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On May 16, 2024, The PCMC Journal received a Certificate of Indexing for meeting the standards of the National and Regional Journal Selection Committees for indexing in the Western Pacific Region Index Medicus (WPRIM) for 2024. Ms. Maria Violeta Intia from the DOST-PCHRD awarded the certificate to Editor-in-Chief, Dr. Paul Pasco. Also in attendance for PCMC were Dr. Mary Ann Bunyi, Deputy Executive Director for Education, Training and Research Services, Dr. Caridad Santos, Clinical Research Department Manager, Dr. Ma. Lucila M. Perez, Clinical Trial and Research Division Head, and Ms. Baby Lynnie Fegalan, Healthcare Library Section Head.

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Contents

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2. The manuscript should be arranged in sequence as follows: (1) Title Page (2) Abstract (3) Text (4) References (5) Tables (6) Figures & Illustrations. A manuscript for an original article should not exceed 25 typewritten pages (including tables, figures, illustrations and references). The text for case reports should not exceed 10 pages, including the visual aids and references.

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For original articles, the abstract should contain no more than 200 words and should have a structured format consisting of the objective, methodology, results and conclusion. For case reports, the abstract should be from 50 to 75 words and need not be structured. At least 3 keywords, preferably using terms from the Medical Subject Headings (MeSH) list of Index Medicus, should be listed horizontally under the abstract for cross-indexing of the article.

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1. Generally, the text should be organized consecutively as follows: Introduction, Materials and Methods, Results and Discussion (and Conclusion).

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ARTICLE

Antimicrobial stewardship: attitudes, perceptions, and practices of healthcare workers in a pediatric tertiary hospital

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OBJECTIVE: This study aims to determine the healthcare workers' (HCWs) attitudes, perceptions, and practices regarding Antimicrobial Stewardship (AMS) at the Philippine Children's Medical Center (PCMC).

MATERIALS AND METHODS: This cross-sectional study employed a validated online survey.

RESULTS: The study included 288 healthcare workers, predominantly female (77.35%) and aged 31-40 years (47.74%), with physicians being the largest professional group (57.14%). HCWs had positive attitudes toward AMS. They perceived moderate to high antimicrobial resistance (AMR) levels in different contexts but believed the hospital had lower AMR levels than the country. HCWs agreed that AMR impacts antimicrobial choices, patient outcomes, and safety. Contributors to AMR were prescribing inappropriate antimicrobials, unnecessary prescriptions, poor patient adherence, and inadequate infection control measures. HCWs, except medical technologists, were aware of the Antimicrobial Stewardship Program (ASP) and its interventions. Only nurses and pharmacists were aware of the hospital policies against AMR. Barriers to AMS implementation include inadequate training in antimicrobial use, lack of infectious disease/ microbiology services, lack of electronic medication management services, and personnel shortages. HCWs had high self-reported AMS practices, but a practice gap in single-dose surgical antibiotic prophylaxis was identified, with low physician adherence (50.6%).

CONCLUSION: This study revealed positive attitudes and high self-reported AMS practices among HCWs. They also perceived moderate to high AMR in different contexts but believed that the hospital has lower AMR levels than the country. Addressing the identified barriers to implementation and practice gaps is crucial for achieving antimicrobial stewardship goals.

KEYWORDS: *Antimicrobial stewardship, AMS, ASP, Healthcare workers, Pediatric.*

Introduction

Antimicrobial resistance (AMR) is a significant global health concern. In 2019, drug-resistant infections caused 1.27 million deaths, with a disease burden of 4.95 million (1). Developing nations, including the Philippines, bear a disproportionate share of this problem. To address this, the World Health Organization (WHO) endorsed the Global Action Plan (GAP) in 2015, urging nations to adopt One-Health-based national action plans (NAP) against AMR (2). In response, the Philippines initiated its Philippine Action Plan to Combat AMR and National Policy on Infection Prevention and Control in 2015 and 2016 (2). These policies underscored the importance of antimicrobial stewardship (AMS) and the establishment of Antimicrobial Stewardship Programs (ASPs) as essential tools against AMR. AMS is a comprehensive set of actions promoting the responsible use of antimicrobials. ASP, an integral component of AMS, is a multidisciplinary, coordinated approach designed to ensure the judicious use of antimicrobials to curb AMR while optimizing patient care (3). Notably, it was not until 2019 that the Philippine Children's Medical Center (PCMC) formally implemented its ASP, marking a crucial milestone in addressing AMR within the institution.

A fundamental objective within the ASP is to enhance comprehension, foster positive attitudes, and promote prudent practices concerning prescribing, dispensing, administering, and utilizing antimicrobial agents (4). While numerous studies have acknowledged the role of healthcare workers (HCWs), including nurses, pharmacists, medical technologists, and physicians (5-9), in combatting AMR, there is little research on their attitudes, perceptions, and practices concerning AMS, especially within local contexts (10,11). Given the AMR's persistent challenges and the pivotal role HCWs play, examining their views and practices concerning AMS is imperative.

This study aims to determine the HCWs' attitudes, perceptions, and practices related to AMS at the Philippine Children's Medical Center. Specifically, we aim to determine their socio-demographic profile and the relationship between their attitudes, perceptions, and practices, considering their professions and years of experience at the institution. The insights gained from this research will serve as valuable guidance for enhancing policies and guidelines at PCMC, contributing to our efforts to combat the enduring threat of AMR.

Materials and Methods

This cross-sectional study was conducted at PCMC, a pediatric tertiary hospital with a 200-bed capacity. HCWs, including physician prescribers (residents, fellows, consultants), nurses, pharmacists, and medical technologists, were recruited via purposive sampling. Eligibility criteria

included HCWs with a valid Professional Regulation Commission (PRC) license currently serving in the hospital and returning a completed questionnaire. Medical technologists not involved in microbial tests and cultures and HCWs from other institutions were excluded. The calculated sample size was 246 using proportion sampling techniques, a design effect 1.0, an anticipated frequency of 50%, a 95% confidence interval, and a 5% margin of error.

The survey questionnaire entitled "Antimicrobial stewardship: Attitudes and practices of Healthcare providers in selected health facilities in Uganda" (12), was adapted for local use in the Philippines with permission from its original authors. Content validity was ensured through expert panel evaluation, applying COSMIN criteria for item relevance. Items with an item-level content validity index (I-CVI) above 0.80 were accepted. Face validity was assessed by seeking stakeholders' input to refine the survey instrument. After validation, the questionnaire underwent pilot testing with 30 randomly selected HCWs to assess completion time and gather feedback.

The final questionnaire consisted of four parts. The first part was a checklist of the respondents' personal information--age, sex, profession (nurse, pharmacist, medical technologist, physician prescriber), and years of experience at PCMC. The second section comprised nine questions on the attitudes of HCWs regarding AMS. These questions employed a 4-point Likert scale (1= Strongly disagree, 2= Disagree, 3= Agree, 4= Strongly agree). The third part included 25 questions on HCWs' perception of the level of AMR, the impact of AMR, policies to combat AMR, ASP and ASP intervention, and the barriers to effective AMS in the hospital. The questions were 4- and 5-point Likert-type (1= Strongly disagree, 2= Disagree, 3= Agree, 4= Strongly agree; 1=Not important, 2=Slightly important, 3= Moderately important, 4= Very important, 5= Extremely important; 1= Very low, 2=Low, 3=Moderate, 4=High, 5=Very high), close-ended (yes, no, or I don't know), and multiple choice questions. The fourth part included 18 questions on practices related to antimicrobial stewardship and required "yes," "no," or "I don't know" answers.

