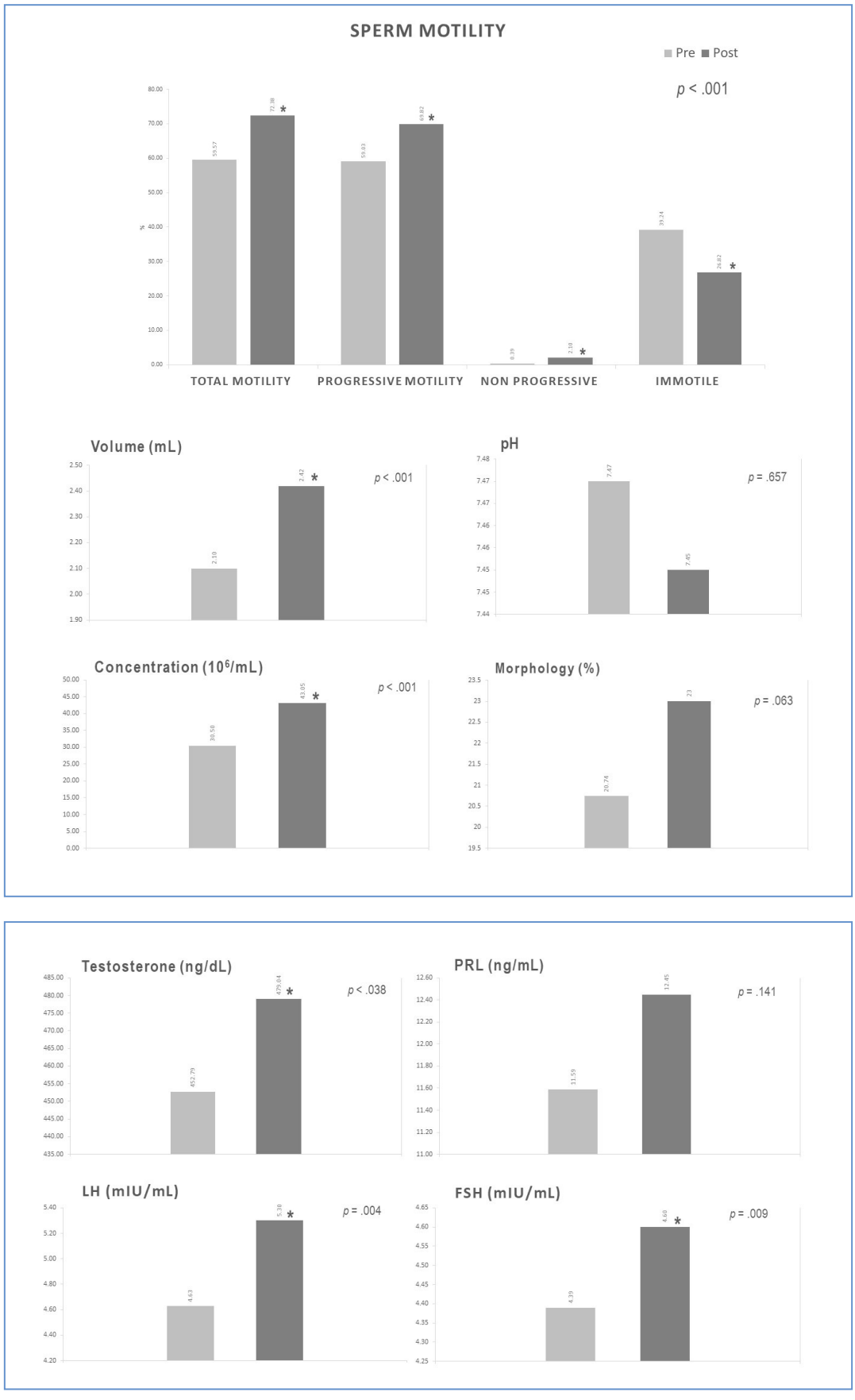

Fig 2. Comparison of semen analysis and male's hormonal profiles between pre and post-NAC administration. Volume = volume of semen (mL); pH = pH of semen; Concentration = concentration of sperm (10^6/mL); Total motility = total motility of sperm (%); Progressive motility = progressive motility of sperm (%); Non-progressive = non-progressive motility of sperm (%); Immotile: immotile sperm (%); Morphology = morphology of sperm; Testosterone (ng/dL); LH = Luteinizing hormone (mIU/mL); FSH = Follicle stimulating hormone (mIU/mL); PRL = Prolactin (ng/ml).
*$p < .05$

TABLE 2. Comparison of semen analysis and male's hormonal profile between pre and post-NAC administration

Outcome	Comparative risk		MD, 95%CI	*p*-value
	Pre	Post		
Volume (mL)	2.1 ± 0.6	2.42 ± 0.5	0.32 (0.15, 0.49)	<.001*
pH	7.47 ± 0.3	7.45 ± 0.5	-0.03 (-0.15, 0.09)	.657
Concentration	30.5 ± 23.2	43.1 ± 27.2	12.55 (7.84, 17.27)	<.001*
Motility (%)				
Total	59.6 ± 17.9	72.4 ± 14.9	12.82 (9.29, 16.34)	<.001*
Progressive	59.0 ± 18.4	69.8 ± 16.3	10.78 (6.94, 14.62)	<.001*
Non- progressive	0.4 ± 1.4	2.1 ± 4.4	1.71 (0.72, 2.69)	.001*
Immotile	39.2 ± 18.9	26.8 ± 14.6	-12.42 (-16.17, -8.68)	<.001*
Morphology (%)	20.74 ± 11.5	23 ± 11.6	2.26 (-0.13, 4.65)	.063
Testosterone (ng/dL)	452.8 ± 155.1	479.0 ± 163.6	26.25 (1.43, 51.07)	.038*
LH (mIU/mL)	4.6 ± 1.7	5.3 ± 2.3	0.68 (0.22, 1.13)	.004*
FSH (mIU/mL)	4.4 ± 1.9	4.6 ± 1.9	0.21 (0.05, 0.37)	.009*
PRL (ng/mL)	11.6 ± 6.3	12.5 ± 6.1	0.86 (-0.29, 2.02)	.141

Mean (SD) for continuous variables, and as frequency (percentage) for categorical variables Volume = volume of semen (mL); pH = pH of semen; Concentration = concentration of sperm (10^6/mL); Total motility = total motility of sperm (%); Progressive motility = progressive motility of sperm (%); Non-progressive = non-progressive motility of sperm (%); Immotile: immotile sperm (%); Morphology = morphology of sperm; Testosterone (ng/dL); LH = Luteinizing hormone (mIU/mL); FSH = Follicle stimulating hormone (mIU/mL); PRL = Prolactin (ng/ml).
*$p < .05$

abnormalities or dysfunction. Overall pregnancy rate was 29.3 (27/92) percent. Non-smoking participants were associated with positive pregnancy outcomes (19/27: 70 percent) as stated in Table 1.

DISCUSSION

The demographic characteristics of participants were as follows: age was around 35 years old. Mean ages of our participants were similar to Jannatifar's study whereas other studies included participants in their early 30s.[25-28] The duration of infertility in the current study was three years. Safarinejad, Barekats and Jannatifar's works reported shorter duration of around two years while participants in Ciftci's study had infertile durations exceeding 4 years.[26-28]

Report from Iran by Barekat in 2016 identified average female spouses at around 26 years old.[27] Ciftci, Safarinejad and Jannatifar's studies reported from Turkiya and Iran did not state the average age of female spouses.[25,26,28] Most muslim women married at a young age. It implied that women's age was not a contributing factor for infertility problems in these studies.

For studies conducted during 2009.[25,26] It was a period of time with a culture respecting traditional values, where starting a family early was a milestone in life. When compared to 2019 having an increased trend in career driven lifestyle moreover the social media namely facebook, twitter, and instagram were not as widely used as they are in the present day, causing a later start in family growth. Barekat's study in 2016 consisted of participants with infertile male post-varicocelectomy, explaining the early concern regarding infertility treatment.[27]

Subjects in Safarinejad's (BMI 26.2 kg/m^2) and Jannatifar's (BMI 29.2 kg/m^2) studies had overweight participants (BMI 25-29.9 kg/m^2).[26,28] Subjects in the current study (26.4 kg/m^2) were obese according to the WHO 2021 for Asian people.[32] The current study presented an obese demographic (54.3%).

Male infertility remains an important issue for couples. Its remedies remain controversial and so further exploration of optimal treatment was needed.[34] The effects of NAC from the current study were increased semen volume, sperm concentration and sperm motility. Sperm morphology did not change as the result of receiving oral NAC. The percentage of normospermia presented a marked increase from 65 to 90 after NAC treatment. All studies with NAC reported increased semen volume except for Barekat's study.[25-28] Reports identified concentration of

spermatozoa increased in Safarinejad's and Jannatifar's studies while others' works informed no change.[25-28] Many works reported that ROS generation was associated with DNA fragmentation.[17-19] Poor chromatin packaging, apoptosis promoting were also relevant consequences on spermatozoa count.[35,36] High ROS generation and DNA damage were demonstrated in immature spermatozoa that could be the explanation of male infertility by inducing oxidation among mature spermatozoa.[37] These processes occurred during sperm migration from the seminiferous tubules to the epididymis.[38]

Motility of spermatozoa was increased as a result of NAC intake in the current study. The findings of the current study are in line with the works of Ciftci's, Barekat's and Jannatifar's while no motility change was reported by Safarinejad.[25-28] Asthenozoospermia (poor motility) was a consequence of increased oxidative stress, excess of tyrosine nitration, and sperm mitochondrial dysfunction.[19,39]

The quality of SA in this study was improved, in line with the previous studies.[25-28] This might come from the antioxidant effects of NAC. Oxidative stress impaired sperm motility and morphology of spermatozoa via lipid peroxidation at cell membrane spermatozoa.[17-19,40] Elevated concentrations of reactive oxygen species (ROS), when concomitant with an insufficiency in antioxidant defenses, precipitate a state of oxidative stress (OS). This caused nuclear and mitochondrial DNA impairments, reduced telomeric length, integrity, and alterations in chromatin structure.[17-19,41]

NAC has a mucolytic effect. Presently, minimal side effects of oral NAC had been reported such as nausea and vomiting. The toxicity of NAC overdose remains incompletely defined within previous literature so it is considered a safe supplement.[42] It was reported to reduce ROS and improve all aspects of sperm parameters. NAC could reduce sperm viscosity, thus making it easier for seminal plasma to pass through the cervix.[43] Sperm morphologies in the current and Ciftci's study[25] were not changed because the base value of morphology was already within normal range, resulting in an insignificant improvement. The morphology of spermatozoa from the previous study reported significantly better results due to their starting morphology parameters being under normal range.[25-28]

PRL levels in the current study declared no change. This finding was similar to previous reports.[25-28] As NAC leads to increased testosterone level, improving sperm quality but it has no effect on PRL level. From the current study, there was a significant increase in FSH and LH (both values staying within normal range) as well as testosterone levels. Trends of increasing testosterone level after NAC administration were also reported in Safarinejad's work in 2009 and Jannatifar's study in 2019 despite representing significant decrease in FSH and LH.[26,28] Testosterone levels within normal range had been reported to improve spermatogenesis.[44] The increase in testosterone level explained the decreased effect in FSH and LH as per negative feedback in the hypothalamic-pituitary axis.[45] It is unexplainable to why this study had an increase in FSH and LH unlike other studies. The rise of FSH and LH is statistically significant with a lack of clinical significance. Average age of male participants in the current study was around 35 years old which made our participants older than those in previous studies. Average male age in the studies by Ciftci, Safarinejad, Barekat and Jannatifar ranged from 30.1 to 34.7 years old.[25-28] The rising in FSH and LH among male participants in the current study might stem from increasing age. Even though our participants exhibited elevated normal level of FSH and LH, the testosterone level was increased in comparison to previous literature.[26,28] Steiner et al reported the large RCT in year 2020 that combination of antioxidant agents namely ascorbic acid, vitamin E, selenium, L-carnitine, zinc, folic acid, lycopene and vitamin D did not improve semen parameters among male infertility couples.[46] Another large RCT by Schisterman in year 2020 also stated that supplement of folic acid and zinc to male infertility couples did not improve semen quality and clinical live birth.[47] Comparisons of the current study to the previous studies were reported in Table 3. Antioxidant in the current study was NAC. It was a new data for one member of antioxidants that needed further investigation. The findings of the current study could not argue the landmark RCT papers of Schisterman and Steiner.[46,47]

Limitation of the study was single data measurement of SA and hormonal levels. Fluctuation of SA and hormonal levels should be corrected by multiple measurement and average calculation. One-third of female couples (27/92) were initially included and later diagnosed of pathologic female during process of infertile investigation. Incidental findings of pregnancy were reported among normal female during process of investigation. Randomized controlled trial with placebo and study group should be performed in the next study.

Among spontaneous pregnancy groups, infertility duration was shorter (2.0 vs 3.9 years), male participants were younger in age (31.7 vs 36.6 years old), apparently normal females (27 vs 0 cases), and non-smoking males (19/27) compared to non-pregnancy group (31/65). Suggestion among normal females in younger age group,

TABLE 3. Comparison Outcome of semen analysis, hormonal profiles and pregnancy outcome in NAC supplement in infertile men from various study.

Authors	Cifci		Safarinejad		Barekat		Jannatifar		Present	
Years	2009		2009		2016		2019		2023	
Country	Turkiya		Iran		Iran		Iran		Thailand	
Designs	RCT		RCT		RCT		RCT		SCT	
Population	IN		IOST		IVV		IAT		IMN	
Age (years)	33.1		32.0		30.1		34.7		35.1	
BMI			26.2				29.2		26.4	
UD	No		No		No		No		Yes*	
Duration	4.1		≥ 2		2.1		2.1		3.4	
WHO	1999		1992		2010		2010		2021	
S/C (n)	60/60		105/106		15/20		50/50		92/92	
Cases (n)	120		211		35		100		92	
NAC	600		600		200		600		600	
Control group	Placebo		Placebo		Untreated		Placebo		After	
INT	12		26		12		12		12	
SA	C	S	B	A	C	S	B	A	B	A
Vol	4.0	2.5	2.8	3.4	3.5	3.9	3.6	4.0	2.1	2.4
Conc	22.3	21.9	22.6	26.8	42.4	45.4	46.5	51.1	30.5	43.1
Mot	22.4	31.3	20.3	24.8	43.6	58.2	31.4	35.2	59.6	72.4
Morph	25.4	26.4	7.4	9.2	1.9	2.7	1.9	4.0	20.7	23.0
HP	C	S	B	A	C	S	B	A	B	A
T			522.2	579.9			387	437	452.8	479.0
LH			4.6	4.2			4.2	4.1	4.6	5.3
FSH			2.6	2.1			4.1	3.7	4.4	4.6
PRL			159.6	97.8			10.6	10.6	11.6	12.5
SPO					10	33.1			0	29.34

Note: Data are presented as mean (SD) for continuous variables, and as frequency (percentage) for categorical variables. RCT = Randomized Controlled Trial's literature; SCT = Self-controlled study design's literature; IN = Idiopathic with normozoospermia; IOST = Idiopathic oligoasthenoteratozoospermia; IVV = Infertile male with varicocele with varicocelectomy; IAT = Infertile male with asthenoteratozoospermia; IMN = Idiopathic Infertile male with most normozoospermia; BMI = Body Mass Index (kg/m^2); UD = underlying Disease of participants namely hypertension, dyslipidemia, and diabetes mellitus; Duration = Duration of Infertility (years); WHO = World Health Organization Manual for Human Semen Analysis; S = Study's group; C = Control's group; n = Number of participants; NAC = N-Acetylcysteine (mg/day); INT = duration of NAC oral supplement (weeks); SA = Semen Analysis; B = Before study's group, A = After study's group; Vol = Volume of semen (mL); Conc = Concentration of sperm (x10^6/ml); Mot = Motility of sperm (%); Morph = Normal Morphology of sperm (%); HP = Hormonal Profile; T = Testosterone (ng/dL); LH = Luteinizing hormone (mIU/mL); FSH = Follicle stimulating hormone (mIU/mL); PRL = Prolactin (ng/ml); SPO = Spontaneous Pregnancy Outcome (%)

three months NAC consuming by their male partners could result in spontaneous pregnancy at the rate of approximately 30 percent (27/92). NAC's mucolytic activity could explain the increased pregnancy rate by improving cervical mucus quality without estrogen supplementation.[27]

CONCLUSION

Oral NAC improves male hormonal profiles, sperm quality and quantity with a 30 percent spontaneous pregnancy rate. Young couples, short infertile duration (two years), apparently normal female and non-smoking males were good candidates for oral NAC during the waiting period for appointment of infertile clinic.

What is already known on this topic?

Male infertility was a result of abnormal function of testis, hypothalamic pituitary axis and unexplained causes. NAC exhibited mucolytic, antioxidant and anti-inflammatory properties. Unexplained male infertility had been associated with oxidative stress. Effects of NAC for improving sperm concentration and acrosome reaction were consequences of reducing oxidative stress of sperm DNA. There had yet to be conclusive evidence in the use of NAC to treat male infertility issues.

What does this study add?

Oral NAC demonstrates potential as a treatment with a 30 percent spontaneous pregnancy among young couples with short infertility duration within three months.

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The Outcomes of Peripherally Inserted Central Catheter (PICC) Insertion in Pediatric Patients at Siriraj Hospital

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ABSTRACT

Objective: Peripherally Inserted Central Catheters (PICC) are widely used for intermediate to long term venous access. Venipunctures and catheterizations in pediatric patients can be challenging and traumatizing to children's veins due to frequent and painful needle sticks. This study aims to demonstrate the outcomes of PICC insertion and management in pediatric patients by the Anesthesia Line Service Team (ALiST) at Siriraj Hospital.