The survey was conducted after obtaining approval from the Institutional Research–Ethics Committee (IR-EC). The survey questionnaire was distributed to the target respondents via online announcement platforms, including section and hospital announcement Viber groups. Before participating in the survey, respondents were provided with informed consent, which explained the confidentiality of their information, the maintenance of anonymity, and the voluntary nature of their participation. Respondents were given 10-15 minutes to complete the survey, with the flexibility to do so at their convenience, during breaks or outside their work or duty hours. Data collection spanned over one month.

Survey responses were automatically collected and tallied using Google Sheets, with all valid data included in the subsequent analysis. All information collected was prospectively reviewed and coded in Microsoft Excel and JASP 0.16.3. Frequency and distribution percentages were used to determine the socio-demographic profile of healthcare workers according to age, sex, profession, and years of experience. When grouped according to the profession, Kruskal-Wallis and Friedman's tests determined the significant difference between healthcare workers' attitudes, perceptions, and practices about AMS. The Spearman correlation test correlated the years of experience with attitudes.

RESULTS

Table 1 provides an overview of the demographic characteristics of the 288 respondents in our study. The largest age group was 31-40 years-old (47.74%) and majority were female (77.35%). In terms of years of experience at the institution, 37.98% had 1-5 years of experience. Physicians, including residents, fellows, and consultants, constituted the largest professional group at 57.14%, followed by nurses at 31.01%.

Table 1. Demographic Characteristics of Respondents (N=287)

	N	%
Age		
21-30	69	24.04
31-40	137	47.74
41-50	35	12.20
51-60	30	10.45
Older than 60	16	5.56
Sex		
Female	222	77.35
Male	65	22.65
Profession		
Medical Technologist	4	1.39
Nurse	89	31.01
Pharmacist	30	10.45
Physician	164	57.14
Resident	46	16.03
Fellow	55	19.16
Consultant	63	21.95
Years of experience in the institution		
Less than 1 year	52	18.12
1-5 years	109	37.98
> 5-10 years	41	14.29
> 10-15 years	33	11.50
More than 15 years	52	18.12

Attitudes of healthcare workers toward AMS in this hospital

We utilized a 4-point Likert scale with response options ranging from 1 to 4 (1= Strongly disagree, 2= Disagree, 3= Agree, 4= Strongly agree) and a midpoint set at 2.5. Responses above this midpoint were classified as 'Positive Attitude,' indicating agreement, while those at or below were deemed 'Negative Attitude,' signifying disagreement.

Over-all attitudes toward AMS were generally positive across all professional groups, with scores ranging from 3.40 to 3.80 out of 4. Notably, 283 out of 288 respondents (98.26%) exhibited positive attitudes. The nurses had lower attitude scores than other professional groups, with the Kruskal-Wallis test, $H(5) = 20.827$, $p < 0.001$, confirming significant differences in attitudes only between nurses and pharmacists ($p < 0.001$). The items on familiarity with the goals of ASP and the provision of adequate training on AMS practices consistently received lower ratings across all groups.

Table 2. Attitudes of Healthcare Workers Toward AMS in this Hospital

	Medical Technologist	Nurse	Pharmacist	Physician (Consultant)	Physician (Fellow)	Physician (Resident)
I understand what antimicrobial stewardship (AMS) is.	3.75	3.33	3.83	3.56	3.47	3.45
I am familiar with the goals of the AMS program in this hospital.	3.50	3.27	3.77	3.43	3.33	3.46
Implementation of AMS programs is essential.	3.75	3.42	3.87	3.81	3.70	3.74
Antimicrobial stewardship (AMS) involves the appropriate and optimal selection and administration of antimicrobials in appropriate dose, route, intervals and duration.	3.75	3.50	3.90	3.68	3.70	3.78
Antimicrobial stewardship (AMS) interventions can improve patient outcomes if the selection of antimicrobial dose, formulation, frequency and duration of administration are all well optimized.	3.50	3.52	3.90	3.71	3.71	3.74
Implementing effective AMS strategies or interventions in the hospital can significantly reduce the development and spread of antimicrobial resistance.	3.75	3.47	3.87	3.73	3.80	3.78
Implementing AMS practices can lead to a decrease in the length of hospital stay for patients.	3.75	3.45	3.83	3.60	3.64	3.67
The implementation of effective and diligent AMS practices can significantly reduce inappropriate antimicrobial use within this hospital.	4.00	3.52	3.87	3.81	3.73	3.72
This hospital provides adequate training on AMS practices.	2.75	3.11	3.27	2.98	3.16	3.22
OVERALL	3.611	3.40	3.80	3.60	3.58	3.62

Attitudes of healthcare workers in relation to their years of experience in this hospital

We investigated the relationship between HCWs' years of work experience at this hospital and their attitudes toward AMS. The analysis showed a negative association with Spearman's correlation coefficient of -0.142 ($p < 0.05$, $N = 288$). This correlation is statistically significant at the 0.05 level. However, in line with Cohen's conventions, the effect size associated with this correlation was considered small.

Perception of healthcare workers on the level of AMR in different contexts

The respondents rated their perceived levels of AMR from "Very low" to "Very high" in various contexts, including the country, our hospital, their specific ward or unit, and first-line antibiotics for common bacterial infections in children under five.

The perceived levels of AMR in the country, hospital, ward or unit, and common bacterial infections in children under five years old were consistently rated as moderate to high (1-1.8: Very low; 1.81-2.6: Low; **2.61-3.4: Moderate; 3.41-4.2: High;** 4.21-5: Very high) across all professional groups. In the context of AMR, all professions believed the hospital had lower AMR levels than the rest of the country. Statistical analysis utilizing the Friedman test ($\chi2(3) = 152.018$, $p < 0.001$) followed by Conover's Post Hoc comparisons revealed significant differences in perceptions of country-level AMR levels in comparison to other contexts ($p_{bonf} < 0.001$).

Table 3. Perception of Healthcare Workers on the Level Of AMR in the Country, Hospital, their Ward or Unit and to First-Line Antibiotics for Common Bacterial Infections in Children in this Hospital who are less than 5 Years Old

	Medical Technologist	Nurse	Pharmacist	Physician (Consultant)	Physician (Fellow)	Physician (Resident)
In the country	3.75	3.32	4.00	3.36	3.46	3.48
In the hospital	3.00	2.93	3.17	3.24	3.36	3.24
In their ward or unit	3.00	2.73	2.61	2.92	3.04	3.02
To first-line antibiotics for common bacterial infections in children in this hospital who are less than 5 years old	3.00	2.88	3.13	2.91	2.98	2.98

Perceptions of healthcare workers on the impact of AMR

We used 4- and 5-point Likert scales to assess HCWs' perceptions of the impact of AMR on antimicrobial choices and patient outcomes and safety. Overall, respondents agreed that AMR affects antimicrobial choices. Additionally, the impact of AMR on patient outcomes and safety was rated as moderate to high. Nurses perceived AMR to have a lower impact on prescription choices and patient outcomes than other groups.

Specifically, nurses' perceptions of the impact of prescription choices differed significantly from most other groups, as did their views on patient outcomes compared to consultants and fellows. These differences were statistically significant H (5) = 22.146, $p < 0.001$, with Bonferroni-adjusted p-values indicating significant distinctions when comparing nurses to other groups, such as pharmacists ($p < 0.009$), consultants ($p < 0.007$), fellows ($p < 0.008$), and residents ($p < 0.003$).