Materials and Methods: This is a retrospective, descriptive study, collecting data from January 2018 to December 2021. The inclusion criteria were pediatric patients aged 15 years with body weight equal to or exceeding 5 kg with no history of previous complicated central venous accesses. The primary outcome is the success rate of insertion. The characteristics of patients, sizes and types of catheter, reason of removal and complications were also reported.

Results: 124 PICCs were inserted in pediatric patients. The median age of patients was 5.0 years with a median height of 107.8 cm and a median weight of 10.0 kg. The successful insertion rate was 96.92% and all insertions were inserted using ultrasound-guided technique with or without fluoroscopy. No acute complications were noted during insertion. Most patients received either intravenous sedation (39.5%) or general anesthesia (26.6%) during the procedure. The mean duration of catheter indwelling was 66.48 days. Reasons for removal of PICC included completion of therapy and patient demise (70.97%), catheter malfunction (8.06%), accidental removal (4.03%), infection (8.06%) and patient non-adherence (1.61%).

Conclusion: Our research demonstrates a notably high rate of successful PICC placement among pediatric patients with data indicating a minimal occurrence of complications and an extended duration of catheter usage.

Keywords: Peripherally inserted central catheter; pediatric PICC; complications (Siriraj Med J 2024; 76: 135-143)

INTRODUCTION

The Peripherally Inserted Central Catheter (PICC) is a single or multi-lumen catheter inserted from a peripheral vein into a central vein. Although the upper arm is the most common insertion site in adults, lower extremities, scalp veins (for small babies) may be occasionally utilized if the vein's caliber is large enough, providing an uninterrupted path to the superior vena cava or inferior vena cava (in the lower torso).[1,2] Pediatric PICC was initially introduced in the 1970s for parenteral nutrition in neonates.[1-3] PICC is considered an alternative and/or a supplement to conventional venous lines.[4] Over time, PICC has also found uses in providing long-term intravenous access for medications such as antibiotic regimens in children. PICC is also an alternative to a Totally Implantable Venous Access (TIVAD) devices for pediatric cancers since placing TIVAD in small children poses multiple concerns.[5]

Generally, the indwelling duration of a PICC ranges from 0 days to 6 weeks.[1] An uncomplicated PICC represents

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the best practice for children to receive medications, intravenous fluids, or have blood samples taken (for PICCs larger than 2 French). PICC has gained popularity in pediatrics because of its ability to establish safe, long-term intravascular access, provide comfort, reduce the need for repeated venipunctures, and facilitate the transition to home intravenous therapy.[6,7]

Currently, PICC placements in our institution is a collaborative effort involving multidisciplinary specialties including pediatricians, interventional radiologists, and the anesthesiologists. We initiated involvement in PICC placement in 2010, and over time, it expanded from a one-man service to a team-based approach with the official establishment of the Anesthesiology Line Service Team (ALiST) which comprises of 25 physicians and 14 nurse anesthetists in our institute in 2018. The elective PICC placement service was initiated when the primary care team sent a request to the ALiST. Each individual patient was evaluated for suitability, device type, location of placement, appropriate sedation or anesthetic technique (if required). The nurse co-ordinator then queued up the patients for placement within 24-48 hours. NPO (Nil Per Os) order was selectively ordered for all children required sedation or anesthesia. The scope of this service includes in-hospital patients, critically ill individuals, and ambulatory patients of various ages, ranging from children weighing as small as 5 kg to adult patients.

The objective of this study is to outline the effectiveness and results of PICC insertion in pediatric patients. This encompasses various aspects, such as catheter specifications, selection of anesthetic techniques during insertion, post-insertion complications, and factors influencing catheter removal. Furthermore, the study investigates the relationship between complications and variables like catheter size and patient body weight.

MATERIALS AND METHODS

Following an approval from Siriraj Institutional Review Board (approval number Si 1033/2021, date of approval: December 27th, 2021), written informed consent was exempt for this retrospective chart review. The data was collected for pediatric patients who had PICC inserted by ALiST between January 1st, 2018 to December 31st, 2020. The inclusion criteria included pediatric patients aged 15 years or younger with a body weight of 5 kg or greater. Patients with a known history of central vein stenosis were excluded. Hospital numbers and patient details, as well as procedural information, were retrieved from the ALiST team database within the Department of Anesthesiology, Faculty of Medicine Siriraj Hospital. Other data were retrieved from patients' medical records which were stored in electronic files.

PICC insertion technique

All patients' preparation and procedural consents were obtained in adherence to the standard hospital protocol. After administering appropriate anesthesia or sedation, venous sono-anatomy was examined on the selected extremity to determine the optimal route for PICC insertion. The upper extremity of the patient was positioned with 45-degree shoulder rotation, allowing for up to a 90-degree elbow flexion. For lower extremity insertion, the patient was placed in a supine position with the hip externally rotated and the knee flexed at approximately 45 degrees to expose the medial thigh. The skin at the proposed insertion site was disinfected with a 2% chlorhexidine gluconate in 70% isopropyl alcohol. The procedure performing anesthesiologist surgically scrubbed their hands and donned sterile gowns and gloves. An additional anesthesiologist or nurse anesthetist was assigned to manage anesthesia or sedation specifically. A local infiltration of 1% plain lidocaine was administered prior to venipuncture with a 21Ga ultrasound enhanced-tipped needle under direct ultrasound guidance. Subsequently, either a 0.018 inch flexible-tipped or spring wire was inserted through the needle, which was then exchanged to a dilator or dilator with peel-away sheath. In case of trimmable PICCs, the catheter was trimmed to a premeasured length, estimated from the in-situ wire from the puncture site to either the distal superior vena cava (SVC, for upper extremities) or distal inferior venacava (IVC, for lower extremities). The PICC was then inserted over the guidewire (using the Seldinger technique) or through a peel-away sheath (using a modified Seldinger technique). When inserting a PICC in the upper torso, intracavitory electrocardiogram (iECG) was used for tip confirmation, while in lower torso insertions, fluoroscopy was used for tip confirmation. For non-trimmable PICCs, the excess portion was carefully coiled externally near the exit site. The location of the catheter tip was later radiographically confirmed using a portable x-ray machine. The tip was considered appropriately positioned if it resided in either the SVC, or the IVC. In younger children (under 10 years of age), the PICC was sutured with 4-0 nylon, while older pediatric patients who could cooperate had a non-suturing securing device used for stabilization. Finally, the exit site was covered with a chlorhexidine impregnated gel patch and a transparent bio-occlusive dressing.

The ALiST nurse provided guidance to caregivers (floor nurses or parents) and maintained regular contact

with all PICC patients, either through phone conversations or in-person visits until the PICC was removed or in the unfortunate event of the patient's passing. Detailed follow-ups included monitoring for occlusion, exit-site related issues, dislodgements, infections, and other relevant concerns, all of which were systematically recorded. The available PICC options at our institution included a 3 French single-lumen Nutriline PICC (Vygon, France), a 4 French single lumen, a 5 French double-lumen Arrow® (Teleflex Inc, USA) and a 5 French double-lumen Power-PICC (Bard Inc, USA).

The post-catheter insertion care order sheet was provided to ward or ICU nurses. Additionally, a twice-daily reminder sheet for normal saline (NSS) flush and heparinized NSS lock was introduced. To minimize excessive pressure generated by smaller barrel syringes, only a 10-mL syringe was allowed for saline flush and lock. For pre and post-medications, a 5-mL NSS flush volume (using a 10-mL syringe) was recommended. A 10 units/mL heparinized NSS solution was utilized for PICC lock unless heparin was contraindicated. Dressings were changed weekly unless they became saturated or obviously soiled.

In cases where a port could be flushed but did not yield any blood return (for PICCs larger than 2-Fr), it was categorized as a withdrawal occlusion. Total occlusion was identified when a port was impossible to flush or withdraw. The caregiver was instructed to notify the ALiST service in case of both withdrawal and total occlusion. Treatment options, including observation, gentle 10-mL NSS flush with push-pause technique or thrombolytic lock therapy, was considered in accordance with the established PICC occlusion guideline. The patient's care team also had to oversee the exit site for any signs of bleeding, redness, exudative discharge, limb edema as well as any catheter malfunctions such as dislodgement, breakage or leakage.

Statistical analysis

Data collection included patient demographics, PICC characteristics, procedure outcomes (success or failure), indwelling duration and complications including catheter occlusions, suspected infections, leakages, breakages or ruptures.

Descriptive statistical analysis was used to calculate and report quantitative data, including mean ± standard deviations, median with minimum and maximum values, or interquartile range (IQR). For categorical data, frequencies and percentages were used. Appropriate statistical tests, such as the Chi-square test, unpaired T-test, and Mann–Whitney U test were used to analyze categorical variables. All the data was compiled and analyzed using SPSS Statistics v.29.0 (SPSS, Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Definition

Catheter occlusion can be categorized as withdrawal occlusion when the port can be flushed but fails to yield blood return. If the catheter becomes uninjectable, it is defined as total or complete occlusion. Suspected catheter related infection is considered in patients with an indwelling PICC for over 48 hours who experience fever, leukocytosis and/or clinical signs of sepsis with positive hemoculture taken from either port of the PICC. Catheter dislodgement is defined as the mark on the PICC at the exit site being displaced or shifted from its previous position by more than 10 cm. Catheter malfunctions included breakage, leakage, perforation, retention of foreign bodies (tip of syringe or stopcock), discoloration, or deformity (flaccid, floppy or catheter rigidity).

The termination of PICC was determined by the following conditions: 1) completion of therapy or patient demise, 2) catheter malfunctions, 3) inadvertent removal, 4) suspected infection and 5) patient non-adherence.

RESULTS

During the study period, a total of 1,096 consultations for PICC insertions were compiled. Among these, 149 patients were 15 years old or younger. However, 19 patients were ineligible due to weighing less than 5 kg or less, and two more were excluded because of their history of central venous abnormalities. This resulted in a final cohort of 130 patients for data collection. Furthermore, four patients ultimately received central venous catheter insertions instead of PICCs, and two patients had missing data. Consequently, there were 124 pediatric PICC insertions available for analysis, as illustrated in Fig 1.

Patient's demographics data was shown in Table 1. There was a slightly higher proportion of female patients, accounting for 52.4% (65 out of 124). Most patients fell within the 2-10 years age group, comprising 54.8% (68 out of 124), with a median weight of 16 kg. The majority of patients, 96.0%, underwent PICC placement in the operating theater, while only 4.0% (5 patients) had the procedure done at the bedside. The primary indications for PICC placement were intravenous access (54.0%), total parenteral nutrition (28.2%) and chemotherapy (17.7%).

The successful insertion rate was 96.92% (with a 95% confidence interval (CI) ranging from 92.4% to 98.8%).

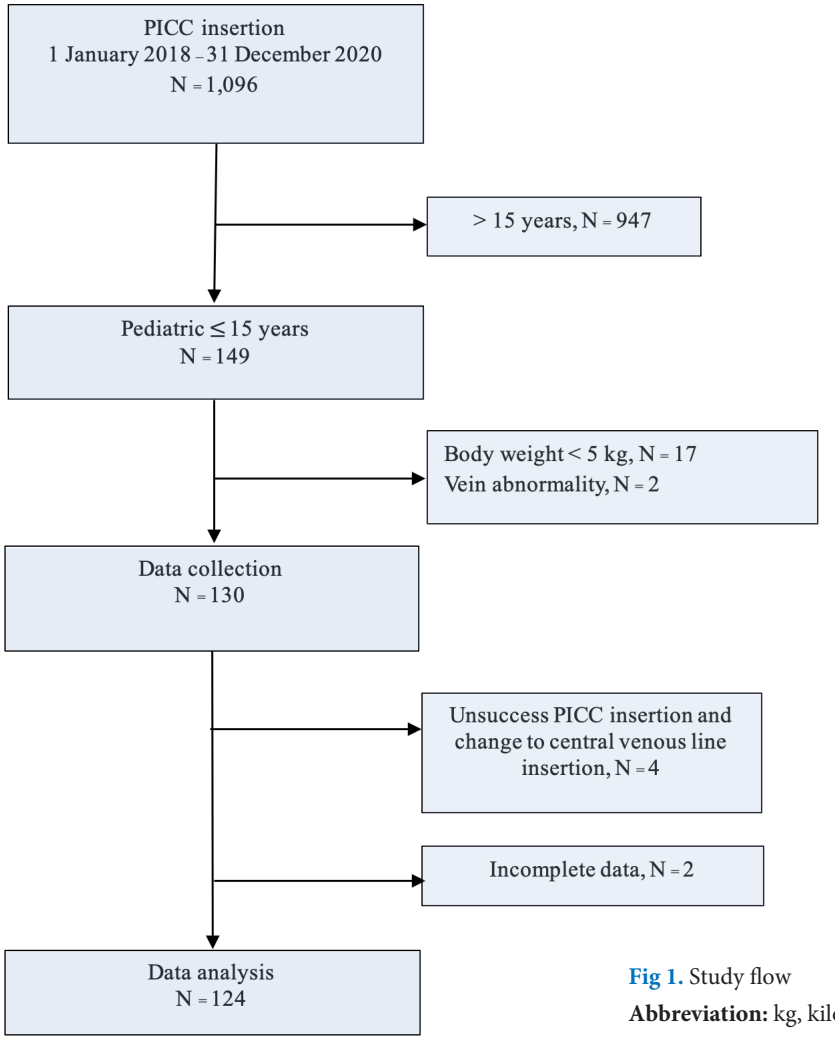

Fig 1. Study flow
Abbreviation: kg, kilogram

TABLE 1. Baseline characteristics of patients.

	n (%)
Total number of patients	124 (100%)
Sex	
Male	59 (47.6%)
Female	65 (52.4%)
Age (year), median (range)	5.0 (0.3-15.0)
Age (year), median (IQR)	5.0 (2.0, 8.9)
Age	
3 months-2 years	30 (24.2%)
>2 years-10 years	68 (54.8%)
>10 years	26 (21.0%)
Body weight (kg), median (IQR)	10.0 (10.0-25.8)
Height (cm), median (IQR)	109.0 (85.0-126.0)
Setting	
Operating theater	119 (96.0%)
Bedside	5 (4.0%)
Indications	
Intravenous access	67 (54.0%)
Total parenteral nutrition	35 (28.2%)
Chemotherapy	22 (17.7%)

All PICCs were inserted with ultrasound guidance, with or without real-time fluoroscopy. Notably, there were no immediate complications observed during insertion.

The PICC sizes and accessed veins are presented in Table 2 which revealed 75% of patients had PICCs placed in the upper extremities. For infants requiring PICCs larger than 2-Fr due to frequent blood sampling needs, these were placed in their lower extremities. In this study, the most used catheter sizes were 4-French (41.1%), followed by 5-French (29.8%) and 3-French (29.1%) as detailed in Table 2. Since our PICC services did not formally extend to babies smaller than 5 kg, the 3-French PICC represented the smallest size included in our study. We primarily employed iECG to verify the placement of PICCs in the upper torso or when inserting PICCs at the bedside (48.4%). Fluoroscopy was utilized for confirmation in cases of PICCs placed in lower extremities or for small infants (50.0%). Landmark-guided placement was recorded in only 2 patients (1.6%) in this study.

Majority of children received some form of sedation or anesthesia. The intravenous sedation was employed for most patients (38.7%), followed by general anesthesia (26.6%). There are some large and cooperative children exclusively received only local anesthesia during the procedure (28.2%). Details about the anesthesia techniques can be found in Table 2.

We identified 11 documented catheter-related infections, accounting for 9.73% of cases, as shown in Table 3. No statistically significant correlation was observed between the infection rate and factors such as catheter size, catheter placement site, or the duration of the indwelled catheter.

Nonetheless, we encountered 26 instances of catheter malfunctions, which emerged as the most prevalent post-insertion complication in this study, comprising 20.97% of cases. While it appeared that catheter malfunction might occur more frequently with smaller catheter sizes, these differences did not reach statistical significance, as shown in Table 4.

The mean duration of indwelling catheter was 66.48 days (4 – 402 days). Most patients, 66.94%, retained their catheters until therapy was completed or until their passings. Detailed reasons for PICC removal are presented in Table 5.

DISCUSSION

In our study, we observed that PICC insertion in the pediatric population accounted for 11.3% of all PICC insertions carried out by anesthesiologists in our institute, demonstrating a notably high success rate of 96.92%. The late complications most frequently encountered in this population were catheter malfunction and catheter infection.

TABLE 2. Catheter sizes, accessed veins, confirmation techniques and anesthesia techniques.

	n = 124 (100%)
Catheter sizes	
3-French	36 (29.1%)
4-French	51 (41.1%)
5-French	37 (29.8%)
Veins accessed	
Upper arm veins (Basilic vein, Brachial vein, Cephalic vein)	93 (75.0%)
Lower extremity veins (Saphenous vein, distal Femoral vein)	31 (25.0%)
Confirmation techniques	
Landmark	2 (1.6%)
iECG (intracavitory ECG)	60 (48.4%)
Fluoroscopy	62 (50.0%)
Anesthesia techniques	
Local anesthesia	35 (28.2%)
Intravenous sedation	49 (39.5%)
General anesthesia	33 (26.6%)
N/A	8 (6.5%)

NA = not applicable or missing information regarding anesthesia technique

TABLE 3. Factors associated with infections.

Factor	Infection (n=10)	Non-infection (n=114)	p-value
Catheter size			
3-French	5 (13.9%)	31 (86.1%)	0.325
4-French	3 (5.9%)	48 (94.1%)	
5-French	2 (5.4%)	35 (94.6%)	
Site			
Upper extremity veins (basilic vein, brachial vein, cephalic vein)	3 (9.7%)	28 (90.3%)	0.710
Lower extremity veins	7 (7.5%)	86 (92.5%)	
Duration of catheter (weeks)			
≤ 6 weeks	4 (6.0%)	63 (94.0%)	0.510
> 6 weeks	6 (10.7%)	50 (89.3%)	

TABLE 4. Factors associated with catheter malfunctions.