Table 4. Healthcare workers' perception on the impact of antimicrobial resistance on the choice of antimicrobial prescriptions and patient outcomes and safety

	Medical Technologist	Nurse	Pharmacist	Physician (Consultant)	Physician (Fellow)	Physician (Resident)
On choices of anti-microbial prescrip-tions *(ratings from 1 to 4)**	3.50	3.25	3.63	3.60	3.53	3.57
On patient outcomes and safety *(ratings from 1 to 5)* **	3.75	3.71	3.93	4.19	4.18	4.17

1-1.9: Strongly disagree; 2-2.9: Disagree;* ***3-3.9: Agree**; 4- Strongly agree*
1-1.8: Very low; 1.81-2.6: Low; 2.61-3.4: Moderate;* ***3.41-4.2: High*; 4.21-5: Very High*

Perception of healthcare workers on the factors contributing to AMR in the hospital

The respondents rated all the factors listed in Table 5 as "Very important" to "Extremely important" contributors to AMR in this hospital. The top four factors across multiple groups include prescribing inappropriate antimicrobials, prescribing antimicrobials when not needed, poor adherence of patients to prescribed antimicrobial regimens in outpatient settings, and inadequate infection prevention and control measures. Nurses consistently rated the importance of all the factors lower than other professional groups.

Table 5. Perception of healthcare workers on the factors contributing to AMR in the hospital

	Medical Technologist	Nurse	Pharmacist	Physician (Consultant)	Physician (Fellow)	Physician (Resident)
1. Prescribing the inappropriate antimicrobials	4.25	3.92	4.53	4.52	4.49	4.37
2. Prescribing Antimicrobials when not needed	3.75	3.75	4.43	4.65	4.49	4.41
3. Poor adherence of patients to prescribed antimicrobial regimen (outpatient)	4.25	4.07	4.43	4.48	4.53	4.46
4. Poor access to treatment guidelines within the hospital	4.00	3.97	4.30	4.19	4.24	4.24

5.	Lack of continuing education and updated information on antimicrobial susceptibility patterns	4.00	3.97	4.47	4.38	4.35	4.41
6.	Empiric antimicrobial prescribing without laboratory investigation	4.00	3.82	4.43	4.08	4.04	3.83
7.	Poor access to antibiograms to guide prescription	4.00	3.83	4.37	4.35	4.26	4.11
8.	Use of antimicrobials for longer than the prescribed standard duration	4.00	3.79	4.43	4.33	4.22	4.22
9.	Lack diagnostic (laboratory or ancillary) tests	4.00	3.92	4.40	4.10	4.00	3.83
10.	Lack of/inadequate infection prevention and control measures	4.25	3.98	4.43	4.51	4.29	4.24
11.	Lack of control in the access and prescription of antimicrobials	4.00	3.91	4.30	4.29	4.16	4.15
12.	Lack of antimicrobials in the pharmacy's inventory	4.25	3.92	4.17	3.98	4.04	3.98
13.	Substandard antimicrobials in the pharmacy's inventory	3.75	3.91	3.97	4.24	4.00	3.89
14.	Influence of pharmaceutical companies on the hospital	4.00	3.79	3.90	3.68	3.53	3.39

*1-1.8: Not important; 1.81-2.6: Important; 2.61-3.4: Moderately important****; 3.41-4.2: Very important; 4.21-5: Extremely important***
Reliability: α = 0.971

Awareness of healthcare workers on hospital policies to combat AMR and on Antimicrobial Stewardship Program (ASP) and ASP interventions

We assessed the respondents' knowledge of the hospital policies to combat AMR and ASP and its policies and interventions by comparing their answers to correct responses, as illustrated in Table 6. The passing score was set at 75% correctness.

Table 6. Awareness of healthcare workers on hospital policies to combat AMR, and on Antimicrobial Stewardship Program (ASP) and ASP interventions

Question	Correct Answer
Hospital policies to combat AMR	
1. Has the hospital implemented national policies and guidelines for the appropriate use, availability, and distribution of high-quality antimicrobials in its pharmacy?	Yes
2. Has the hospital instituted protocols for antimicrobial treatment and prophylaxis?	Yes
3. Does the hospital participate in a national or local antimicrobial awareness campaigns?	Yes
4. Has the hospital instituted guidelines or regulations requiring antimicrobials to be dispensed only on prescription by a qualified healthcare worker?	Yes
5. Does the hospital monitor antimicrobial consumption to estimate usage?	Yes
6. Does the hospital have action plans in place to identify and report trends in antimicrobial resistance (AMR)?	Yes
7. Has the hospital reviewed and adopted the antimicrobials listed in the Philippine National Formulary?	Yes
8. Does the hospital have a surveillance system for antimicrobial use that includes national consumption data and current infection treatment guidelines?	Yes
9. Has the hospital used government generated and reported AMR reports / information?	Yes
10. Is this hospital part of a functioning national antimicrobial resistance surveillance system covering antimicrobials in hospitals and outpatient clinics?	No
11. Is a functional infection prevention and control (IPCC) committee with standard operating procedures (SOPs), guidelines and protocols available and accessible to all sectors in the hospital?	Yes

	Question	Correct Answer
Antimicrobial Stewardship Program (ASP) and ASP interventions		
1.	Is there any existing, formal, institution-wide antimicrobial stewardship program in this hospital?	Yes
2.	A policy that requires prescribers to document the dose, duration, route, frequency, and indications of all antimicrobial prescriptions in the medical chart	Yes
3.	A policy requiring antimicrobial pre-authorization by an AMS clinician/ID specialist for specific antimicrobials	Yes
4.	A policy governing treatment duration, such as Automatic Stop Order (ASOP) that requires prescriptions to be regularly reviewed	Yes
5.	Antimicrobial formulary, restriction, and approval systems	Yes
6.	Antimicrobial Order Forms (AOF), which require clinicians to justify their antimicrobial use	Yes
7.	Antimicrobial combination therapies (use of multiple antimicrobials) used as initial empiric treatment of severe infections	Yes
8.	Streamlining (switching to a more targeted narrow-spectrum antimicrobial once an organism is identified via culture)	Yes
9.	De-escalation (discontinuing the empirical antimicrobial if the culture is negative)	Yes
10.	Dose optimization (i.e., account for individual patient characteristics such as age, renal function, and weight; causative organism; site of infection; and pharmacodynamics of the drug) when prescribing antimicrobials	Yes
11.	A systematic plan for converting parenteral to oral (I.V. to P.O.) administration of antimicrobial once a patient meets defined clinical criteria	Yes
12.	Are there diagnostic pathways for patients with reported bacterial infections?	Yes
13.	Are there guidelines for reporting for adverse reactions to antimicrobials?	Yes
14.	Are antibiograms developed and distributed at least quarterly?	Yes
15.	Are antibiograms utilized to assess antimicrobial resistance trends within the hospital?	Yes
16.	Do physicians use rapid diagnostic tests without stewardship advice?	Yes
17.	Does the hospital monitor hospital-specific antimicrobial resistance?	Yes
18.	Does the microbiology laboratory practice selective reporting of susceptibility testing (reporting only relevant antibiotics' results)?	Yes

As seen in Table 7, only nurses and pharmacists met the passing threshold for knowing the hospital policies to combat AMR. Generally, understanding of ASP and its interventions was satisfactory (>75%) across the various professions except for medical technologists.

Table 7. Healthcare workers' knowledge of hospital policies to combat AMR, Antimicrobial Stewardship Program (ASP) and ASP interventions

	Medical Technologist	Nurse	Pharmacist	Physician (Consultant)	Physician (Fellow)	Physician (Resident)
Hospital policies to combat AMR	58.3	75.1	80.8	62.3	72.7	73.2
ASP, and ASP Interventions	66.7	84.0	85.4	75.3	82.8	88.3

Note: Scores are in percentage of total possible correct answers.

Perception of healthcare workers on barriers to antimicrobial stewardship (AMS) in the hospital

We assessed the perception of HCWs on barriers to AMS in this hospital using a multiple-choice question. The top three most commonly identified barriers to AMS across all groups were 1. lack of HCWs' training and education in antimicrobial use; lack of infectious disease/microbiology services; 2. lack of electronic medication management services, and

3. personnel shortages (specifically, a shortage of AMS full-time staff). Table 8 shows the frequencies and percentages of respondents who identified each item as a barrier to AMS.

Table 8. Perception of healthcare workers on barriers to Antimicrobial Stewardship (AMS) in the hospital

	Medical Technologist n (%)	Nurse n(%)	Pharmacist n (%)	Consultant n (%)	Fellow n (%)	Resident n (%)	Total n(%)
1. Healthcare workers' lack of training and education in antimicrobial use	2 (50)	60 (67.42)	25 (83.33)	49 (77.78)	40 (72.73)	37 (80.44)	213 (73.96)
2. Lack of time among the antimicrobial stewardship team	2 (50)	40 (44.94)	24 (80)	26 (41.27)	17 (30.91)	14 (30.44)	123 (42.71)
3. Lack of leadership to promote antimicrobial stewardship at the facility	1 (25)	35 (39.33)	8 (26.67)	18 (28.57)	13 (23.64)	15 (32.61)	90 (31.25)
4. Lack of support and cooperation from senior clinicians in this hospital	1 (25)	38 (42.70)	18 (60)	17 (28.98)	16 (29.10)	13 (28.26)	68 (23.61)
5. Lack of infectious disease or microbiology services	3 (75)	55 (61.80)	18 (60)	56 (88.89)	48 (97.23)	33 (71.74)	213 (73.96)
6. Lack of pharmacy resources	2 (50)	40 (44.94)	18 (60)	17 (28.98)	15 (27.27)	22 (47.83)	114 (39.58)
7. Unwillingness of healthcare providers to change their prescribing practices	1 (25)	32 (3.96)	20 (66.67)	35 (55.56)	20 (36.36)	19 (41.30)	95 (32.99)
8. Lack of enforcement by hospital management/executive	1 (25)	30 (33.71)	9 (30)	21 (33.33)	15 (27.27)	15 (32.61)	91 (31.60)
9. Lack of an electronic medication management system	2 (50)	53 (59.55)	22 (73.33)	43 (68.25)	37 (67.27)	28 (60.87)	185 (64.24)
10. Inadequate time for AMS activities among healthcare providers	2 (50)	47 (52.81)	17 (56.67)	32 (50.79)	19 (34.55)	21 (45.65)	138 (47.92)
11. Personnel shortages/ lack of manpower (e.g., full-time AMS staff)	1 (25)	58 (65.17)	27 (90)	40 (63.49)	28 (50.91)	22 (47.83)	176 (61.11)
12. Inadequate funding for antimicrobial stewardship strategies, activities, or personnel	2 (50)	39 (43.82)	17 (56.67)	29 (46.03)	17 (30.91)	15 (32.61)	119 (41.32)
13. Opposition to antimicrobial stewardship from healthcare workers (HCWs)	1 (25)	31 (34.83)	12 (40)	18 (28.57)	10 (18.18)	9 (19.57)	81 (28.13)
14. Paucity of data on improved outcomes with AMS programs in the health facility	2 (50)	31 (34.81)	8 (26.67)	27 (42.86)	20 (36.36)	19 (41.30)	107 (37.15)
15. None of the above	0 (0)	1(1.12)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.35)

Practices of healthcare workers towards AMS: Comparison of self-reported and observed practices

Table 9 provides information on the practices of different professional groups toward AMS. Each row represents specific practices related to a profession, while each column represents a professional group reporting those practices. For instance, a physician-specific practice (row) intersection with their own group's report (column) indicates their self-reported practices. The intersections of physician-specific practices (row) with columns representing other professional groups show how often these other groups perceive physicians to engage in AMS practices. This allows for comparing the group's self-reported practices with those observed by professional groups other than themselves.

The questions required "yes" (coded as 1), "no," or "I don't know" (both coded as 0) responses. The answers were added to give practice scores and were interpreted as "high," "fair," and "poor" if they ranged between 80-100%, 50-79%, and <50% of the maximum possible score.

Regarding physicians' self-reported and observed practices, they had high self-reported practice scores in most areas except for avoiding unnecessary use of broad-spectrum antimicrobials, using a single dose of an IV antibiotic for surgical procedures, reviewing antimicrobial prescriptions for inpatients in all ward rounds, and regularly communicating team-based assessment of antimicrobial use to prescribers and the Infection Prevention and Control Committee (IPCC). The lowest self-reported practice concerned the use rate of a single IV antibiotic dose for surgical prophylaxis, with only 50.6% adherence reported. Nurses and pharmacists also observed low adherence to this protocol among physicians (52.8% and 43.3%, respectively).

Pharmacists had a high self-reported practice of reviewing antimicrobial prescriptions during all ward rounds. However, all pharmacists (100%) believed that their group reviews prescriptions in all ward rounds, while only 72% of physicians reported the same practice, $H(3)=36.463$, $p<0.001$, $z=3.511$, $p_{bonf}=0.001$.

Nurses had a high self-reported practice of reviewing antimicrobial prescriptions during all ward rounds. However, more nurses (85.4%) believed their group reviews prescriptions in all ward rounds compared to physicians (58.5%), $H(3)=34.340$, $p<0.001$, $z=4.245$, $p_{bonf}=<0.001$. Additionally, more nurses (88.8%) reported communicating with the Infection Prevention and Control Committee compared to physicians (66.5%), $H(3)=17.718$, $p<0.001$, $z=3.937$, $p_{bonf}=<0.001$.

Table 9. Practices of healthcare workers towards AMS: frequencies of self-reported and observed practices

	Medical Tech-nologists	Nurses	Pharmacists	Physicians
Physicians				
Physicians use local guidelines to initiate prompt, effective antimicrobial treatment within one hour of presentation or as soon as possible in patients with life-threatening infections.	0	85.4	96.7	89.6
Physicians avoid the unnecessary use of broad-spectrum antimicrobials.	**0**	**71.9**	**53.3**	**79.3**
Physicians document the clinical indications, formulation, dose, route, frequency, duration, and review dates of antimicrobial use.	0	89.9	83.3	89.0
Physicians only use a single dose of an IV antimicrobials for surgical procedures.	**0**	**52.8**	**43.3**	**50.6**
Physicians switch to the appropriate, narrower-spectrum antimicrobials when susceptibility testing indicates resistance.	0	85.4	90.0	89.0
Physicians review antimicrobial prescriptions for hospital inpatients in all ward rounds.	0	85.4	73.3	73.2
Physicians review antimicrobial treatments within 48 hours of initiation and discontinue their use if no evidence of infection is found.	0	77.5	73.3	72.0
Physicians review antimicrobial treatments within 48 hours of initiation and appropriately switch from intravenous to oral administration when indicated.	0	80.9	76.7	81.1
Physicians modify their antimicrobial prescribing practices based on the results of adverse event monitoring.	0	94.4	86.7	90.9
Physicians modify their antimicrobial prescribing practices based on the results of antimicrobial susceptibility reports.	0	93.3	93.3	95.7
Physicians modify their antimicrobial prescribing practices based on the results of antimicrobial prescribing and medication error audits.	0	82.0	76.7	82.3
Physicians modify their antimicrobial prescribing practices based on the results of antimicrobial usage data.	0	89.9	83.3	83.5
Pharmacists				
Pharmacists review antimicrobial prescriptions for hospital inpatients in all ward rounds.	**0**	**91.0**	**100**	**72.0**
Nurses				
Nurses review antimicrobial prescriptions for hospital patients in all ward rounds.	**0**	**85.4**	**40.0**	**58.5**
Healthcare workers				
HCWs instruct patients and caretakers about the use of prescribed antimicrobial medications.	25.0	89.9	100	90.2
In antimicrobial treatment policy decisions, HCWs actively seek the input and perspectives of other stakeholders while promoting the adoption of best practices.	0	87.6	86.7	78.7
HCWs regularly take part in a team-based evaluation of antimicrobial usage, considering both the quality and the quantity.	50.0	82.0	83.3	68.9
HCWs regularly communicate the results of their team-based assessments of antimicrobial use to prescribers and the Infection Prevention and Control Committee.	**75.0**	**88.8**	**86.7**	**66.5**

Note: Values are the percentage of that respondent category that perceives the practice as being done. Highlighted cells are the groups for which significant differences in perception were observed.