Factor	Catheter malfunction (n=26)	Catheter well-used (n=98)	p-value
Catheter size			
3-French	11 (30.6%)	25 (69.4%)	0.193
4-French	10 (19.6%)	41 (80.4%)	
5-French	5 (13.5%)	32 (86.5%)	
Body weight (kg), median (range)	13.8 (7.0-73.2)	16.6 (5.0-73.0)	0.214

TABLE 5. Reasons for PICC removal.

Reason	n (%)
Total number	124
Missing data or loss to follow up	9 (7.26%)
Completion therapy & Demise	88 (70.97%)
Catheter breakage, rupture, occlusion	10 (8.06%)
Inadvertent removal	5 (4.03%)
Suspected infection	10 (8.06%)
Patient non-adherence	2 (1.61%)

Placing PICC in children presents numerous challenges. The vascular anatomy in pediatric patients differs significantly from that in adults and is influenced by factors such as body size and the activities associated with their development stage.[8] Infants younger than one year are not predominantly engaged in activities that involve standing or use of arms extensively. As a consequence, this leads to the development of smaller limbs and smaller limb vessels when compared to adults, making PICC placement more difficult.[9] The placement of PICC smaller than 3-Fr made blood sampling nearly impractical.[10] Co-operation and immobility of extremities are not guaranteed. Confirming the tip location is also fraught with extreme technical difficulties. PICC placement in pediatric patients requires a more intricate setup, which is time-consuming when compared to the relatively simpler process of placing one in adults. The procedure requires an experienced team, and we often provide sedation or anesthesia to facilitate the procedure and lessen the psychotraumatic experience of the small children. Following an official PICC consultation, the preliminary screening was performed by an ALiST nurse to determine the appropriate location for the procedure (bedside or OR). The anesthesiologist was then consulted to confirm the plan, the type of PICC, the choice of sedation or anesthesia including the proper NPO time. The parents or legal guardians were then approached for an informed consent. The procedure was usually executed on the following day or the first day after the weekend. Almost all PICCs placed in children larger than 5 kg in our institution were placed by the ALiST, while some were serviced by the radiology team who also take care of babies smaller than 5 kg and patients with complicated central venous access history (children born with diseases that mandate lifelong total parenteral nutrition and have been accessed for central veins multiple times). For small neonates, the PICCs were inserted by the neonatologist team.

In this study, all pediatric PICCs were performed by experienced anesthesiologists who have extensive skills in both pediatric and adult PICCs. Notably, most of our patients also received either intravenous sedation or general anesthesia, providing limb inactivity and ensuring the serenity of both the patient and the team. Safe sedation/anesthesia also offers children and their legal guardians' acceptance and comfort. Even pediatric PICC placements by radiology interventionists in our hospital (not included in this report) were all performed under sedation or anesthesia. In the Neonatal Intensive Care Unit (NICU), PICCs are usually inserted without the direct involvement of the anesthesia team. However, it's worth noting that many neonatologists often administer mild sedation to these tiny infants, and their delicate and underdeveloped limbs can usually be easily physically restrained. This combined effort ensures safe and successful PICC placement in the NICU setting.[11,12]

The study determined that the size of the catheter and the patient's body weight did not show a significant association with catheter malfunction. Smaller catheter sizes, however, are associated with a higher occurrence of occlusions.[12] The selection of the appropriate PICC size should be based on the size of the access vein and the necessary therapies, rather than being solely determined by the patient's age. Generally, smaller catheters with fewer lumens are associated with fewer complications. However, it is important to note that very small catheters are more prone to occlusion. If blood sampling through the PICC become necessary, a minimum size of 3 French (3Fr) or larger is required. The incidence of catheter infections in our study was reported in 11 cases (9.73%), which is approximately 3 folds of that reported by earlier studies which were ranging from 2-4%.[13-15] However, our study had the remaining catheters in place for an average of 66 days, whereas the other studies had an average placement duration of 14 to 45 days. This suggests that our study indicates a potential relationship between the infection rate and the number of days the catheters remain in place.

We also encountered another time-consuming aspect of PICC placements involving children with complex venous anatomy. These patients typically have a history of multiple bowel surgeries or lifelong short bowel syndrome, often requiring hospitalizations since birth and having a history of multiple prior central venous accesses. In these patients, the venipunctures under ultrasound guidance typically proceed without significant issues. However, the process of threading a wire or placing a PICC becomes unfeasible. Venography reveals a network of collateral veins instead of a large prominent vein leading to the SVC or IVC. Due to our limited expertise and inadequate equipments (including hydrophilic wires, balloon catheters, and a dedicated radiology suite), we subsequently compiled a list of these patients and referred them to seek PICC placements from intervention radiologists or vascular surgeons, who possess the necessary resources and skills to handle these cases effectively.

As our service is exclusively managed by the anesthesiology department, the convenient availability of anesthesia during the procedure has led to a significant increase in the number of patients undergoing the procedure with either sedation or general anesthesia. Despite the

rising costs and increased personnel requirements, this approach may enhance acceptance among parents and older children. A tranquil and calm patient during the procedure may potentially result in a higher success rate.

This report had several limitations. First, it was based on dataset with a limited number of patients. The study design was a retrospective chart review, which inherently lacked the capability to address specific questions or establish causality for different therapeutic approaches. Key details, such as the number of insertions attempts and the duration of insertions, were not documented. Furthermore, there are significant gaps in information, particularly regarding follow-up data. Nonetheless, this report plays a crucial role in shedding light on the occurrence of complications, prompting the involved team to maintain vigilance in monitoring potential complications that may occur following PICC insertion in a pediatric population.

Establishing the PICC service by the anesthesiologists at our institution presents a unique and potentially challenging model that may be hard to replicate. Its origin trace back to an individual's initiative to provide intravenous accesses primarily to private patients by special requests which later expanding to encompass regular patients. The service gained traction among junior anesthesia colleagues who shared similar interests, leading to its acceptance as a viable solution by administrators. What began as a one-person service has evolved into a team-based approach. We are currently in the process of transforming this service further into a multidisciplinary approach. We are incorporating information technology for database management and improving accessibility for other specialties providing similar services. Collaboration with the hospital quality development, the infectious control unit, and experts such as radiologists and vascular surgeons has propelled the initiative towards becoming a comprehensive hospital PICC center. By consolidating human workforces and minimizing redundancy, we aim to enhance unit efficiency and take it to the next level.

CONCLUSION

This study represents the first report of PICC insertion in pediatric patients within a university hospital in Thailand. Our findings demonstrated a notably high success rate of insertions and no immediate complications were identified during the study period. The prevalent complications observed were catheter malfunctions and infection. The participation of fully trained medical personnel and attentive caregivers is vital to guarantee proper post-insertion care and to maintain a complication-free experience for the entire duration of PICC use. The ALiST team at Siriraj is available by direct contact to provide a consult or assist the other institutions to start the PICC service.

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Data availability

The dataset can be provided upon request to the corresponding author.

Conflict of interest

The authors declared no conflict of interest.

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Metastatic Death Following Ophthalmic Artery Chemotherapy for Retinoblastoma: A Systematic Review and Meta-analysis

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ABSTRACT

Objective: The use of ophthalmic artery chemotherapy (OAC) as a front-line and salvage therapy for retinoblastoma has grown. However, the risk of metastatic death in these patients remains unclear.

Materials and Methods: This study of metastatic deaths in OAC may benefit physicians managing retinoblastoma patients. A literature search of Medline, Scopus, Science Direct, and CINAHL was conducted from conception until November 2023. The primary outcome was metastatic death in patients treated with OAC.

Results: From the 219 evaluated articles, nine met the inclusion criteria. A total of 596 (635 eyes) patients were treated with OAC; and 20 cases resulted in death due to metastasis of the retinoblastoma. The metastatic mortality rate was 2.5% (95% confidence interval: 0.8%-4.2%) which was statistically significant ($p < 0.05$). The central nervous system was the most common site of metastasis, followed by multiple sites of metastasis.

Conclusion: OAC treatment is associated with the risk of metastatic death, but it is lower than the overall mortality rate of retinoblastoma. Further studies to identify the risk of metastasis are needed.

Keywords: Retinoblastoma; metastasis; ophthalmic artery chemotherapy; mortality; central nervous system (Siriraj Med J 2024; 76: 144-151)

INTRODUCTION

Retinoblastoma, which typically develops before the age of five, is the most common malignant intraocular tumor in children.[1] The mean incidence ranges from 11.2-12.4 per 1 million in children younger than five.[2,3] Current treatment modalities include enucleation, chemotherapy, local therapy with laser photocoagulation, cryotherapy, and radiotherapy. Irrespective of the chosen therapeutic approach, the objective of the treatment is to preserve patients' lives, ocular globes, and vision. Systemic chemotherapies, such as the combination of carboplatin, etoposide, vincristine, or vincristine, doxorubicin, and cyclophosphamide, have been used as adjuvant and salvage therapies. Although they carry a relatively low risk of neutropenic death and platinum-induced ototoxicity,[4,5] these regimens include topoisomerase II inhibitors and

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may elevate the risk of second malignant neoplasms, particularly acute myeloid leukemia (AML).[6,7] External beam radiotherapy has previously been used as salvage therapy to prevent enucleation -- the surgical removal of the eyeball and optic nerve -- in patients with treatment-resistant retinoblastoma. It has yielded satisfactory results, however, this approach may elevate the risk of secondary malignant neoplasms.[8,9] To resolve these issues, direct chemotherapy administration has gained attention. Originating in Japan, ophthalmic Artery Chemotherapy (OAC) is now widely used as both a primary and salvage therapy, with promising results.[10,11] However, enucleation remains a necessary step for patients with affected eyes unresponsive to treatments. Delayed enucleation, often due to parental hesitancy[12] or treatment-related factors,[13] can lead to disease progression. Moreover, there is a risk of distant metastasis from retinoblastoma due to potential micrometastasis, even when the localized disease is under control. These reasons raise concerns about OAC and increase the likelihood of metastasis of the retinoblastoma. Given the unclear risk of metastatic death associated with OAC, conducting a systematic review and meta-analysis on this mortality aspect could be valuable for physicians managing retinoblastoma patients.

MATERIALS AND METHODS

Data sources and research methodology

A comprehensive literature review was conducted using databases such as Medline, Scopus, ScienceDirect, and CINAHL from inception to November 2023. The search focused on keywords like intraarterial infusion, retinoblastoma, and death, utilizing Medline's suggested synonyms to broaden the search scope. The search was limited to English-language published articles. Detailed search methodologies are outlined in Electronic Supplementary Material 1. Additionally, references from relevant reviews, articles, letters, and protocols were examined for applicable studies. Contacting experts in the field was not performed.

Inclusion and exclusion criteria

The meta-analysis included studies that met the following criteria: (1) human studies, (2) clear indication of OAC as the treatment method, and (3) explicit reporting of deaths during the study period. Studies were excluded if they were (1) not research articles, (2) failed to report the total number of patients treated with OAC, (3) did not provide data on the total number of metastatic deaths post-OAC, (4) included populations overlapping other studies, and/or (5) involved participants who had previously or were concurrently undergoing intravenous chemotherapy. The systemic review process is depicted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, shown in Fig 1.

Data extraction and evaluation

The selected articles were systematically organized using the EndNote X7, Thomson Reuters, New York, USA citation management. Initial steps involved removing duplicates, followed by a review of titles and abstracts by the first author, focusing on specific words, such as "report" to exclude case reports. Following this, the remaining abstracts were reviewed. For data abstraction, a structured form was designed by the first author and validated by the fourth author. This information was utilized to gather information on aspects such as study design, location, patient demographics, treatment characteristics, follow-up duration, and detailed mortality descriptions within each study. The first and last authors independently extracted this information, resolving any discrepancies through consensus. The evaluation of the risk bias in the studies was determined using a methodology proposed by *Murad et al 2018*.[14] This involved translating positive answers (e.g., "yes" or "clear evidence", or "no alternative explanation") into a numerical value of one. Total scores of 1-3, 4-5, and 6-8 were categorized as "good", "fair", and "poor", respectively.

Statistical methods

A binary random-effects model, following the DerSimonian-Laird approach, was implemented using OpenMetaAnalyst software, tailored for Windows 8.[15] The I^2 statistic was used to assess the heterogeneity of the underlying population. The interpretation of I^2 was as the followings: 0-25% indicated insignificant heterogeneity, 26-50% indicated low heterogeneity, 51-75% indicated moderate heterogeneity, and >75% indicated high heterogeneity.[16] We performed meta-regression using the random effects model to further investigate factors affecting the heterogeneity of the meta-analysis.

RESULTS

Study characteristics

A systematic search across various literature databases yielded 219 unique articles. After applying the inclusion and exclusion criteria, nine articles were selected for systematic review and meta-analysis (Table 1). These studies were conducted in China,[17-20] Egypt,[21] Switzerland,[22] Turkey,[23,24] and the United States,[25] which demonstrates a diverse racial composition of the participants. In this meta-analysis, 596 participants

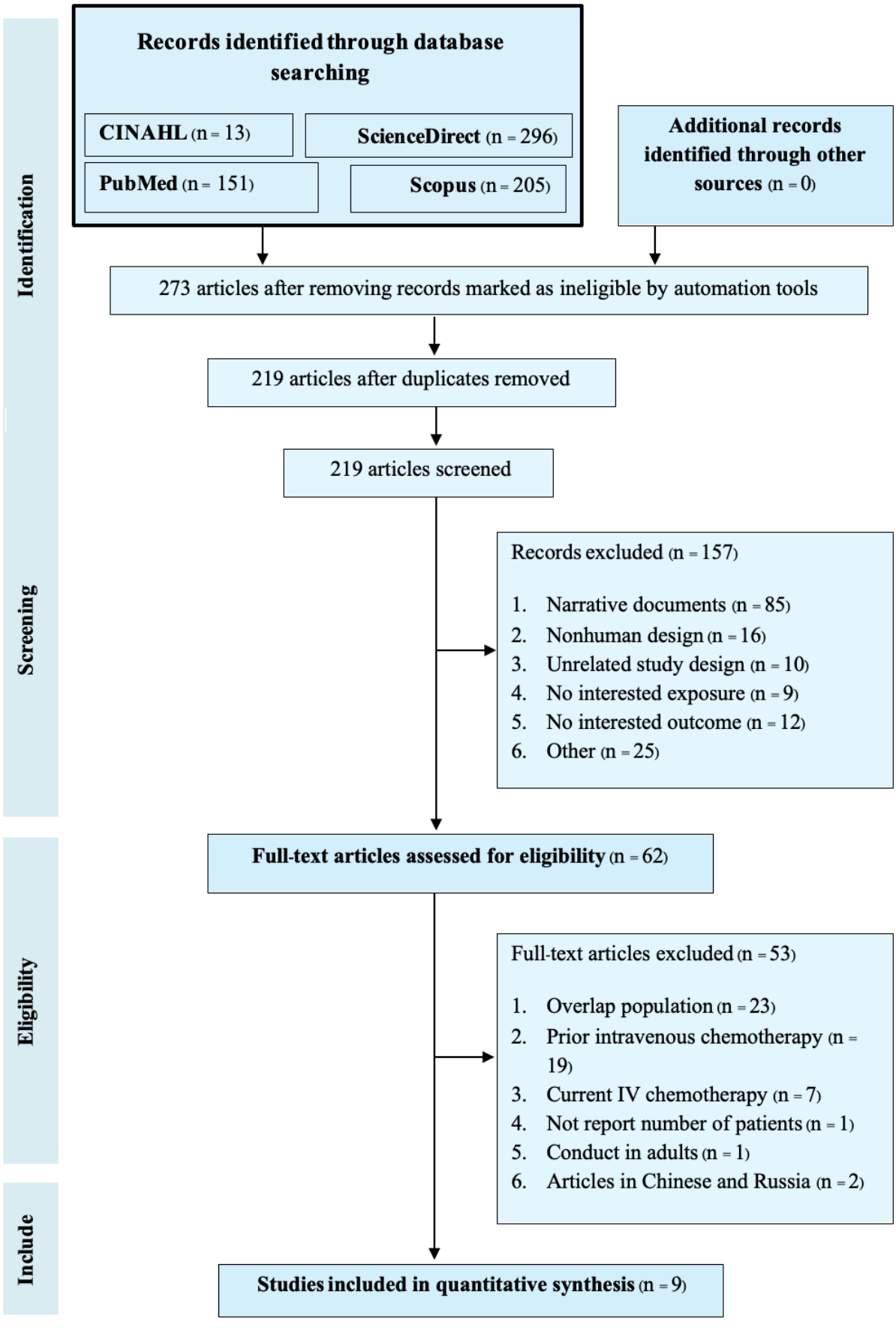

Fig 1. PRISMA diagram for the systematic review.