Discussion

Attitudes

Our study showed a positive attitude towards AMS among all professional groups. Pharmacists had the highest attitude scores towards AMS, while nurses had the lowest. It is important to note that despite nurses having the lowest scores, their overall attitude towards AMS remained positive. These findings align with a study by Kimbowa *et al*. (12), which also reported positive AMS attitudes across professional groups, with pharmacists scoring the highest and nurses scoring the lowest.

Our HCWs agreed with AMS' crucial role in combating AMR, curbing its spread, and reducing hospital stays. This aligns with the findings of Kimbowa *et al.* (12). and Pagcatipunan *et al.* (10), where HCWs also recognized that implementing AMS strategies can minimize the risk of AMR development, reduce patient's length of stay, and improve patient outcomes.

Our study, however, identified a need for greater familiarity with AMS goals and a demand for more comprehensive AMS-related training within our hospital. This need for education and training is consistent with existing literature, which suggests that while HCWs generally appreciate the importance of AMS, they often need a deeper understanding of what an AMS program entails (13). This highlights the importance of educational initiatives to introduce AMS goals and provide insights into the corresponding interventions and their practical implementation for HCWs. Recognizing that a positive attitude is a critical facilitator for successful AMS and ASP (13), the implementation of targeted AMS-related training programs to leverage this positive outlook could significantly enhance knowledge, improve our HCW's attitudes, and positively impact their practices, as evidenced by several studies (14-16).

Our study identified a weak, negative correlation between HCWs' years of experience and their attitudes toward AMS, suggesting a slight decline in attitude scores as the years of work experience in the hospital increased. Interestingly, this finding challenges the conventional notion that more time spent in a healthcare setting naturally leads to stronger support for AMS initiatives. A study by Charani *et al*. (17) on antimicrobial prescribing practices, while not directly addressing attitudes, revealed that senior physicians often consider themselves exempt from following established policies and practice guidelines, as they operate within a culture of perceived autonomous decision-making, relying more on personal knowledge and experience than formal policy. In the context of AMS attitudes, such perception could contribute to less positive AMS attitudes in more senior HCWs, emphasizing the significance of continuous education and reinforcement of stewardship principles, even among experienced HCWs.

However, it is important to interpret this result cautiously, given the relatively weak correlation observed.

Perceptions

HCWs perceived moderate to high levels of AMR in various contexts, including the country, our hospital, their wards or units, and first-line antibiotics for common bacterial infections in children under five. Notably, within the hospital, HCWs perceived AMR as less severe than the national level, aligning with findings from other surveys (18,19). Nurses consistently rated the impact lower than other groups, a pattern inherent to the nursing group rather than the questionnaire's content. While not directly applicable to our study, other studies (20,21) reveal a similar limited interest in AMS-related concepts among nurses despite intersecting with their work. Their hesitancy to engage fully in AMS arises from perceiving it as the domain of physicians and pharmacists, the absence of formal policies outlining their roles, a culture favoring physician prescriber authority, and a belief that AMS tasks extend beyond traditional nursing roles, posing an additional burden (20,21). An additional study to further explore these themes may offer valuable insights and enhance nurses' engagement in our hospital's AMS initiatives.HCWs agreed that AMR impacts antimicrobial choices, patient outcomes, and patient safety. Over the years, the emergence of AMR has led to notable shifts in prescribing practices, such as changes in empiric therapy choices, with a tendency to use broader-spectrum antimicrobials and other agents with reduced efficacy and increased toxicity (22). In our hospital, empiric antimicrobial therapies are tailored to the resistance pattern of the organisms, ideally guided by the hospital-wide and unit-specific antibiograms and the data from the Antimicrobial Resistance Surveillance Program (ARSP) results. The impact of AMR on patient safety and outcomes, including all-cause and infection-related morbidity and mortality rates, is a well-recognized consequence of AMR (22).

HCWs identified our hospital's most critical contributors to AMR: inappropriate prescription of antimicrobials, unnecessary prescription of antimicrobials, patient non-adherence to outpatient therapy, and inadequate infection control measures. These findings are congruent with those of Balliram *et al.,* Burger *et al.,* and Abera *et al.,* where inappropriate and over-prescription of antimicrobials and patient non-adherence to antimicrobial therapy in the outpatient department were also identified as primary drivers of AMR (23-26). Considering these findings and drawing upon prior research, it may be advisable to consider initiatives such as educating physician prescribers about the selection of appropriate antimicrobials, making local antimicrobial guidelines like the National Antibiotic Guidelines (NAG)

available, and promoting active consultations with infectious disease experts to facilitate the successful implementation of AMS (26).

Only nurses and pharmacists met the threshold for awareness of hospital policies against AMR, which, especially for pharmacists, is not surprising. As critical stakeholders in antimicrobial management, pharmacists are involved in procuring, dispensing, monitoring, and enforcing policies related to judicious antimicrobial use in this hospital (4). Clinical pharmacists, integral members of the AMS team, often engage with IPCC policies and AMR awareness campaigns. On the other hand, the limited exposure may account for the need for more policy awareness among trainees with shorter years of experience (2-3 years), such as fellows and residents, who primarily focus on their clinical duties during onboarding. Similarly, some consultants, despite potentially having longer years of experience, may not be full-time hospital employees, leading to limited physical presence and involvement in hospital activities, including policy awareness.

Most HCWs, except for medical technologists, demonstrated awareness of the hospital's ASP and associated interventions, including pre-authorization, formulary restrictions, streamlining, de-escalation, dose optimization, and intravenous to oral (IV to PO) antimicrobial switch. This observation is unsurprising as these aspects of AMS are typically within the purview of prescriber physicians, pharmacists, and nurses. However, recognizing the crucial role of medical technologists in diagnostic stewardship and the creation of hospital-wide antibiograms (7), it is imperative to extend efforts to educate them about AMS policies and practices.

In our study, the following were identified as top barriers to AMS: inadequate training and microbiology services, absence of electronic medication management, and personnel shortages. These findings are similar to the results of local studies by Pagcatipunan *et al.* and Diño *et al.* (10,11).

The lack of adequate training in AMS consistently emerges in our survey and can be considered an actionable target. Although our hospital has Gram staining, cultures, and automated susceptibility testing capacities, the absence of other microbiology services was identified as a prominent AMS barrier. However, the limited diagnostic capacity for molecular identification or rapid testing for a wide range of microorganisms is likely the barrier the HCWs intended to highlight. Some studies suggest interventions like enhancing diagnostic capacity through collaboration with larger institutions with advanced microbiology laboratory capabilities or expanding our hospital's microbiology laboratory facilities through a dedicated national action plan with allocated funding (27).

communication of guidelines to prescribers (31).

Discrepancies were observed between HCWs' self-reported and observed AMS-related practices, particularly in avoiding broad-spectrum antimicrobials, conducting consistent antimicrobial prescription ward rounds, and communicating with the IPCC. This presents an opportunity to identify practice gaps and provide targeted feedback to specific professional groups.