TABLE 1. Description of included studies

Author	Study design	Study location and year of the study	Demographics	Treatment characteristics	Follow-up duration (months)
Chen et al., 2020	Retrospective chart review	Multicenter, China (April 2009 - January 2017)	**N (patients/eyes):** 110/115 **Age (months):** ND (1.0-67.0) **Sex (male %):** 59.1 **ICRB:** D-E **Unilateral (%):** 95.5	**Naïve eyes (%):** 100.0 **OAC only (%):** 44.3 **Enucleation after treatment (%):** 26.1	ND (6.0-83.0)
Wen et al., 2023	Open-label RCT	Multicenter, China (June 2015 - June 2018)	**N (patients/eyes):** 72/72 **Age (months):** 25.5±14.4 **Sex (male %):** 56.0 **ICRB:** D-E **Unilateral (%):** 100.0	**Naïve eyes (%):** 100.0 **OAC only (%):** 100.0 **Enucleation after treatment (%):** 29.2	36.1 (2.5-54.1)
Liang et al., 2022	Retrospective chart review	Shanghai, China (January 2016 - December 2018)	**N (patients/eyes):** 116/116 **Age (months):** 22.0 (12.6-120.0) **Sex (male %):** 53.0 **ICRB:** D-E **Unilateral (%):** 100.0	**Naïve eyes (%):** 100.0 **OAC only (%):** 34.0 **Enucleation after treatment (%):** 6.0	39.0 (22.0-57.0)
Othman et al., 2020	Prospective study	Assiut/Sheikh Zayed, Egypt (January 2016 - March 2019)	**N (patients/eyes):** 16/23 **Age (months):** 11.1 (2.0-48.0) **Sex (male %):** 50.0 **ICRB:** B-E **Unilateral (%):** 56.3	**Naïve eyes (%):** 100.0 **OAC only (%):** 50.0 **Enucleation after treatment (%):** 8.7	18.5 (9.0-36.0)
Oto et al., 2020	Retrospective chart review	Istanbul, Turkey (2011-2017)	**N (patients/eyes):** 21/21 **Age (months):** ND **Sex (male %):** ND **ICRB:** B-E **Unilateral (%):** 100.0	**Naïve eyes (%):** 100.0 **OAC only (%):** 52.4 **Enucleation after treatment (%):** 28.6	40.8 (12.0-65.0)
Qi et al., 2022	Retrospective chart review	Zhengzhou, China (June 2015 - June 2019)	**N (patients/eyes):** 140/160 **Age (months):** 21.64±14.67 **Sex (male %):** 58.6 **ICRB:** B-E **Unilateral (%):** 87.5	**Naïve eyes (%):** 100.0 **OAC only (%):** 100.0 **Enucleation after treatment (%):** 14.4	28.5 (2.0-60.0)
Tuncer et al., 2016	Retrospective chart review	Istanbul, Turkey (October 2011 - September 2015)	**N (patients/eyes):** 22/26 **Age (months):** 18.0 (6.0-55.0) **Sex (male %):** 54.6 **ICRB:** D-E **Unilateral (%):** 91.7	**Naïve eyes (%):** 100.0 **OAC only (%):** ND **Enucleation after treatment (%):** 33.3	29.0 (6.0-46.0)
Munier et al., 2016	Retrospective chart review	Lausanne, Switzerland (1977-2014)	**N (patients/eyes):** 25/25 **Age (months):** 33.3±25.9 **Sex (male %):** ND **ICRB:** D-E **Unilateral (%):** 100.0	**Naïve eyes (%):** 20.0 **OAC only (%):** ND **Enucleation after treatment (%):** 0.0	41.7 (19.6-89.5)
Yannuzzi et al., 2015	Retrospective chart review	New York, United States (August 2014 - March 2015)	**N (patients/eyes):** 72/77 **Age (months):** 19.3 (ND) **Sex (male %):** 47.2 **ICRB:** C-E **Unilateral (%):** 63.6	**Naïve eyes (%):** 100.0 **OAC only (%):** ND **Enucleation after treatment (%):** 13.0	44.9 (ND)

Data are presented as median (max-min) or mean±standard deviation
Abbreviations: CMT: chemotherapy, OAC – Ophthalmic artery chemotherapy, ICRB: International Classification of Retinoblastoma, ND: No data

(635 eyes) were studied. Among these, 89.9% (n = 536 patients) were diagnosed with unilateral retinoblastoma. The size of the studies included was small, with a median participant count of 72 (range: 16-140). The participant group showed a balanced gender distribution, with males comprising a median of 54.5% (range: 47.2-59.9%). All subjects were pediatric patients, with ages spanning from 11 to 34 months. The median follow-up period ranged from 1.5-3.7 years. The overall quality of the articles was considered fair, with a median risk of bias score of 5. In brief, all included studies had clear inclusion criteria, adequate exposure and outcome ascertainment, and sufficient follow-up time. There were no challenge/rechallenge of the ophthalmic artery chemotherapy and dose-response relationship related to metastatic death observed from all included studies. A detailed summary of the study quality can be found in Table 2.

Metastatic mortality rates

Metastatic mortality rates were assessed among 596 patients, with at least 24 instances of metastasis identified.[17-20,25] The most common site of metastasis was the brain, followed by bones. The average duration from the start of ophthalmic artery chemotherapy to metastasis onset was 25.5 months in one study.[25] For patients with metastasis, the post-OAC survival time ranged from 10.2 to 27.3 months according to *Chen et al,*[17] and 8.4 to 23.0 months per *Wen et al's* findings.[18]

The rate of enucleation following ophthalmic artery chemotherapy was 16.2% (95% confidence interval: 9.4%-22.9%, $I^2 = 84.87$, n = 108/635 eyes, N = 9). We also found 20 instances of metastatic deaths in the included studies. The meta-analysis revealed a pooled weighted metastatic death rate, or the mortality rate considering the study size, of 2.5% (95% confidence interval: 0.8%-4.2%, n = 20/596 patients, N = 9), and this rate was statistically different from zero ($p < 0.05$) (Fig 2). The heterogeneity of the studies was moderate ($I^2 = 51.42\%$) so the use of the pooled rate estimates should be with caution.

We further investigated the effect of two factors on the proportion of metastatic death: 1) the length of follow-up time, and 2) the percent of patients treated with IAC only in each study. We found that increasing the length of follow-up time slightly lowered the metastatic death rate (β coefficient = -0.002 (95%CI: -0.005-0.000), N = 9, p = 0.045). In addition, increasing the percentage of patients who received IAC only slightly increased the metastatic death rate (β coefficient = 0.001

TABLE 2. Quality of the included studies.

Authors	(Representative of the) Selection	Ascertainment (exposure)	Ascertainment (outcome)	Alternative causes	Re-challenge	Dose-response	Follow-up duration	Sufficient reporting	Summary risk of bias
Chen et al., 2020	Yes	Yes	Yes	Maybe	No	No	Yes	Yes	5
Wen et al., 2023	Yes	Yes	Yes	No	No	No	Yes	Yes	6
Liang et al., 2022	Yes	Yes	Yes	Maybe	No	No	Yes	Yes	5
Othman et al., 2020	Yes	Yes	Yes	Maybe	No	No	Yes	No	4
Oto et al., 2020	Yes	Yes	Yes	Maybe	No	No	Yes	No	5
Qi et al., 2022	Yes	Yes	Yes	No	No	No	Yes	Yes	6
Tuncer et al., 2016	Yes	Yes	Yes	No data	No	No	Yes	Yes	5
Munier et al., 2016	Yes	Yes	Yes	No data	No	No	Yes	Yes	5
Yannuzzi et al., 2015	Yes	Yes	Yes	No data	No	No	Yes	Yes	5

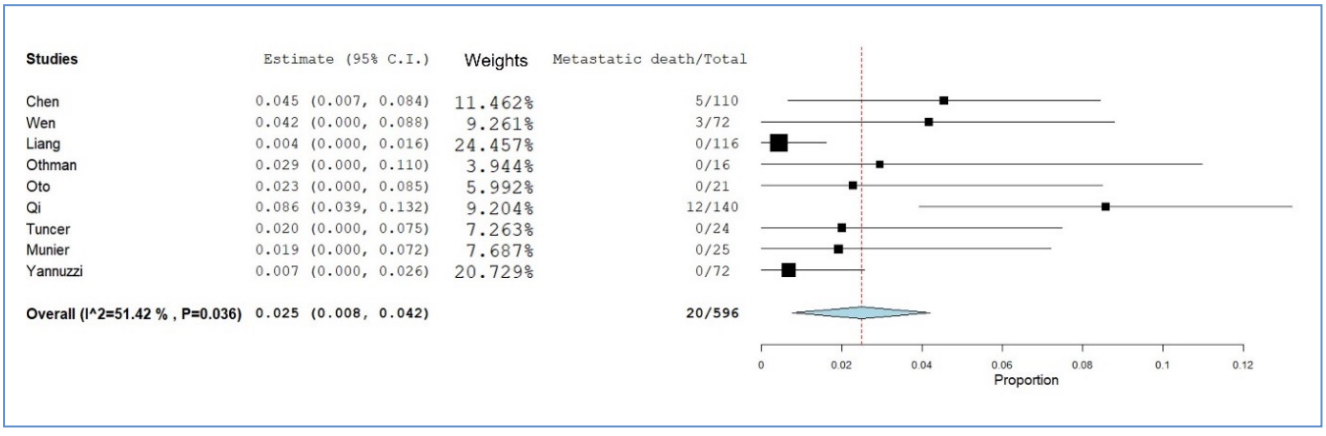

Fig 2. Forest plot demonstrating the proportion (%) of metastatic death of retinoblastoma treated with ophthalmic artery chemotherapy.

(95%CI: 0.000-0.001), p = 0.021). We therefore concluded that the length of follow-up time, and the percent of patients treated with IAC only affected the heterogeneity of this meta-analysis.

DISCUSSION

Treating retinoblastoma poses the dual challenge of preventing metastasis and preserving vision. With the introduction of OAC, the management of retinoblastoma has undergone drastic changes, with OAC serving both as front-line and salvage therapy. This study's findings show a metastatic mortality rate of 2.5% among retinoblastoma patients treated with OAC, which closely aligns with the 2.1% (14/655) rate noted in a systematic review.[26] The overall mortality rate for retinoblastoma ranges from 1-9%,[26,27] with a specific study reporting a 1.7% metastatic death rate following primary enucleation over a follow-up period of 2.1 years (range 0.4-4.8).[28] This study also found that the most frequent metastatic deaths were attributed to CNS complications, with post-OAC survival times spanning 8.4 to 27.3 months, which is longer than those reported post-enucleation (6-14 months).[28] Despite global improvements in survival rates, including in countries with limited resources, high-risk histopathological features,[29] and delayed enucleation[30,31] appear to be the leading cause of metastatic deaths in retinoblastoma. While adjuvant systemic chemotherapy is effective in mitigating the risk of metastatic deaths in patients with high-risk histopathological features[32] and may theoretically decrease the risk of metastasis in those receiving OAC, evidence from a study of patients treated with a combination of OAC and systemic chemotherapy[17] shows that the risk of metastasis cannot be completely eliminiated by systemic chemotherapy (a fact physicians should be aware of). We also noted that CNS was the predominant site for metastasis, which emphasizes the need for regular imaging to detect metastasis early in patients.

This study has several limitations that need to be addressed. First, our systematic review and meta-analysis found only nine studies focusing on the use of OAC for retinoblastoma treatment without previous or concurrent intravenous (IV) chemotherapy. These strict exclusion criteria, designed to minimize the confounding effects from IV treatments, yielded a smaller case pool. This approach also led to the exclusion of several other studies, such as one by *Abramson et al*,[33] which reported three metastatic deaths among 1,139 patients treated with OAC and other modalities, possibly including IV chemotherapy. Second, even though high-risk pathological features are predictive factors of metastatic death, there is no data on whether eyes unresponsive to OAC harbored high-risk histopathological features. If these patients also had high-risk pathological features, the metastatic death could be affected by high-risk histopathological features instead of only by OAC. Additionally, the median follow-up period in our analysis ranged between 1.5 to 3.7 years. If studies with shorter follow-up times had extended their duration, more metastasis may have been detected. As evidenced by a systematic review that reported seven additional metastatic cases beyond study endpoints in follow-ups, the median follow-up time ranged from 7 to 74 months.[26]

This systematic review and meta-analysis provides valuable insights into metastatic mortality among retinoblastoma patients treated with OAC. This study also highlights several clinical and research concerns, such as the prevalence of CNS metastasis as a leading cause of death post-OAC, with instances occurring 8.4 to 27.3 months after treatment. This finding highlights the importance of discussing the risk of distant metastasis, especially CNS metastasis, with patients' parents since

the clinical outcome of patients with extraocular diseases is dismal even when treated with intensive therapy.[34,35] Future studies should identify the risk of distant metastasis in those receiving OAC in addition to uncovering more information such as the OAC to be synthesized, and what reporting system (WHO,[36] PROCESS,[37] or CARE[38]) should be followed. This systematic review and meta-analysis also revealed that several studies failed to include vital information, including previous and concomitant treatment, enucleation rate post-OAC, number of participants who failed to follow-up, and cause of death (Table 1). Therefore, it was not possible to meta-analyze some information in our study.

CONCLUSION

In conclusion, while OAC is associated with a risk of metastatic death in retinoblastoma, the risk appears to be on par with the mortality rate associated with the condition. Therefore, it is important to communicate the risk of potential distant metastasis to patients' parents and pursue further studies to identify the risks of metastasis following OAC treatment.

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Conflict of interest

None.

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Impact of COVID-19 on Health Status and Management of Patients with CNS Demyelinating Diseases: A Single-Center Study

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ABSTRACT

Objective: Study the effects of COVID-19 on health status and alterations in managing patients with CNS-IDDs.

Materials and Methods: A questionnaire-based approach was commenced at the MS and Related Disorders Clinic at Siriraj Hospital in Thailand from March 2021 to December 2021. The data obtained from the questionnaire was subjected to statistical analysis.

Results: The study comprised 92 patients with CNS-IDDs, with 72.8% female and a mean age of 44.6±14.0 years. Overall, 67.4% of patients were vaccinated following Thai National guidelines. Only two patients were confirmed to have contracted COVID-19 infection. The most common treatment administered in the 92 CNS-IDD patients was Azathioprine (39.1%), prednisolone (32.6%), then 14.1% each in MMF and Rituximab. Sixty-one patients (66.3%) reported no relapse in the past year and no statistically significant difference among the diseases. The mean self-rated quality of life (QoL) score was 8.0±1.9 before the COVID-19 pandemic then drastically decreasing to 5.4±2.4 during the pandemic period. Overall, 56.5% indicated at least some impact on physical well-being, and 69.6% reported challenges to psychological health. 16.3% postponed or canceled their appointments during the COVID-19 pandemic, and 8.3% transitioned from face-to-face meetings with doctors in the clinic to telemedicine or telephone follow-up.

Conclusion: Our study revealed that patients with CNS-IDDs experienced no significant change in relapse and a low incidence of COVID-19 infection. During the pandemic, overall, patients' QoL decreased both physically and psychologically.

Keywords: Covid-19; questionnaire; CNS demyelinating diseases; quality of life; impact of the COVID-19 (Siriraj Med J 2024; 76: 152-159)

INTRODUCTION

The coronavirus disease (COVID-19) outbreak, triggered by severe acute respiratory coronavirus 2 (SARS-CoV-2) was identified in 2019.[1] Its clinical manifestations vary from asymptomatic cases to severe symptoms and even death. Older age and coexisting medical conditions like diabetes, hypertension, and cardiovascular disease are poor prognostic factors and independent predictors of COVID-19-related mortality.[2]

Besides respiratory symptoms, various neurological symptoms have been documented, including headaches, dizziness, encephalopathy, unconsciousness, stroke, convulsions, neuropathy-like inflammation, and altered taste or smell. While the likelihood of COVID-19 infection is not higher in individuals with Multiple Sclerosis (MS) than in the general population, certain factors increase the risk of a severe COVID-19 infection, such as steroid use, specific disease-modifying therapies, older age, and

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severe disabilities. Like other viral infections, COVID-19 can exacerbate immune-mediated diseases. During the COVID-19 pandemic, physicians had to consider various aspects of care of patients with CNS demyelinating diseases (CNS-IDDs), and this was not limited to only the impact of COVID-19 on patients but also changes in care practices, monitoring, and management protocols, addressing psychological and social effects, and providing guidance on COVID-19 vaccinations in these patients. While many studies have reported on this issue, most are limited to Asia. In the context of the COVID-19 pandemic, vaccines were paramount for MS patients. Israel stood out as a country with a high vaccination rate, with 91.2% of the population receiving the BNT162b2 COVID-19 vaccine during the pandemic.[3] Achiron et al. demonstrated the safety of the COVID-19 BNT162b2 vaccine in MS patients without increasing the risk of relapse activity.[4] Another study also confirmed the safe use of the COVID-19 BNT162b2 vaccine and its efficacy against COVID-19 in MS patients.[5] Globally, the Multiple Sclerosis Society recommends all patients with MS be vaccinated against COVID-19. However, reports on the impact of COVID-19 in patients with Neuromyelitis optic spectrum disorders (NMOSD) are scarce.[6] This study aims to investigate the impact of the COVID-19 pandemic on patients' quality of life (QoL) through easy, self-rated patient assessments among Thais with CNS-IDDs in a single center.

MATERIALS AND METHODS

Study design

We conducted a questionnaire survey among patients with CNS-IDDs who attended the Multiple Sclerosis and Related Disorders Clinic at Siriraj Hospital, Mahidol University, Thailand, between March and December 2021.

Our inclusion criteria were patients who (1) were aged 18 or older, (2) had undergone serum AQP4-antibody testing at least once, and (3) had a follow-up period of at least 6 months. We excluded patients with incomplete information or communication problems that hindered their ability to respond to the questionnaire. We recorded demographic data, including age, gender, diagnosis, attack history, and disability, measured by the Extended Disability Status Scale (EDSS) score at screening.[7] During follow-up visits, patients engaged in a self-rating survey using the questionnaire to evaluate their QoL. In instances of doubt, the research assistant provided clarification and assistance in questionnaire comprehension for those who required it. We then analyzed the data accordingly.

Statistical analysis

This study analyzed data using descriptive statistics for social science research of baseline characteristics. Data was analyzed using PASW Statistics for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). Frequency and percentages were calculated, along with the mean standard for the level of satisfaction, the standard deviation for measuring the data distribution, and organizing data presentation in a tabular or chart format. A P-value of less than 0.05 indicated statistically significant.

RESULTS

Demographic data

Of the 97 patients who attended the clinic during the study period, five were excluded due to other diagnoses than CNS-IDDs; two had other specified inflammatory diseases (CNS vasculitis), one had another established inflammatory disease (Hashimoto encephalopathy), one had Cyclic Vomiting Syndrome, and the last one had IgG-4 Related disorder. Among the 92 remaining patients, 40 (43.5%) had NMOSD (of which 36 were AQP4-positive), 27 had MS (29.3%), comprising 26 RRMS and 1 SPMS, 9 (9.8%) had Myelin oligodendrocyte glycoprotein antibody disorders (MOGAD), and 16 (20.7%) had other CNS-IDDs, including five with isolated Transverse myelitis (TM) (2 single TM, and 3 recurrent TM), five with isolated Optic neuritis (ON) (3 recurrent ON and 2 single ON), four with brainstem syndrome, and two with Tumefactive MS. We diagnosed CNS-IDDs based on current international diagnosis criteria (MS[8], NMOSD[9], MOGAD[10], Isolated TM[11], Isolated ON[12], and Tumefactive.[13] (Fig 1).

There were 67 females (72.8%) and 25 males (27.2%). There were statistically significant differences (P<0.05) in gender and age, with a mean age of 44.6±14.0 years. When categorized by age group, the highest prevalence was observed among individuals aged between 21-40 and 41-60 years (Fig 2).

Most patients had a Bachelor's Degree in Education (40.2%). The average EDSS score was 1.2±1.4. Totally 22 patients (23.9%) reported depression, anxiety, or insomnia at least once in the last 6 months. There was equal distribution of these psychological well-being regardless of their specific disease (29.6% for MS, 25% for NMOSD, 11.1% for MOGAD, and 18.8% for other CNS-IDDs; p=0.46). Most patients (67.4%) were vaccinated following Thai National guidelines.[14] Of the total 92 patients, 19 (20.7%)) with CNS-IDDs were tested for SAR-CoV2 during the study period, and only two MS (2.2%) were positive with mild symptoms. Both individuals successfully recovered, and no MS attacks were observed during their COVID-19 infection period (Table 1).

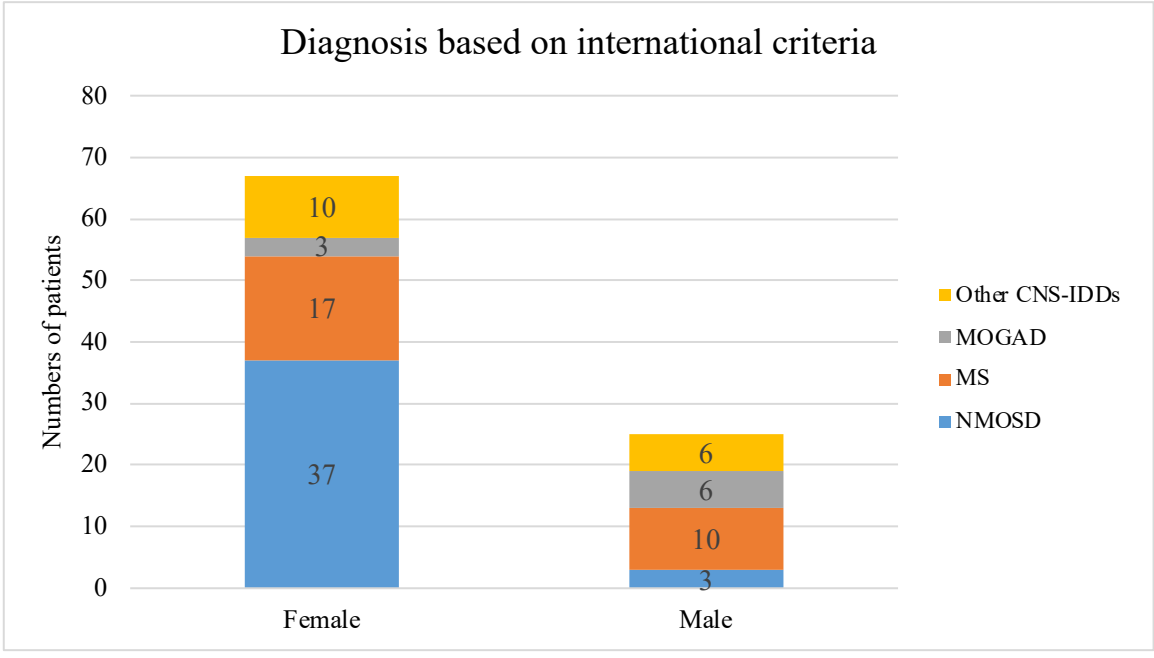

Fig 1. Distribution of CNS demyelinating diseases.
Abbreviation: NMOSD, neuromyelitis optica spectrum disorders; MS, Multiple sclerosis; MOG, MOG-IgG-Associated Disorders

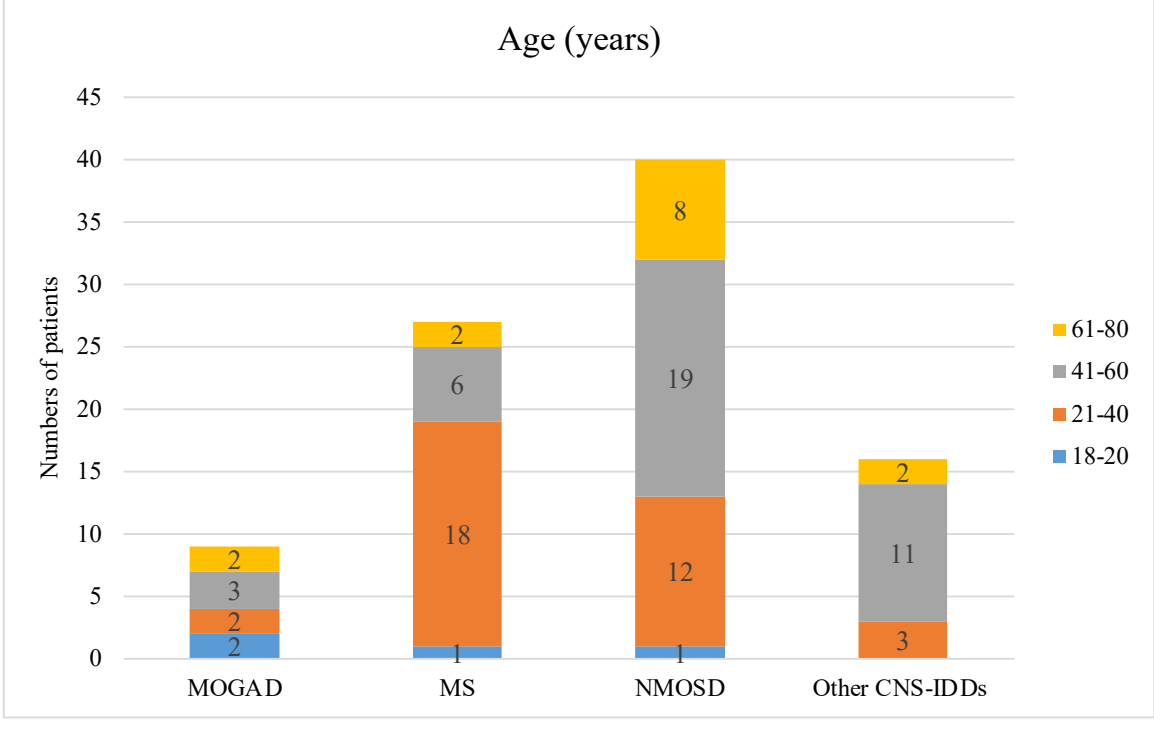

Fig 2. Patients with CNS demyelinating diseases classified by age.
Abbreviation: NMOSD, neuromyelitis optica spectrum disorders; MS, Multiple sclerosis; MOG, MOG-IgG-Associated Disorders

The most common treatment administered in all CNS-IDD patients was Azathioprine (39.1%), being least commenced in MS than other groups), followed by prednisolone (32.6%; 5 MS, 13 NMOSD, 6 each for MOGAD and 6 other CNS-IDDs). Rituximab was used in 12 cases (14.1%; 5 MS, 6 NMOSD, 1 MOGAD). MMF was used in 12 patients (14.1%; 2 MS, 8 NMOSD, one each for MOGAD and other CNS-IDDs) (Table 1). Additionally, seven cases (7.6%) reported treatment changes in the last 6 months.

TABLE 1. Demographic data of patients with CNS demyelinating disease.

Parameter	Mean +/- SD)	MS (n= 27)	NMOSD (n= 40)	MOGAD (n= 9)	Other CNS-IDDs (n=16)	P-value
Sex; n (% in the same group)						0.009
Female		17 (57.9)	37 (85.1)	6 (61.3)	10 (57.5)	
Age (year; mean±SD)	44.6±14.0	37.4±12.1	47.6±13.9	44.3±18.4	49.5±10.9	0.011
Highest Education (available data)		27	36	9	15	0.096
Primary School		3	4	2	6	
Junior High School		0	3	0	1	
Senior High School		2	2	2	1	
Diploma/High Vocational		0	5	2	2	
Certificate						
Bachelor Degrees		15	15	3	4	
Master Degrees		7	6	0	0	
Doctor Degrees		0	1	0	1	
EDSS (mean±SD)	1.2±1.5	1.0±1.7	1.2±1.4	1.5±1.3	1.2±1.5	0.864
No new attack in the past year; n (%)		18 (61.3)	28 (64.4)	4 (40.9)	11 (63.3)	0.529
Current treatment n (% in the same group)		27	38	8	15	
DMD		7 (23.9)	0	0	0	0.002
Aza		3 (10.2)	21 (48.3)	5 (51.1)	7 (40.6)	0.002
MMF		2 (6.8)	8 (18.4)	1 (10.2)	1 (5.8)	0.087
Rituximab		5 (17.0)	6 (13.8)	1 (10.2)	0	0.314
Prednisolone		5 (17.0)	13 (29.9)	6 (61.3)	6 (34.5)	0.064
No treatment		0	2 (4.6)	1 (10.2)	1 (5.8)	0.292
Psychological problems either depression, anxiety, or insomnia in the past 6 months; n (%)		8 (27.3)	10 (23)	1 (10.2)	3 (17.3)	0.406

Relapses during COVID-19 pandemic

Sixty-one patients (66.3%) reported no relapse in the past year and no statistically significant difference among the diseases (66.7% of MS, 70% of NMOSD, 44.4% of MOGAD, and 68.7% of other CNS-IDDs; p=0.529). For those who ever had a relapse, NMOSD seemed to have the highest average number of relapses (Fig 3). In relapse cases, patients were asked to self-rate their status compared to their pre-attack condition through a scoring system from zero to ten (0-2 = worse, 3-4 = stable, 5-6= fair, 7-9 = good, and 10 = excellent). Most patients self-reported a positive recovery with an average score of 8.9±2.2.

Self-rated quality of life

We asked patients to rate their feelings regarding QoL on a scale of 1-2 = bad, 3–4 = poor, 5-6 = fair, 7-9 = good, and 10 = excellent. Before the COVID-19 pandemic, most patients indicated a good (56.5%) and excellent (25.0%) QoL with an average self-rated QoL scale of 8.0±1.9. A drastic decrease to 5.4±2.4 and a general decline in their QoL during the pandemic were observed (Fig 4A & B). Similar results were seen in all groups of CNS-IDDs (mean pre-COVID and during COVID-pandemic scale were 8.3±2.0, 5.9±2.0 for MS, 8.1±1.7, 5.4±2.1 for NMOSD, 7.7±1.9, 5.3±3.0 for MOGAD, and 7.7±2.3, 4.9±3.1 for other CNS-IDDs, respectively)

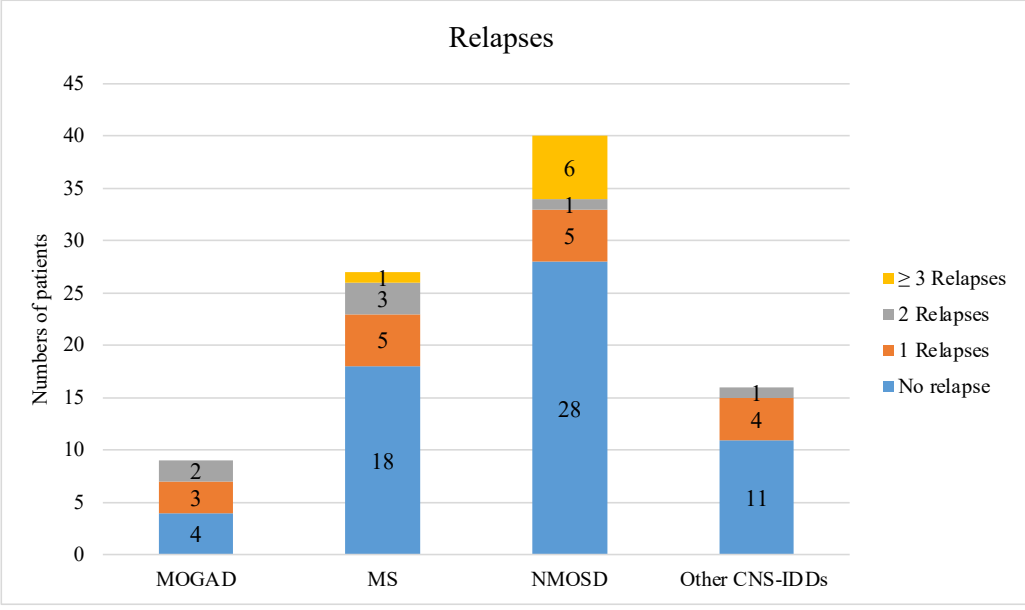

Fig 3. Number of relapses in the past year classified by each disease.
Abbreviation: NMOSD, neuromyelitis optica spectrum disorders; MS, Multiple sclerosis; MOG, MOG-IgG-Associated Disorders

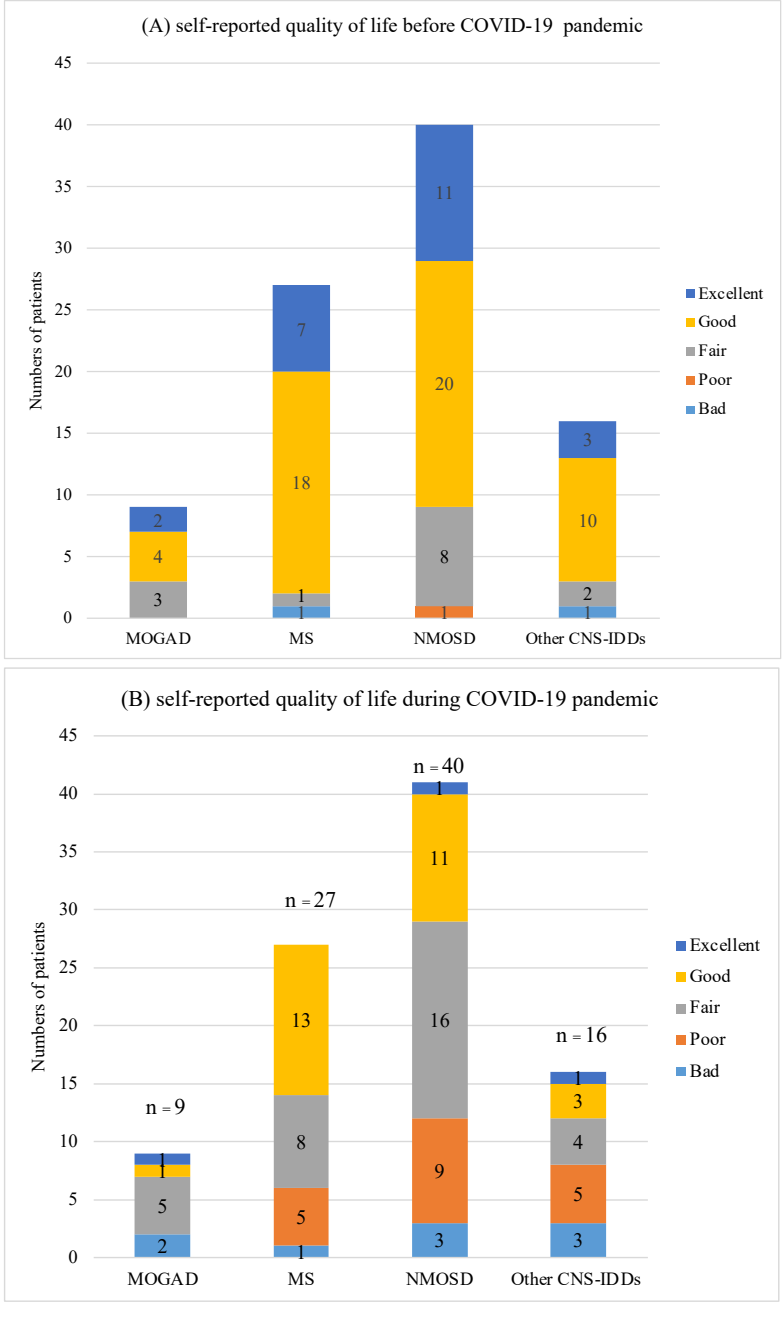

Fig 4. Self-reported quality of life before (A) and during (B) COVID-19 pandemic.
Abbreviation: NMOSD, neuromyelitis optica spectrum disorders; MS, Multiple sclerosis; MOG, MOG-IgG-Associated Disorders

Next, we conducted a detailed sub-survey to assess the negative impacts of the COVID-19 pandemic on physical and psychological well-being. Patients were asked to self-rate the impact of COVID-19, defined as 0 = no impact, 1-2 = little impact, 3–5 = some impact, 6-8 = significant impact, and 9-10 = very bad. Forty (43.5%) reported no impact on their physical wellness; 12 of 27 MS (44.4%), 18 of 40 NMOSD (45%), 4 of 9 MOGAD (44.4%), 6 of 16 other CNS-IDDs (37.6%). Twenty-eight (30.4%) reported no impact on their psychological wellness; 8 of 27 MS (29.6%), 10 of 40 NMOSD (25%), 4 of 9 MOGAD (44.4%), 6 of 16 other CNS-IDDs (37.6%). On the other hand, 52 patients (56.5%) indicated at least some level of impact on physical well-being, and 64 (69.6%) reported challenges to psychological health. (Fig 5A & B).