Establishing a shared understanding of what constitutes an antimicrobial prescription ward rounds can be beneficial to addressing the gap in practices related to antimicrobial prescription ward rounds. Implementing standardized documentation policies (31) and more comprehensive prescription charts (32) can help achieve this goal. Studies have shown that these measures can help prevent unnecessary or prolonged use of antimicrobials and reduce overall antimicrobial consumption without impacting patient outcomes (32).

Another effective strategy is routinely monitoring antimicrobial usage, especially broad-spectrum agents, and providing feedback to HCWs about institutional antimicrobial utilization and global Point Prevalence Survey (PPS) results (31). Such measures can effectively guide physicians' prescribing practices and promote adherence to AMS strategies, as demonstrated in a local study (31) where repeated surveillance and hospital-wide PPS identified targets for quality improvement of antimicrobial prescribing and raised awareness among HCWs.

Involving other HCWs, such as nurses and pharmacists, in AMS programs at the ward level can also enhance collaboration and improve communication among team members. Since AMS is a collaborative, multidisciplinary effort, integrating nurses and pharmacists can facilitate better coordination among HCWs (31).

Recommendations

Our study relied on self-administered survey questionnaires, which introduces the potential for self-reporting and social desirability biases, as participants may provide answers they perceive as socially desirable rather than reflecting their attitudes and perceptions towards AMS. Additionally, relying solely on self-reports may not capture the full complexity of healthcare workers' attitudes and perceptions towards AMS. Therefore, future research should consider incorporating other qualitative methods, such as interviews or focus group discussions, to gain a deeper and more nuanced understanding of HCWs' attitudes and perceptions.

This is a single-center study, which limits the generalizability of the results to other healthcare settings. To improve the generalizability, future researchers can extend

scope of their studies to include multiple healthcare facilities.

Moreover, this study serves as a baseline exploration of the attitudes, perceptions, and practices of HCWs towards AMS. It is intended to generate research questions and provide a foundation for further investigations. Future research can build upon this baseline study by exploring specific emerging themes, such as the impact of AMR on antimicrobial prescription practices and patient outcomes. Researchers may also focus on specific professional groups to conduct more in-depth studies that account for different HCWs' unique perspectives and practices.

Conclusion

Our study at the Philippine Children's Medical Center revealed generally positive attitudes and high self-reported practices of AMS among HCWs. A need for enhanced education and training on AMS goals and practices was identified. HCWs perceived moderate to high AMR levels in different contexts but believed the hospital had lower AMR levels than the country. HCWs agreed that AMR impacts antimicrobial prescription choices, patient outcomes, and safety. The top contributors to AMR in this hospital were inappropriate prescription of antimicrobials, unnecessary prescription of antimicrobials, patient non-adherence to outpatient therapy, and inadequate infection control measures. HCWs, except medical technologists, were aware of the ASP and its interventions, while only nurses and pharmacists were aware of the hospital policies against AMR. Barriers to effective AMS implementation included insufficient AMS training, limited access to microbiology services, and electronic medication management and staffing challenges. Practice gaps, particularly in single-dose surgical antibiotic prophylaxis, were identified. The findings from this study offer valuable, actionable insights and recommendations for enhancing the hospital's Antimicrobial Stewardship Program as it aims to strengthen its AMS interventions.

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References

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0. Epub 2022 Jan 19. Erratum in: Lancet. 2022 Oct 1;400(10358):1102. doi: 10.1016/S0140-6736(21)02653-2. PMID: 35065702; PMCID: PMC8841637.

2. Department of Health. Antimicrobial stewardship program in hospitals: Manual of procedures. 2016.

3. World Health Organization [Internet]. Antimicrobial stewardship programmes in healthcare facilities in low- and middle-income countries: a WHO practical toolkit. Geneva: World Health Organization; 2019 [cited 2023 Nov 13]. Available from: https://apps.who.int/iris/handle/10665/329404. License: CC BY-NC-SA 3.0 IGO.

4. Philippine Children's Medical Center (PCMC). Antimicrobial stewardship (AMS) program: PCMC's institutional manual of antimicrobial stewardship program. 2022.

5. Abbas S, Lee K, Pakyz A, Markley D, Cooper K, Vanhoozer G, Doll M, Bearman G, Stevens MP. Knowledge, attitudes, and practices of bedside nursing staff regarding antibiotic stewardship: A cross-sectional study. Am J Infect Control. 2019 Mar;47(3):230-233. doi: 10.1016/j.ajic.2018.09.008. Epub 2018 Nov 22. PMID: 30471970.

6. Ourghanlian C, Lapidus N, Antignac M, Fernandez C, Dumartin C, Hindlet P. Pharmacists' role in antimicrobial stewardship and relationship with antibiotic consumption in hospitals: An observational multicentre study. J Glob Antimicrob Resist. 2020 Mar;20:131-134. doi: 10.1016/j.jgar.2019.07.009. Epub 2019 Jul 16. PMID: 31323427.

7. Centers for Disease Control and Prevention [Internet]. Core elements of hospital antibiotic stewardship programs. Atlanta: The Centers for Disease Control and Prevention; [cited 2023 Nov 13]. Available from: https://www.cdc.gov/antibiotic-use/healthcare/pdfs/core-elements.pdf.

8. Trikha S, Dalpath SK, Sharma M, Shafiq N. Antibiotic prescribing patterns and knowledge of antibiotic resistance amongst the doctors working at public health facilities of a state in northern India: A cross-sectional study. J Family Med Prim Care. 2020;9:3937-43.

9. Wushouer H, Wang Z, Tian Y, Zhou Y, Zhu D, Vuillermin D, Shi L, Guan X. The impact of physicians' knowledge on outpatient antibiotic use: Evidence from China's county hospitals. Medicine (Baltimore). 2020 Jan;99(3):e18852. doi: 10.1097/MD.0000000000018852. PMID: 32011504; PMCID: PMC7220442.

10. Pagcatipunan MR, Halili S Jr, Arciaga RS, Makalinaw SR, Gonzales ML, Garcia RD, Aguirre C, Ong-Lim AL, Luna I, Gallardo E, Lim J, Aguilar D, Pererras N. Antimicrobial stewardship (AMS) program in private hospitals in the Philippines: Its acceptability, barriers, and enablers. Pediatric Infectious Disease Society of the Philippines Journal. 2020 Jul-Dec;21(2):24-38.

11. Diño PET, Aquino SS, Depante DDM, Peña IG. Determination of the enablers and challenges in the implementation of pharmacy-based antimicrobial stewardship (AMS) program in a level 3 hospital in Manila. Acta Med Philipp. [Online ahead of print] Published online July 25, 2023. Available from: https://actamedicaphilippina.upm.edu.ph/index.php/acta/article/view/6658

12. Kimbowa IM, Eriksen J, Nakafeero M, Obua C, Lundborg CS, Kalyango J, Ocan M. Antimicrobial stewardship: Attitudes and practices of healthcare providers in selected health facilities in Uganda. PLoS One. 2022 Feb 3;17(2):e0262993. doi: 10.1371/journal.pone.0262993. PMID: 35113932; PMCID: PMC8812957.

13. Scheepers LN, Niesing CM, Bester P. Facilitators and barriers to implementing antimicrobial stewardship programs in public South African hospitals. Antimicrob Steward Healthc Epidemiol. 2023 Feb 23;3(1):e34. doi: 10.1017/ash.2022.355. PMID: 36865702; PMCID: PMC9972532.