Questionnaire development

To ensure the practical applicability of our questionnaire in real-life scenarios, an initial test involved five non-medical healthy individuals. The assessment revealed no need for revisions, affirming the questionnaire's robustness and suitability for the study's context.

Missing/unattended appointment

Fifteen patients (16.3%) postponed or canceled their appointments during the COVID-19 pandemic. The predominant concern was difficulties in traveling to the clinic (32.2%). Consequently, 8.3% transitioned from face-to-face meetings with doctors in the clinic to telemedicine or telephone follow-up.

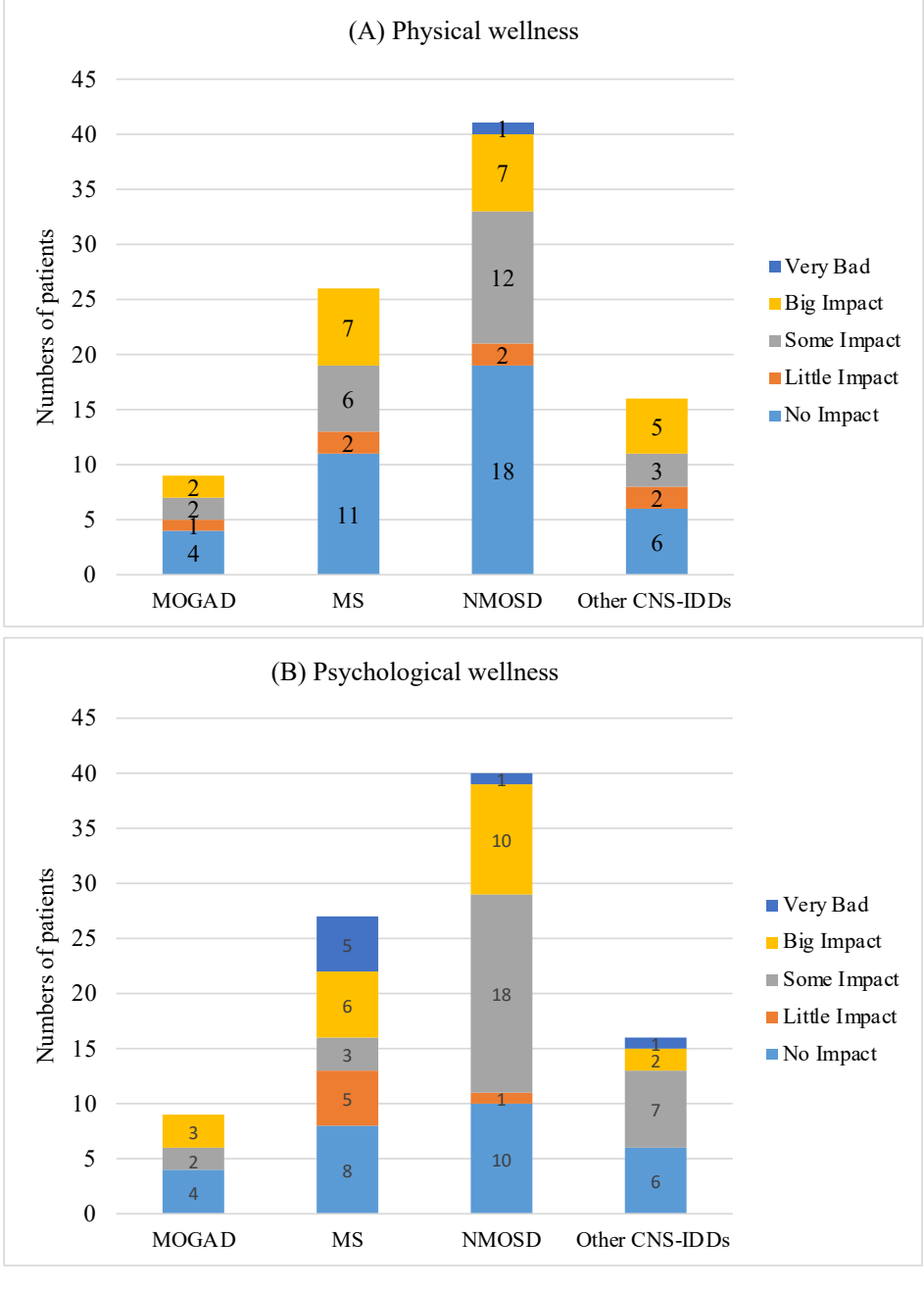

Fig 5. Self-rated questionnaire regarding the impact of the COVID-19 pandemic.
Abbreviation: NMOSD, neuromyelitis a spectrum disorders; MS, Multiple sclerosis; MOG, MOG-IgG-Associated Disorders

DISCUSSION

Our questionnaire survey of patients with CNS-IDDs revealed no significant increased relapse in our clinic during the COVID-19 pandemic. We found only two patients with confirmed COVID-19 infection, possibly due to a healthcare policy based on the national vaccination campaign and primary screening by healthcare providers at the hospital. Therefore, those suspected of being infected were transferred to a quarantine area. We found a low relapse rate in all patient groups in the past 6 months. These findings correspond to a previous study.[15] This encompasses patients with MS, NMOSD, and MOGAD, who reported no significant changes in the frequency of relapse.[4]

The surge of the COVID-19 pandemic inevitably led to symptoms of depression, anxiety or insomnia, and other conditions.[16] Furthermore, social distancing led to a perception of lower social support, strained family relationships, loss of freedom, and uncertainty.[17] All these reasons explain the significant decrease in self-reported QoL during the pandemic compared to prior. Such psychosomatic and behavioral responses to stress are a psychological mechanism of self-defense. It is a natural, ordinary, and necessary response when people face dangerous situations. It's important to note that our patients' unusually low EDSS scores during the pandemic may have been influenced by the selective inclusion of patients who could travel to the clinic and engage in sufficient activities.

Our findings reveal that nearly 10% of patients transitioned from going to the clinic to telemedicine communication or telephone follow-up. Telemedicine provides a convenient, cost-effective, and readily accessible means of information exchange and communication through the Internet and associated technologies. This approach allowed patients to receive quality assessment and treatment without the need to visit a clinic for follow-up during the COVID-19 pandemic.[18,19] Also, it allowed a way to reassure patients of their health and concerns during social distancing. If patients were reassured to cope with the COVID-19 pandemic and carefully adjust their lifestyle (e.g., regularly washing hands, social distancing, and wearing masks, etc[20], they could better fight through this challenging situation.[16,21]

Our study has limitations as the study was a single-center study with a limited number of patients, especially during COVID-19. However, this study is an example of the threatened situation by the dreadful disease on our CNS demyelinating diseases. It provides a picture of how that impacts the patient and may help modify how to help the patient in the future.

CONCLUSION

Our study shows that patients with CNS demyelinating diseases experienced low relapse and a low prevalence of COVID-19 infection during the pandemic. During the pandemic, patients' QoL drastically decreased in both physical and psychological conditions.

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Association of Oxygen Therapy Concentration and Duration with Retinopathy of Prematurity Incidence at Naresuan University Hospital

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ABSTRACT

Objective: This study aimed to evaluate the association between the concentration and duration of oxygen therapy and the development and severity of retinopathy of prematurity (ROP). Additionally, it sought to examine the incidence of ROP at Naresuan University Hospital.

Materials and Methods: A retrospective observational cohort study was conducted, utilizing data from the medical records of infants admitted to the Neonatal Intensive Care Unit at Naresuan University Hospital, Phitsanulok, Thailand, from January 1, 2016, to December 31, 2022. The duration of various oxygen therapies was recorded in hours, and the concentration of oxygen administered per hour was calculated as the average fraction of inspired oxygen for each infant. These data were subsequently analyzed using STATA version 11.0.

Results: Out of 100 eligible infants, 27 (27%) were diagnosed with ROP at different severity levels: 17 infants (62.96%) with ROP stage 1, 9 infants (33.33%) with stage 2, and 1 infant (3.70%) with stage 3. There were no cases of Stage 4 or 5 ROP. The adjusted risk ratio revealed that infants receiving an average FiO2 of 0.3 or higher had a 1.64 times greater risk of developing ROP [95%CI 1.03-2.62], (P-value=0.038). Further analysis using mean difference regression showed a significant correlation between the duration of oxygen therapy and the severity of ROP.

Conclusion: This study suggests that regulating oxygen therapy to not exceed an FiO2 of 0.3 and administering it strictly as needed may mitigate the risk of developing ROP and its severe manifestations.

Keywords: Retinopathy of prematurity; severity of retinopathy of prematurity; premature infant; oxygen concentration; duration of oxygen therapy (Siriraj Med J 2024; 76: 160-166)

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting the retina of premature infants, with a potential progression to retinal neovascularization.[1,2] In aggressive cases, this disease can progress to a severe stage, resulting in permanent visual impairments unless early diagnosis and appropriate treatment are provided.[3] Infants previously diagnosed with ROP remain at risk for developing other vision abnormalities, such as strabismus, amblyopia, and cataracts, even after treatment with laser photocoagulation or cryotherapy.

Das et al. conducted a prospective cohort study to evaluate the effect of supplemental oxygen on the development of ROP at Dhaka Shishu Hospital, Bangladesh from July 2012 to December 2014.[4] The study included infants with a birth weight ≤2500 g or born at <34

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weeks of gestation, as well as selected premature infants weighing between 1500 g and 2500 g with conditions requiring cardiorespiratory support, prolonged oxygen therapy, apnea of prematurity, anemia requiring blood transfusion, and neonatal sepsis. Following the third and final ROP screening, 38 of the 120 participants (31.67%) were diagnosed with ROP. Among 35 participants who received oxygen for more than 218 hours, 25 of them developed ROP, indicating a relative risk (RR) of 4.67 [95%CI 2.71- 8.03], p=0.0001. Five participants exposed to 41-60% oxygen concentration in inhaled air (FiO2 0.4-0.6) developed ROP, a concentration found to be a statistically significant risk factor for ROP with an RR of 3.48 [95%CI 2.61-4.64], p=0.001. Multivariate logistic regression analysis revealed that extremely low birth weight, mechanical ventilation, oxygen duration >218 hours, and SpO2 >95% were significant risk factors.

Teoh et al. carried out a prospective, observational cohort study in Kuala Lumpur Maternity Hospital, Malaysia, between December 1, 1989 and December 31, 1992, to assess the association between the duration of oxygen therapy and exchange transfusion and ROP development in infants with a birth weight <1500 g.[5] The study included 113 newborns admitted to the neonatal intensive care unit (NICU) who survived for at least 6 months. These infants were treated with supplemental oxygen to maintain specific arterial oxygen tension levels and received endotracheal intubation and intermittent positive pressure ventilation for severe respiratory conditions. The infants were weaned off ventilatory support and supplemental oxygen As soon as their clinical condition and blood gases improved, they were weaned off ventilatory support and supplemental oxygen. Exchange blood transfusions were performed for indirect serum bilirubin levels exceeding 280 micromol/l or in cases of unresponsive overwhelming septicemia. have not responded to antibiotic treatment. Among the 113 participants, 36 infants (31.9%) developed ROP, with logistic regression analysis indicating that both prolonged supplemental oxygen therapy (OR=1.156, [95%CI 1.056-1.254], p=0.0005) and exchange transfusions (OR=5.754, [95%CI 1.002-32.997], p=0.049) significantly increased the risk of ROP.

Kanya Chutasmit et al. Carried out a retrospective, cross-sectional, comparative study at the Division of Neonatology, Department of Pediatrics, Faculty of Medicine at Siriraj Hospital to study incidence and risk factor of prematurity between January 2010 and December 2019.[6] The study include infants with a birth weight ≤1,500g or born at <33 weeks of gestation. The study include 1,247 infants, there were 174 (14%) had ROP at various stages and 26 (2.1%) had threshold ROP requiring treatment. The study compared risk factor between pre-threshold and threshold ROP group revealed that lower gestational age and positive-culture septicemia were found to be a statistically significant risk factor.

To date, no definitive conclusions have been established regarding the correlation between the parameters of oxygen therapy, including its concentration and duration, and the onset and severity of ROP. Therefore, this study aims to evaluate these relationships, aiming to contribute to the development of effective prevention and mitigation strategies for ROP. Additionally, it seeks to examine the incidence of ROP at Naresuan University Hospital.

MATERIALS AND METHODS

This retrospective observational cohort study collected data from infants admitted to the Neonatal Intensive Care Unit, Naresuan University Hospital, Phitsanulok, Thailand, from January 1, 2016 to December 31, 2022. The medical records of all included infants were reviewed following approval from the Institutional Review Board of Naresuan University (COA No. 082/2022).

Inclusion criteria for infants who underwent ophthalmologic screening for ROP were as follows:

1) Infants with a birth weight ≤1,500 grams.
2) Infants with a gestational age ≤30 weeks.
3) Infants with a birth weight between 1,500-2,000 grams or with a gestational age >30 weeks, who experienced medically unstable course, required cardiorespiratory support, or were identified as at-risk for developing ROP by pediatricians or ophthalmologists.

Exclusion criteria included infants with:

1) Cyanotic heart disease.
2) Congenital abnormalities affecting the brain or eyes, such as cataracts, glaucoma, ocular neoplasms, or holoprosencephaly.
3) Incomplete medical data.

All eligible infants underwent ophthalmologic screening and were diagnosed with ROP by an ophthalmologist, using the International Classification of ROP (ICROP3) standards.[7] ROP screening was initiated either after the infant reached 31 weeks' postmenstrual age or 4 weeks after birth, whichever came later, and it continued until the retina was fully vascularized to the ora serrata. However, if a pediatrician determined that an infant exhibited unstable clinical signs or vital signs to an extent that precluded the use of dilating eye drops for ophthalmologic examination, the ROP screening was deferred until the infant's condition stabilized sufficiently for evaluation.

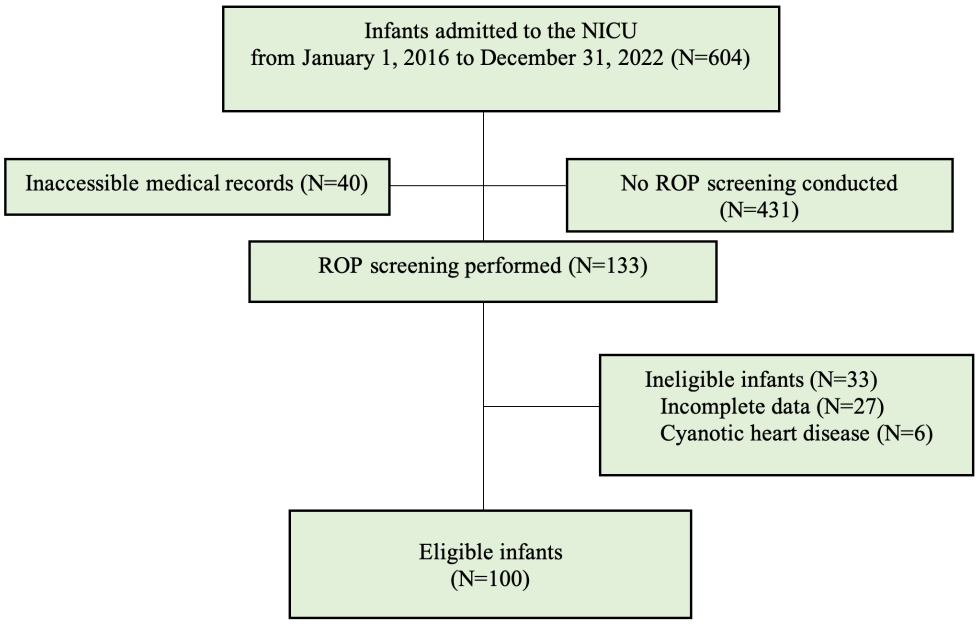

Fig 1. Flow diagram of study's screening and selection process.

Data containing both antenatal and postnatal periods were comprehensively collected. The scope of data included the duration of oxygen therapy, measured in hours from birth to the ophthalmologic assessment, and the concentration, expressed as the mean fraction of inspired oxygen (average FiO2) per infant. Records of ROP diagnoses were collected, along with the results of the most severe cases of ROP in each eye. In the absence of ROP detection during the initial assessment, follow-up examinations were conducted at intervals of two to three weeks until full retinal vascularization was confirmed.

Statistical analysis

Data analysis was conducted using STATA version 11.0. The statistical methods applied were as follows:

1) Descriptive statistics were utilized to analyze the data. Continuous variables conforming to a normal distribution were summarized using the mean and standard deviation, while those deviating from normality were described using the median and interquartile range. Categorical data were expressed as percentages and frequencies.
2) Comparative analysis between two independent numerical variable groups was conducted using an independent t-test for normally distributed data and the Mann-Whitney U test for data with a non-normal distribution. For categorical variables, the exact probability test was used, with findings reported as P-values.
3) Variables associated with ROP were selected based on insights from extant research, with the adjusted risk ratio (95% confidence interval; 95% CI) calculated using the multiple logistic regression analysis to ascertain factors linked with ROP onset.
4) The relationship between oxygen therapy duration and ROP severity was examined by calculating the mean difference in oxygen therapy duration (95% CI) through mean difference regression analysis.
5) A P-value < 0.05 was considered statistically significant.

RESULTS

A total of 100 eligible infants were screened for ROP. Their gestational ages ranged from 23 to 36 weeks (31.04 ± 3.16 weeks), birth weights ranged from 490 to 2,715 grams (1,475.20 ± 516.76 grams), the duration of oxygen therapy varied from 8 to 1,835 hours (560.62 ± 529.96 hours), and the oxygen concentration ranged from an FiO2 of 0.21 to 0.61 (0.27 ± 0.07). Ophthalmologic examinations identified ROP in 27 infants (27%), with a distribution of severity across different stages: of ROP, stage 1 in 17 infants (62.96%), stage 2 in 9 infants (33.33%), and stage 3 in 1 infant (3.70%). No cases of stage 4 or 5 ROP were detected.