14. Ashraf S, Ashraf S, Ashraf M, Imran MA, Choudhary ZA, Hafsa HT, Awais AB, Kalsoom L, Farooq I, Habib Z, Ashraf S, Iqbal QUA, Ghufran M, Sherazi SSH, Akram MK, Akmal R, Rafique S, Nawaz K, Safdar Z, Siddique UN, Hassan M, Arshad S, Virk AR, Ashraf M, Saboor QA, Humayun A, Izhar M. Knowledge, attitude, and practice of clinicians about antimicrobial stewardship and resistance among hospitals of Pakistan: a multicenter cross-sectional study. Environ Sci Pollut Res Int. 2022 Feb;29(6):8382-8392. doi: 10.1007/s11356-021-16178-2. Epub 2021 Sep 6. PMID: 34490566; PMCID: PMC8421064.

15. Kjærsgaard M, Leth RA, Udupi A, Ank N. Antibiotic stewardship based on education: minor impact on knowledge, perception and attitude. Infect Dis (Lond). 2019 Oct;51(10):753-763. doi: 10.1080/23744235.2019.1648856. Epub 2019 Aug 7. PMID: 31389732.

16. Tahoon MA, Khalil MM, Hammad E, Morad WS, Awad SM, Ezzat S. The effect of educational intervention on healthcare providers' knowledge, attitude, and practice towards antimicrobial stewardship program at National Liver Institute, Egypt. Egypt Liver J. 2020;10(5):[page range if available]. doi:10.1186/s43066-019-0016-5

17. Charani E, Castro-Sanchez E, Sevdalis N, Kyratsis Y, Drumright L, Shah N, Holmes A. Understanding the determinants of antimicrobial prescribing within hospitals: The role of "prescribing etiquette". Clin Infect Dis. 2013 Jul 15;57 (2):188–196. doi:10.1093/cid/cit212

18. Setiawan E, Cotta MO, Abdul-Aziz MH, Sosilya H, Widjanarko D, Wardhani DK, Roberts JA. Indonesian healthcare providers' perceptions and attitude on antimicrobial resistance, prescription and stewardship programs. Future Microbiol. 2022 Mar;17:363-375. doi: 10.2217/fmb-2021-0193. Epub 2022 Feb 25. PMID: 35212232.

19. García C, Llamocca LP, García K, Jiménez A, Samalvides F, Gotuzzo E, Jacobs J. Knowledge, attitudes and practice survey about antimicrobial resistance and prescribing among physicians in a hospital setting in Lima, Peru. BMC Clin Pharmacol. 2011 Nov 15;11:18. doi: 10.1186/1472-6904-11-18. PMID: 22085536; PMCID: PMC3231801.

20. Zhao W, Xu Y, Liu R, Zhao T, Ning Y, Feng Y, Kang H, Li S, Han X, Shang L. Knowledge, attitudes, and practices of bedside nurses regarding antimicrobial stewardship in China: An explanatory sequential mixed methods study. J Nurs Manag. 2023. doi:10.1155/2023/9059920.

21. van Gulik N, Hutchinson A, Considine J, Driscoll A, Malathum K, Botti M. Perceived roles and barriers to nurses' engagement in antimicrobial stewardship: A Thai qualitative case study. Infect Dis Health. 2021 Aug;26 (3):218-227. doi: 10.1016/ j.idh.2021.04.003. Epub 2021 May 11. PMID: 33994163.

22. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. Clin Microbiol Infect. 2016 May;22(5):416-22. doi: 10.1016/ j.cmi.2015.12.002. Epub 2015 Dec 17. PMID: 26706614.

23. Balliram R, Sibanda W, Essack SY. The knowledge, attitudes and practices of doctors, pharmacists and nurses on antimicrobials, antimicrobial resistance and antimicrobial stewardship in South Africa. S Afr J Infect Dis. 2021 Apr 21;36(1):262. doi: 10.4102/ sajid.v36i1.262. PMID: 34485504; PMCID: PMC8378097.

24. Burger M, Fourie J, Loots D, Mnisi T, Schellack N, Bezuidenhout S, Meyer JC. Knowledge and perceptions of antimicrobial stewardship concepts among final year pharmacy students in pharmacy schools across South Africa. S Afr J Infect Dis. 2016;31(3):84–90. doi:10.1080/23120053.2016.1192808

25. Abera B, Kibret M, Mulu W. Knowledge and beliefs on antimicrobial resistance among physicians and nurses in hospitals in Amhara Region, Ethiopia. BMC Pharmacol Toxicol. 2014;15:26. doi:10.1186/2050-6511-15-26

26. Baraka MA, Alsultan H, Alsalman T, Alaithan H, Islam MA, Alasseri AA. Health care providers' perceptions regarding antimicrobial stewardship programs (AMS) implementation-facilitators and challenges: a cross-sectional study in the Eastern province of Saudi Arabia. Ann Clin Microbiol Antimicrob. 2019 Sep 24;18(1):26. doi: 10.1186/s12941-019-0325-x. PMID: 31551088; PMCID: PMC6760054.

27. Khanal S, Acharya U, Trotter A, Tripathi P, Koirala S, Pahari B, Acharya S. Challenges and opportunities in the implementation of an antimicrobial stewardship program in Nepal. Antimicrob Steward Healthc Epidemiol. 2023;3 (1):E58. doi:10.1017/ash.2022.359.

28. Hawn MT, Knowlton LM. Balancing the Risks and Benefits of Surgical Prophylaxis: Timing and Duration Do Matter. JAMA Surg. 2019 Jul 1;154(7):598-599. doi: 10.1001/jamasurg.2019.0570. PMID: 31017641.

29. Fowotade A, Fasuyi T, Aigbovo O, Versporten A, Adekanmbi O, Akinyemi O, Goossens H, Kehinde A, Oduyebo O. Point Prevalence Survey of Antimicrobial Prescribing in a Nigerian Hospital: Findings and Implications on Antimicrobial Resistance. West Afr J Med. 2020 Jul-Aug;37(3):216-220. PMID: 32476113.

30. Global point prevalence survey for antimicrobial consumption and resistance report 2022-P3 for Philippine Children's Medical Center. [Unpublished report].

31. de Guzman Betito G, Pauwels I, Versporten A, Goossens H, De Los Reyes MR, Gler MT. Implementation of a multidisciplinary antimicrobial stewardship programme in a Philippine tertiary care hospital: an evaluation by repeated point prevalence surveys. J Glob Antimicrob Resist. 2021 Sep;26:157-165. doi: 10.1016/ j.jgar.2021.05.009. Epub 2021 Jun 10. PMID: 34118483.

32. Boyles TH, Whitelaw A, Bamford C, Moodley M, Bonorchis K, Morris V, Rawoot N, Naicker V, Lusakiewicz I, Black J, Stead D, Lesosky M, Raubenheimer P, Dlamini S, Mendelson M. Antibiotic stewardship ward rounds and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates. PLoS One. 2013 Dec 9;8(12):e79747. doi: 10.1371/ journal.pone.0079747. PMID: 24348995; PMCID: PMC3857167.

ARTICLE

Impact of the COVID-19 Pandemic on children diagnosed with diabetic ketoacidosis admitted in a tertiary pediatric hospital

Camille S. Cantalejo, Lorna R. Abad

OBJECTIVE: This study aims to determine the effect of the COVID-19 pandemic on the incidence, severity, and outcome of children diagnosed with diabetic ketoacidosis admitted in a tertiary pediatric hospital.

MATERIALS AND METHODS: Two groups were identified as the basis for classification: pre-pandemic (2017 to 2019) and COVID-19 pandemic (2020 to 2022). The Mann-Whitney U test was utilized to test for the differences in continuous variables, while Pearson's chi-squared test was used to test for differences in categorical variables.

RESULTS: The study involved 136 participants, 63 of whom were recorded in the pre-pandemic period and 73 during the COVID-19 pandemic period. Data revealed no conclusive relationship between sex (p=0.578), age (p=0.225), or height (p=0.876) across the two time frames. However, data showed significant difference between the weight (p=0.007) and BMI (p=0.003) of children with DKA pre-pandemic and during pandemic. This implies that marked changes in weight and BMI reflect possible changes in health behaviors, healthcare access, or other variables that may have altered during the COVID-19 pandemic. Furthermore, there was no discernible difference between pre-pandemic and COVID-19 in terms of severity, incidence, or the amount of time between the onset of symptoms and consultation.