Factors correlating with the development of ROP included gestational age, birth weight, APGAR score, IVH, sepsis, pneumonia, RDS, BPD, NEC, PDA, apnea, oxygen concentration, and duration of oxygen therapy. These factors demonstrated statistical significance when contrasting the ROP and non-ROP groups (P-value < 0.05), as detailed in Table 1.

TABLE 1. Baseline characteristics of infants.

Characteristics	ROP (n=27) n (%)	No ROP (n=73) n (%)	P-value
Gender			
Male	12 (44.4)	43 (58.9)	0.197[a]
Female	15 (55.6)	30 (41.1)	
Maternal age (year)			
Mean (±SD)	30.7 (±7.7)	29.3 (±7.9)	0.422[b]
Parity			
1	10 (37.0)	34 (46.6)	0.209[a]
2	10 (37.0)	23 (31.5)	
3	7 (25.9)	10 (13.7)	
4	0 (0)	6 (8.2)	
Multiple pregnancy	9 (33.3)	17 (23.3)	0.309[a]
Type of delivery			
Cesarean section	21 (77.8)	48 (65.8)	0.248[a]
Vaginal delivery	6 (22.2)	25 (34.3)	
Gestational age (week)			
Mean (±SD)	27.9 (±2.5)	32.2 (±2.5)	<0.001[b]
Postmenstrual age* (week)			
Mean (±SD)	34.9 (±1.9)	37.8 (±1.9)	<0.001[b]
Birth weight (gram)			
Mean (±SD)	974.4 (±318.4)	1660.4 (±449.2)	<0.001[b]
Birth weight classification			
Low birth weight (1,500-2,500 g.)	2 (7.4)	43 (58.9)	<0.001[a]
Very low birth weight (1,000-1,499 g.)	9 (33.3)	23 (31.5)	0.862[a]
Extremely low birth weight (<1,000 g.)	16 (59.3)	4 (5.5)	<0.001[a]
SGA	4 (14.8)	3 (4.1)	0.063[a]
APGAR score at 1 minute			
(Percentile 25, 50, 75)	(2, 4, 7)	(6, 7, 9)	<0.001[c]
APGAR score at 5 minutes			
(Percentile 25, 50, 75)	(6, 7, 9)	(8, 9, 10)	<0.001[c]
Comorbidity			
IVH	24 (88.9)	47 (64.4)	0.017[a]
IUGR	2 (7.4)	4 (5.5)	0.719[a]
Sepsis	25 (92.6)	53 (72.6)	0.032[a]
Pneumonia	19 (70.4)	26 (35.6)	0.002[a]
RDS	25 (92.6)	44 (60.3)	0.002[a]
BPD	20 (74.1)	10 (13.7)	<0.001[a]
NEC	16 (59.3)	27 (37.0)	0.046[a]
PDA	18 (66.7)	17 (23.3)	<0.001[a]
Apnea	18 (66.7)	32 (43.8)	0.043[a]

TABLE 1. Baseline characteristics of infants. (Continue)

Characteristics	ROP (n=27) n (%)	No ROP (n=73) n (%)	P-value
Intervention			
Perinatal steroid	27 (100.0)	54 (74.0)	0.003[a]
Blood transfusion	24 (88.9)	38 (52.1)	0.001[a]
Surfactant therapy	23 (85.2)	34 (46.6)	0.001[a]
Oxygen therapy**			
Average duration (day)			
(Percentile 25, 50, 75)	(25.9, 48.1, 56.8)	(3.5, 10.2, 21.5)	<0.001[c]
Average FiO_2 (hour)			
(Percentile 25, 50, 75)	(0.23, 0.24, 0.29)	(0.22, 0.24, 0.27)	0.003[c]

Abbreviations: SGA, Small for Gestational Age; IVH, Intraventricular Hemorrhage; IUGR, Intrauterine Growth Restriction; RDS, Respiratory Distress Syndrome; BPD, Bronchopulmonary Dysplasia; NEC, Necrotizing enterocolitis; PDA, Patent Ductus Arteriosus; FiO2, Fraction of Inspired Oxygen; SD, Standard deviation
[a] Results of the exact probability test
[b] Results of the independent t-test
[c] Results of the Mann-Whitney U test
*Postmenstrual age at the time of ophthalmologic examination
** oxygen therapy modalities comprised mechanical ventilation, nasal intermittent positive pressure ventilation, continuous positive airway pressure, duo positive airway pressure, heated humidified high flow nasal cannula, standard oxygen cannula, and oxygen box.

Furthermore, the incidence of ROP was higher among infants with lower birth weights: 16 out of 27 infants (59.3%) weighing less than 1,000 grams were diagnosed with ROP. In infants with a birth weight of 1,000 to 1,499 grams, ROP was diagnosed in 9 out of 27 (33.3%), and for those weighing between 1,500-2,499 grams, ROP was found in 2 out of 27 infants (7.4%).

The analysis conducted to determine the adjusted risk ratio revealed a significant correlation between oxygen concentration and the occurrence of ROP. Particularly, infants subjected to an average FiO2 of 0.3 or higher were observed to have a 1.64-fold increased risk of ROP [95%CI 1.03-2.62], with a P-value of 0.038, as shown in Table 2.

TABLE 2. Adjusted risk ratio analysis.

Potential Risk Factor	Adjusted risk ratio	95% CI (Lower – Upper)	P-value
FiO2 ≥ 0.3	1.64	1.03-2.62	0.038*
Gestational age (week)	0.97	0.86-1.09	1.09
Very low birth weight	0.23	0.01-3.81	0.304
SGA	1.24	0.70-2.19	0.467
IUGR	1.86	0.92-3.76	0.085
APGAR score at 1 minute	0.90	0.75-1.08	0.257
APGAR score at 5 minutes	1.03	0.91-1.17	0.645
Sepsis	1.02	0.54-1.92	0.962
Pneumonia	1.16	0.71-1.89	0.565
RDS	4.95	0.16-154.96	0.363
BPD	2.01	0.71-5.70	0.187
Apnea	0.84	0.57-1.24	0.375
Surfactant therapy	0.78	0.16-3.74	0.752

* P-value < 0.05

The data further revealed a significant relationship between the duration of oxygen therapy and the severity of ROP (Table 3). Mean difference regression analysis indicated a strong correlation between the length of oxygen therapy and ROP severity. Specifically, Stage 1 ROP was associated with an additional 23.3 days of therapy [95% CI 13.5-33.0], Stage 2 with an added 31.1 days [95% CI 18.3-43.9], and Stage 3 with an extra 52.7 days [95% CI 16.2-89.2], all compared to infants without ROP. These findings were statistically significant, with P-values of <0.001 for Stages 1 and 2, and 0.005 for Stage 3, as illustrated in Fig 2.

DISCUSSION

The current study, conducted at the Neonatal Intensive Care Unit of Naresuan University Hospital from January 1, 2016, to December 31, 2021, revealed a 27% incidence of ROP in admitted infants. This research notably identified a significant correlation between the concentration of oxygen administered and the onset of ROP, as well as a direct relationship between the duration of oxygen therapy and the severity of ROP. Specifically, infants exposed to high concentrations of oxygen (average FiO2 ≥ 0.3) demonstrated a statistically significant predisposition to ROP. These findings are consistent with those reported in several other studies.[4,5,8-10] However, the observed range of FiO2 in this study contradicts the findings by Das, et al.,[4] who reported an association of ROP with FiO2 ranging from 0.41 to 0.60. This discrepancy could stem from differences in the timing of outcome measurements. Das et al.[4] performed the outcome measurement at the third and final ophthalmologic examination, while the current study carried out the assessment at the initial ophthalmologic examination.

It is important to note that ROP stage 1 may spontaneously regress with controlled risk factors. Conversely, prolonged exposure to high concentrations of oxygen therapy can exacerbate the severity of ROP. The detrimental effects of high-concentration oxygen therapy on ROP development are attributable to the resultant relative hyperoxia. This condition disrupts the balance of oxygen-regulated angiogenic growth factors like erythropoietin and vascular endothelial growth factor (VEGF), marking the initial phase of ROP. The subsequent phase involves the hypoxic retina, which becomes metabolically active yet poorly vascularized,

TABLE 3. Stage of ROP and duration of oxygen therapy.

Stage of ROP	Average duration (day)	Total (n=100)
No ROP	16.08	73
1	39.34	17
2	47.20	9
3	68.80	1

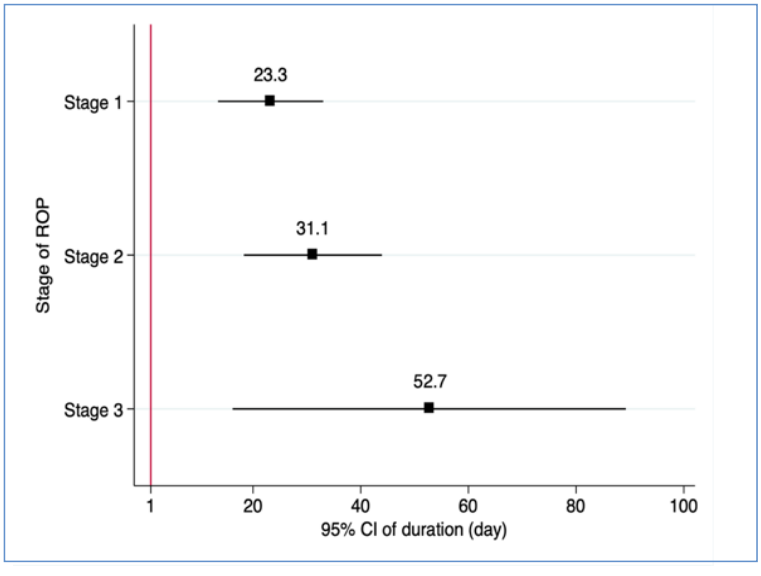

Fig 2. Regression analysis of mean differences in oxygen therapy duration across ROP stages (95% Confidence Interval).

leading to neovascularization. These neovessels, formed due to an overproduction of growth factors, inadequately perfuse the retina and are prone to leakage, resulting in fibrous scar formation and potential retinal detachment.[2]

Interestingly, this study not only highlighted the role of oxygen concentration, but also demonstrated that the duration of oxygen therapy in the ROP group was significantly longer compared to the non-ROP group, a finding consistent with previous studies.[4,5,11-13] Moreover, the relationship between oxygen therapy duration and ROP severity was substantiated by a mean difference regression analysis. The results revealed a statistically significant correlation between the duration of oxygen therapy and the severity of ROP. The mean differences in days for ROP stages 1, 2, and 3, compared to infants without ROP, were 23.3, 31.1, and 52.7, respectively.

In this study, data regarding the concentration and duration of oxygen therapy were comprehensively collected on an hourly basis and subsequently averaged for each infant, facilitating a more accurate statistical analysis. However, this study is limited by its single-center design, which inherently restricts the sample size. Future research conducted across multiple centers could accommodate a larger participant base, thereby enhancing the potential to identify a broader array of risk factors associated with the development of ROP.

CONCLUSION

Infants exposed to high oxygen concentrations, specifically from FiO2 0.3 or higher, exhibited a significantly increased risk – 1.64 times higher – of developing ROP, as evidenced by initial ophthalmologic screening examinations. Moreover, prolonged oxygen therapy was observed to exacerbate the risk of severe ROP. Therefore, it is recommended to limit oxygen provision to a maximum FiO2 of 0.3 and to administer it only when clinically essential. This approach could potentially mitigate the risk of ROP and its severe manifestations. The findings of this study are instrumental in enhancing the understanding and management of premature infants' care, contributing significantly to the body of knowledge in neonatal health.

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Author contribution statement

Krittaporn Phruksarudee: Conceptualization, Data curation, Software, Resources, formal analysis, Writing-Original draft, Visualization and Funding acquisition. **Kanrawee Sungprem:** Conceptualization, Investigation, Supervision, Project administration, Writing-Review & editing and Validation. **Mayuree Montriwet:** Methodology, Writing-Review & editing and validation.

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A Narrative Review Current Physical Therapy Management for Patellar Tendinopathy

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ABSTRACT

Patellar tendinopathy, or jumper's knee, is a common chronic musculoskeletal disease in the tendon that occurs in lower-extremities injuries. It is common in athletes, particularly sports that integrate frequent jumping and landing, such as volleyball (45%), basketball (32%), and distance running (14%), Patellar tendinopathy is usually difficult for such athletes to manage during the active sports season. This review article is recommended for physical therapists for the conservative treatment in competition season and post-operative rehabilitation of patellar tendon injuries. This review article discusses a new intervention for physiotherapy treatment for Patellar tendinopathy that can support a significant improvement in performance in sport and functional daily activity. The ultimate aim is to develop a clinical practice recommendation for physical therapists for the conservative treatment and post-operative rehabilitation of patellar tendon injuries. This review article found that physical therapy is popularly used to treat Patellar tendinopathy and effective interventions consist of exercise, extracorporeal shockwave therapy, high-energy laser therapy, elastic therapeutic taping, and education for prevention of issues. The post-operative rehabilitation protocol for patella tendon injuries aims to decrease pain, improve the range of motion, and ensure early ambulation and a quick return to sport, though in a time period that is decided on a case-by-case basis depending on the person and the sport. Post-operative rehabilitation is highly important for ensuring a safe return to sport and good quality of life.

Keywords: Patellar tendinopathy; exercise; extracorporeal shockwave therapy; high laser therapy; elastic therapeutic tapping and rehabilitation post-operative for patellar tendon protocol (Siriraj Med J 2024; 76: 167-173)

INTRODUCTION

The patella tendon connects the patella bone to the tibia bone. However, there is some debate about the correct nomenclature between the "patella tendon" or "patella ligament", as by definition, a tendon connects muscle to bone while a ligament connects bone to bone. However, the patella tendon acts in knee extension by integrating the quadriceps group muscle to the tibia bone. The patella bone as a sesamoid bone that is involved in knee extension. The patella tendon is involved in the knee extensor mechanism via the linkage of the quadriceps group muscles to the quadriceps tendon, which implicates the patella bone, and therefore, links the patella tendon to the tibia bone.[7]

Patellar tendinopathy (PT), or jumper's knee, is a common chronic musculoskeletal disease in the tendon in lower-extremities injuries and is difficult to manage for athletes during the active sports season.[3,4,7,9] PT occurs due to an overuse loading of the patellar tendon.[1,5] The highest incidence of PT is in sports that integrate frequent jumping and landing movements, such as volleyball (45%), basketball (32%), and distance running (14%).[5,8] The characteristics of PT include a localized anterior knee pain at the point where the patellar tendon attaches

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to the patellar bone and an impaired function.[6,5] Apart from knee pain, PT also impact on the quality of life, so the objective of this review article was to develop a clinical practice recommendation for physical therapists to manage PT for ensuring good daily function. The full etiopathology of PT is unknown, but it is known to be related to a degenerative structural change of the tendon with cell inflammation.[3,6,8] The risk factors for tendon issues to develop into PT include intrinsic factors (such as age, body mass index, leg length difference, hamstring group muscle flexibility, quadriceps group muscle flexibility and strength, hip extensor group muscle strength, patellar mobility, arch height of the ankle, ankle mobility) and extrinsic factors (sports training program, type of sport, physical activity). However, these risk factors have limited evidence to support them, so future research is needed on the risk factors. This would benefit designing an appropriate prevention protocol.[5,15,17,18] Recently, concerns have been raised about the absence of a gold standard for the diagnosis of tendinitis. Current diagnosis tends to combine subjective examination and objective examination, while magnetic resonance imaging (MRI) may be used to confirm a diagnosis. MRI can differentiate between analogous diagnoses, such as patellofemoral joint pain syndrome and PT. PT is present in structural patellar tendon disruptions. In the future, a study to find a gold standard diagnosis would be useful as this would benefit ensuring patients get the most appropriate treatment.[18,23] Current treatments of PT involve various methods, classified into conservative treatment and surgery. Conservative treatment is the first option for PT, and consists of oral medicines, injections, rest, physical therapy, and prevention.[8,17] The following sections describe the current treatment options in more detail and their main pros and cons by the author conducted a review, collected and compiled literature to make this review article. The author has taken this knowledge for guideline clinical practice.

METHODS

Review and research from reliable sources such as PubMed, etc., a total of 23 update literature, most are in the period 2023-2018. Processing time to review research of relate physical therapy for PT about of 6 months, and compose about of 4 months.

Physical therapy

Physical therapy covers various effective interventions and consists primarily of exercise, extracorporeal shockwave therapy, high-energy laser therapy, elastic therapeutic tapping, and education for prevention. These are all described below.

Exercise

There are various types of exercises that are suited for PT, including eccentric exercise, concentric exercise, progressive tendon-loading exercise, heavy slow isotonic exercise, and isometric exercise. Studies on these have been reported their excellent results, but are somewhat controversial.[18]

Eccentric exercise (EE) has a strong evidence base to support it use, and it is popularly used in the management to PT in athletes and non-athletes.[3,4,8,17] Many research studies have revealed that EE can improve function in the short term and help meet long-term goals.8,18 Exercise can help to increase the reconstruction of collagen fiber in the tendon.8 However, EE can increase pain and worsen function when practiced during the competitive season, hence its use is controversial.[1,3,4,7] In this case, incorporating reasonable rest is advised in EE programs for rehabilitation.[8] The success rate is estimated to between 50% to 70% in cases undergoing EE programs.[17] EE is performed on a declining board at a 25° slope, and is performed twice daily. Stage 1 in a typical EE program comprises a single-leg decline squat, in which the eccentric stage is the downward component and the concentric stage is the upward component. The patient is asked to score their pain when performing the exercise according to the visual analog scale (VAS) in the scale of 0-10, usually at this stage VAS ≥ 5. Loading can be added by the patient wearing a weighted backpack or belt to enhance the exercise intensity depending on the kind of sport they participate in, and the patient follows the stage 1 EE program twice a week. Patients in an EE program can return to sport participation generally on average after 1 month.[3] Several studies have reported using a declining board at a 25° slope for single-leg squats, which presents the opportunity for a more progressive outcome than possible with a single-leg flat squat.[18] One research study compared a traditional EE program with a declining board at a 25° slope program carried out over 12 months, and revealed that both groups presented progression toward the desired end outcome, with 41% of participants in the traditional EE group showing effective progression while 94% of the participants in the declining board at a 25° slope group showed improved results.[17]

Progressive tendon-loading exercise (PTLE) therapy is a novel exercise for PT that can be performed, providing it is within the limit of acceptable pain for the patient, during the competition season. One study compared the effectiveness of treatment between PTLE and EE and concluded that PTLE can be more beneficial than EE.[1,3] Progressive load is managed based on a pain VAS ≤ 3 point. PTLE therapy consists of 4 stages. Stage 1 comprises daily isometric (static) exercises performed

by doing a single-leg press or single-leg extension, then holding for 45 seconds in the middle range of knee flexion at an estimated 60°, and a quadriceps group muscle isometric hold for about 70% of the maximum voluntary contraction, for 5 repetitions. Stage 2 comprises alternating exercises, starting by doing the exercise program of stage 1 on the first day and new isotonic (dynamic) exercise management on the second day with a single-leg press or single-leg extension moving in a 10° to 60° range of knee flexion, starting with 15 repetitions for 4 sets and slowly progressing to 6 repetitions for 4 sets with added load and increasing the knee angle to approximately between 90° in flexion to full extension. Stage 3 adds in plyometric (energy storage) running and loading exercises, such as jump squats, cutting maneuvers, and box jumps on every third day, beginning with 10 repetitions for 3 sets for both legs and slowly progressing to 10 repetitions for 6 sets with one leg. Isometric and isotonic exercise can be continuously done in sequence on every first and second day. Stage 4 comprises sport-specific exercise, which depends on the kind of sport played, such as volleyball or basketball. Patients can thus return to sport-specific training, managing to do so every 2–3 days to also allow time for recovery from performing high tendon-loading exercises. Progression is based on the pain level during a pain assessment test, which involves one single-leg squat. Progression in the next step is conditional upon a VAS score ≤ 3 and managing the exercise program in this stage at the lowest level for 1 week. In cases recommended for a return to competition during the active sporting season, patients should have a pain VAS score ≤ 3. At this stage, i.e., stage 4, the aim is to maintain the exercise programs from stage 1 and stage 2 and to perform them twice a week. The approximate time to return to active sport is usually after 4 weeks. This would be an agreeable PTLE program.[3]

Heavy slow isotonic exercise (HSIE) is aimed at improving the signs and symptoms of PT for achieving short-term goals, long-term goals, and a return to competition during the active sporting season. The exercises comprise strengthening the single-leg seated knee extensor group muscle, hip abductor group muscle, and hip extensor group muscle with hip machines and calf raises. The exercises start with less loading and consider increasing the load with signs that there has been progress. One research study compared interventions involving HSIE, EE, and steroid injection in PT, and concluded that HSIE had better outcomes than the other interventions in meeting the short-term goals and long-term goals, and also that patient satisfaction was higher for HSIE (70%) and EE (22%).[8]

Isometric and isotonic contraction exercises can be effective at helping decrease pain during the sporting season according to recent research. Isometric contraction can decrease pain immediately and maintain this benefit 45-minute post intervention. Isotonic contraction can also decrease pain immediately, but it does not maintain this effect and the effect may be diminished or lost 45-minute post intervention. Isometric contraction is typically performed on a leg extension machine by performing knee flexion to 60 degrees, for 45 second repetitions at 70% to 80% maximum voluntary contraction, for 5 sets. Isotonic contraction is also performed on a leg extension machine, typically at 80% maximum voluntary contraction, for 8 repetitions, for 4 sets.[4,7]

Phase of exercise

A PT exercise rehabilitation protocol should comprise three phases based on research. This protocol is beneficial to guide physical therapists in the best course of action for the treatment of PT. In the future, it is recommended to research the most appropriate exercises for PT in each phase.

Phase 1 – Pain modulation and load management

The first step in an exercise program should be focused on pain modulation and load management, particularly during the competitive season. Loading exercises and daily activities can be effective for reducing the signs and symptoms of PT. It is important though to manage the loading and activity to ensure it is appropriate, but the sudden complete discontinuation of existing activities/exercises should be avoided. Research suggests that mid-range isometric exercises are most effective to decrease pain in PT. Recent research has also shown that performing isometric squat exercises can decrease pain during the competitive season.[8]

Phase 2 – Strengthening exercises and load progression

In this second phase, eccentric exercises, isotonic exercises with the lowest pain, and heavy and slow resistance exercises can be initiated. The recommended heavy and slow resistance exercises comprise squats, hack squats, and leg press with a knee extension up to 90 degrees of knee flexion. This exercise can effectively improve hypertrophy of the patellar tendon. The exercise progression involves a gradual increase in difficulty by performing single limb exercises, while wearing a weight belt or a bag with weight. Previous research has shown the effectiveness of eccentric exercise and heavy slow resistance exercise for PT.[8]

Phase 3 – Functional strengthening and a return to sport

In this phase, the focus of functional training is

incorporating kinetic chain movement patterns and high-loading activity. Kinetic chain and movement patterns allow progress for specific sport and include plyometric exercise. The training program should comprise high-energy training, such as agility training, bounding, sprinting, skipping, and jumping. In the training program, it is important to monitor and quantitatively assess the loading. The factors that may prevent progression and a return to sports during the competitive season are dysfunction, pathology, and a severe pain level.[8]

Hight intensity laser therapy (HILT)

Hight intensity laser therapy (HILT) (Fig 1) is a novel modality that is widely applied to musculoskeletal disorders because it can significantly decrease pain and requires fewer clinical visits.[13,20] Previously, low laser therapy was applied to treat tendinopathies. Nowadays, HILT is applied and operated at a wavelength of 1,064 nm. At this wavelength, it has minimal and slow light assimilation to penetrate deep tissue to provide effective treatment.[2,6] HILT is now considered better than low-level laser therapy because HILT can stimulate deeper tissue and penetrate deep tissue more effectively than low-level laser therapy.[2] HILT is particularly effective at increasing the microcirculation, the permeability in blood vessels, the metabolic rate of cells, and oxygen saturation in the patellar tendon.[20,2] HILT can provide photothermal and photochemical effects to promote collagen in the tendon, increase microcirculation, aid permeability in vessels, and provide an anti-inflammation effect.[2,13] Thus, HILT can help repair the tendon and decrease pain.[2] HILT protocols for treatment usually comprise two modes for the analgesic and biostimulation effects. The analgesic mode is used to promote the healing process in the acute phase, while the biostimulation mode is applied to accelerate the cell mechanisms and improve blood circulation in the chronic phase. There are two main laser movement techniques: one used in the analgesic mode, which is applied to the pain area in a circular movement from the center to outside; and a second that is used in the biostimulation mode, which involves application in a linear movement in the pain area.[2] Now, HILT has an evidence base to support its use with guideline protocol parameters (frequency, dose, duration time) for treatment. Research has found that one of the main risk factors for developing tendinopathy is poor blood flow, especially after sporting or daily activity. HILT is particularly useful in this regard as it can significantly increase the microcirculation and oxygen saturation in the patellar tendon. This can influence the healing process, and hence HILT is often used to treat impaired microcirculation in tendinopathy, such as from sport-related overload of the patellar tendon leading to decreased microcirculation.[20] Moreover, studies have found that eccentric and static stretching exercises combined with HILT can significantly improve the signs and symptoms of chronic PT.[6]

Extracorporeal shockwave therapy (ESWT)

Extracorporeal shockwave therapy (ESWT) (Fig 2) was developed from high-intensity focus shockwave therapy that is commonly applied to destroy kidney stones.

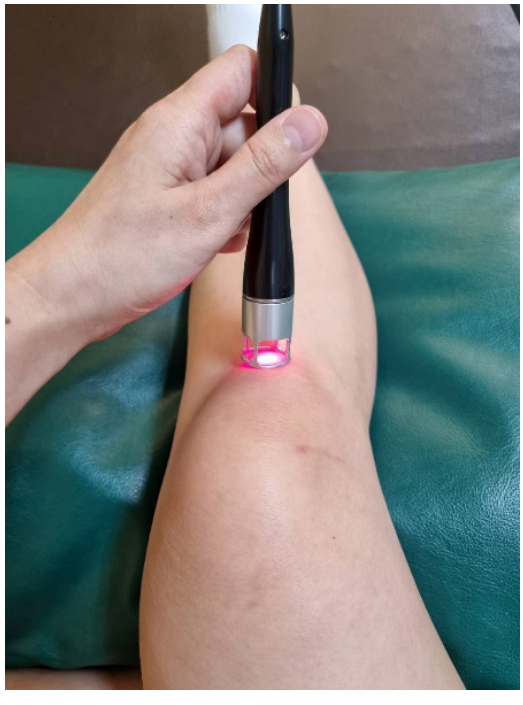

Fig 1. High intensity laser therapy.

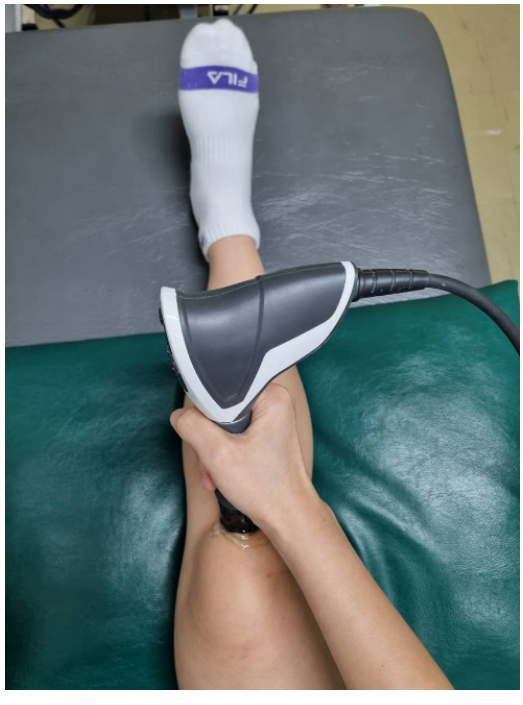

Fig 2. Extracorporeal shockwave therapy.

However, the greatly capability of ESWT to stimulate the healing process was also revealed in research.[14,16] Since the 1990s, ESWT has been applied as a conservative treatment for managing severe chronic tendinopathies, and is highly efficient at decreasing pain and promoting tendon healing.[14,16,23] ESWT is a non-invasive intervention compared to surgery and is the most commonly used treatment for chronic PT that does not respond to other conservative treatment interventions. ESWT is not performed in the acute phase. ESWT involves applying a mechanical stimulus with pulse acoustic waves to enhance biological reactions by stimulating the metabolism of cells.[23] The biological aims of ESWT are to decrease pain, promote blood circulation, release fibrosis, and destroy calcified matter. ESWT can improve the functional outcomes for returning to daily activity and sporting performance.[23] ESWT comprises two types: focus shockwave therapy (FSWT) and radial shockwave therapy (RSWT).[23] FSWT involves an accurate focus on a lesion and is a deep wave form of therapy, and therefor FSWT is applied to chronic PT more than RSWT, which involves a diffuse and shallow wave form. The typical parameters for FSWT used for chronic PT are 1,000–2,500 shocks, 0.08–0.25 mJ/mm^2, 4 Hz, 3–6 sessions, once a week.[22] There has not been enough recent research to suggest RSWT should replace FSWT in chronic PT. However, the best treatment outcome for ESWT is to amalgamate eccentric exercise and foundation physical therapy.[14] In the future, research should address the effects of ESWT on PT and compare the effects between FSWT and RSWT in PT.

Elastic therapeutic taping

Elastic therapeutic taping is popularly used as a conservative treatment for athletes. Elastic therapeutic taping is a precise mechanism to relieve pain.[21] Elastic therapeutic taping can relieve stress on the patellar tendon by modification of the patellar angle, which can relieve stress caused during activities and sport. Clinically, elastic therapeutic taping can significantly relieve pain from any sport, for up to 2 hours after sport, and improve the quality of life.[19] Elastic therapeutic taping improves proprioception in the knee joint. Several research studies have encouraged the use of elastic therapeutic taping for PT in adults to decrease pain and promote functional outcomes.[21] One study found that an infrapatellar strap is effective at decreasing knee adduction and for stimulation of the vastus lateralis muscle that has been previously used in landing movements in sport to decrease the pain on jumping. In addition, an infrapatellar strap can increase the patellar tendon–patellar angle and decrease the patellar tendon length, which can decrease PT. Thus, athletes with PT are used to elastic therapeutic taping as a common sporting treatment. Research has also mentioned the effects of PT include decreasing the strength and flexibility in the quadriceps group muscles, leading to reduced kineties in jumping in some sports. Here, the infrapatellar strap can reduce tension and stress in the patellar tendon and improve proprioception in the knee joint, which can promote jumping kinetics. The guideline for the immediate conservative treatment for PT is thus a strap, because it is self-applicable, low cost, and not dangerous. The infrapatellar strap is also popularly used with adolescents, because in the young it can aid musculoskeletal system development. The contraindication in some physical modalities is they may result in opening up the epiphyseal plates, such as ultrasound therapy and ESWT; however, elastic therapeutic taping is safe for relieving pain in jumping sports.[21]

Prevention

The common prevention measures for PT are education, hamstring stretching exercises, quadriceps eccentric strengthening exercises, lumbopelvic stabilization, and lower extremity stabilization. All athletes should be educated about the signs and symptoms of PT that may arise during sporting participation, although there may be minimal pain during the actual activity because of the tendon's delayed response to loading, but within a 1 day later the pain in the tendon may become moderate to maximal. Regularly after returning to sport, there is a need to control pain to within acceptable limits and to be aware of issues indicated by an increase in pain. The single-leg decline squat is an optimal exercise to detect symptoms and is thus commonly used for self-assessment in athletes to support rehabilitation programs and sport training. Hamstring stretching exercises are used by many athletes to decrease the risk factors for PT. Quadriceps eccentrics strengthening exercises can promote tendon absorption, and the literature shows they can be used for prevention too. Lumbo-pelvic and lower extremity stabilization exercises may be integrated with an ordinary prevention exercise program for promoting function in athletes. However, there is limited information in the current literature on the prevention of PT. In the future, more research needs to focus on prevention, as this would benefit decreasing the risk factors for PT in sports professionals.[8,12,18]

Post-operative patellar tendon rehabilitation protocol

Physicians may consider operative treatment indication is a failure to respond to conservative treatment. The post-operative return to sports time period is on average about

3 to 9 months.[8,17] The goal is to decrease pain, improve the range of motion, and enable early ambulation and a quick return to sport, but decided on a case-by-case basis. In this rehabilitation protocol, by post-operative days 1 to 4, the patient should be able to attempt early ambulation with partial weight-bearing by using crutches and attempt an active full range of motion exercises as can be tolerated, but performed under a non-weight-bearing condition. Post-operative days 5 to 7, the patient may be able undertake mild concentric exercise and eccentric exercise. Post-operative days 8 to 14, the patient may undergo progressive tendon-loading exercise as can be tolerated. Post-operative two weeks, the patient may undergo maximal loading exercises and activities as can be tolerated.[8]

CONCLUSION

Patellar tendinopathy, or jumper's knee, is a common chronic musculoskeletal disease in the patella tendon that can occur with lower-extremities injuries and is difficult to manage for athletes during the season. The key treatments for PT are conservative treatment or surgery. Conservative treatment is the first option for PT, and consists of rest, physical therapy, and prevention.

TABLE 1. Summarizing of physical therapy management.

Physical therapy management	Physiological effect	Result	Appropriate in the case
Exercise			
Eccentric exercise	Increase the reconstruction of collagen fiber in the tendon.	Improve function	Not appropriate in the competition season and appropriate in case at rest, non-athletes
Progressive tendon-loading exercise	Same as above	Same as above	Appropriate in the competition season
Heavy slow isotonic exercise	Same as above	Same as above	Appropriate in the competition season
Isometric and isotonic contraction exercises	Same as above	Same as above	Appropriate in the competition season
Hight intensity laser therapy	Promote collagen in the tendon Increase microcirculation aid permeability in vessels Provide an anti-inflammation effect	Decrease pain Repair the tendon	Requires fewer clinical visits
Extracorporeal shockwave therapy	Promote blood circulation Stimulate the healing process Release fibrosis Destroy calcified matter	Highly efficient at decrease pain Improve function	Not respond to other conservative treatment interventions
Elastic therapeutic tapping	Improves proprioception	Decrease pain Improve function	During activities and sport
Prevention	-	Promote function Reduce repeated injuries	Appropriate in everyone
Post-operative patellar tendon rehabilitation protocol	Promote blood circulation	Decrease pain Improve range of motion Early ambulation Return to sport	Appropriate in post-operative

Physical therapy is popularly used to manage PT. Physical therapy covers various effective interventions, including exercise, extracorporeal shockwave therapy, high-energy laser therapy, elastic therapeutic taping, and education for prevention. Currently, department of orthopedic surgery, Siriraj Hospital, Mahidol University in Thailand is popular to manage PT with physical therapy by exercise combined with novel physical modality such as HILT or ESWT. Physicians may consider operative treatment in cases of a failure to respond to conservative treatment. Rehabilitation forms the key post-operative protocol, with the goal being to decrease pain, improve the range of motion, ensure early ambulation and a quick return to sport, with the approximate time period for this depending on a case-by-case basis.

A limitation and development opportunities

The author found relatively few research studies on physical therapy for patellar tendinopathy. Currently, there is a new physical modality, the peripheral magnetic stimulation, which has not been studied in patellar tendinopathy. The author is of the opinion that is interesting and hope that an excellence opportunity to treatment.

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