CONCLUSION: The demographic and clinical characteristics of patients with DKA across the two study periods indicate a degree of stability in patient profiles. Despite the unique circumstances of the pandemic, patient outcomes in terms of glycemic control and mortality were like those observed pre-pandemic. The significant difference in weight and BMI emphasizes how crucial it is to monitor and respond to modifications in the nutritional status and metabolic health of DKA patients during times of crisis, like the COVID-19 pandemic. Comprehending these changes can provide focused treatments aimed at promoting the best possible health outcomes for susceptible patient groups.

KEYWORDS: *Diabetic Ketoacidosis, Diabetes mellitus, Covid-19 pandemic*

Introduction

Diabetes Mellitus (DM) is a metabolic disorder caused by an absolute or relative insulin shortage and an excess of counter-regulatory hormones. Diabetic ketoacidosis (DKA) is a catastrophic condition seen in patients with Diabetes Mellitus, which could be the presenting manifestation of diabetic patients with both Type 1 and Type 2 DM. DKA in patients with confirmed DM may be triggered by inadequate glycemic management, omission of insulin, infection, or emotional stress. The prevalence of DKA rose in children and teenagers with type 1 diabetes mellitus (T1DM) throughout the COVID-19 pandemic.[9] Studies on its demographic profile, such as age, gender, family history of diabetes, BMI z-scores, and laboratory tests have been established. However, reports on incidence and prevalence are somewhat underrepresented in the Philippines during the COVID-19 pandemic.[1] We investigated how this pandemic affected the lives of children diagnosed with DKA. Symptoms such as weight loss, fatigue, polyuria, nocturia, vomiting, and other typical signs of diabetes may be mistaken for pharyngitis, the flu or another common virus, pneumonia, eating disorders, food poisoning, or urinary tract infections. These might lead to a delayed diagnosis of T1DM, which would then cause diabetic ketoacidosis to advance quickly and raise the risk of complications and mortality.[1,6]

Although the impact of COVID-19 varies by nation, societies are making an effort to cut down on the use of healthcare facilities by preventing virus transmission and reducing rates of illness and death. Children experience less mortality, problems, and frequency as compared to adult age groups.[3] Children who had COVID-19-unrelated diseases during the pandemic, such as diabetes mellitus (DM), were more likely to experience negative outcomes.[9] Several studies showed a notable rise during the COVID-19 pandemic of diabetic ketoacidosis. This may make it more difficult to diagnose T1DM in children, further delaying the initiation of insulin therapy.[6] These findings show the critical need for better prevention methods for DKA in T1DM patients, not just in pandemic situations but in all situations, especially in groups most impacted by health disparities.[2,4,7,11] However, there are limited data about the impact of the pandemic on T1DM in the Philippines.

This study aims to determine the effect of the Covid-19 pandemic on the incidence, severity, and outcome of children diagnosed with diabetic ketoacidosis admitted in a tertiary pediatric hospital. This study aims to: 1) compare the demographic data of children with diabetic ketoacidosis hospitalized in a tertiary pediatric hospital during pre-pandemic (2017-2019) and COVID-19 pandemic (2020-2022) period; 2) compare the incidence of DKA in children during pre-pandemic and pandemic between known and newly diagnosed T1DM children; 3) compare DKA

characteristics in children hospitalized in a tertiary pediatric hospital during pre-pandemic and pandemic in terms of: time interval between onset of symptoms and consultation, severity, length of hospitalization, survival/ mortality; and 4) compare glycemic control based on HbA1c between T1DM children diagnosed with DKA admitted in a tertiary hospital during pre-pandemic and pandemic.

Materials and Methods

This is a retrospective study design. Purposive sampling of children 6 months to 18 years old admitted at the Philippine Children's Medical Center (PCMC) who were diagnosed with diabetic ketoacidosis between 2017 to 2022 were included. Two groups were identified using the period of admission as the basis for classification pre-pandemic (2017 to 2019) and COVID-19 pandemic (2020 to 2022). Children aged less than 6 months were excluded due to the diagnosis of neonatal diabetes. Other types of diabetes mellitus such as Type 2 DM were also excluded.

Case records of children diagnosed with DKA was obtained from the Medical Records Section of PCMC. Data collected include demographic data (age, gender, family history, BMI), clinical symptoms, onset of symptoms, time interval between symptoms and consultation, laboratory tests used such as HbA1c, serum bicarbonate, and venous blood gas. Since the study is a descriptive, no intervention was involved.

Identifying outcomes were patterned from the studies of Al-Alburazzaq *et al.* and Dyzgalo, *et al*., wherein demographic information for each patient, laboratory findings, and clinical outcomes such as timely diagnosis and treatment, regimen, and length of hospital stay was gathered. Severity of DKA was based on the standard definition from the 2022 ISPAD Guidelines of Diabetic Ketoacidosis.

The standard deviation for continuous variables, frequencies (%) and numbers (n) for categorical variables was used. Comparison of the incidence is based on the rate of the DKA/ Total DM for the pre-pandemic and during pandemic period.

The Mann-Whitney U test was utilized to test for the differences in continuous variables, while Pearson's chi-squared test was used to test for differences in categorical variables.[1,6]

Only the information needed for the research was utilized after the study. The participants' identities were likewise treated with confidentiality. The study's data was anonymized, with no way for participants to be re-identified. A waiver consent was obtained from IR-EC and non-disclosure confidentiality agreement was signed.

Results

The study included 136 participants, 63 of whom were recorded in the pre-pandemic period and 73 during the COVID-19 pandemic period.

A Mann-Whitney test showed that there is no significant difference between the age, sex, and height of children with diabetic ketoacidosis hospitalized in a tertiary pediatric hospital during pre-pandemic and COVID-19 pandemic period (Table 1). The weight, and BMI however, showed a significant difference between the two groups with p values of 0.007 and 0.003, respectively. This implies that while age, sex and height remain largely similar across two time periods, there are marked changes in weight and BMI. This reflects possible changes in health behaviors, healthcare access, or other variables that may have altered weight and BMI outcomes during the COVID-19 pandemic compared to the pre-pandemic period. Further studies may be needed to understand the underlying reasons for these changes.

Table 1. Summary of Demographic Characteristics of T1DM Patients

Parameter	Pre- pandemic (N=63) (2017-2019)	COVID-19 Pandemic (N=73) (2020-2022)	p-value
Age (Median)	12	12	0.225
Sex (Male)	35	44	0.578
(Female)	28	29	0.578
Weight (kilograms)	30	40.9	0.007
Height (centimeters)	138	141	0.876
BMI (kg/m^2)	15.8	18.4	0.003

The overall incidence of DKA among old patients was 74%, with 61% occurring pre-pandemic and 47% during pandemic. Similarly, among newly diagnosed patients, the overall incidence was 62%, with 38% occurring pre-pandemic and 52% during pandemic. The chi-square test of independence indicated that there was no statistically significant difference between the incidence of DKA and the period of observation (Table 2).

Table 2. Incidence Rate Of DKA In Children During Pre-Pandemic And Covid-19 Pandemic Between Known And Newly Diagnosed T1dm Children

	Pre-Pandemic (2017-2019)	COVID-19 Pandemic (2020-2022)	Total
Old	61%	47%	74%
New	38%	52%	62%

A Mann-Whitney test showed that there is no significant difference between the time interval, severity, and length of hospitalization. While there was no statistically significant difference in the glycemic control between patients in the study period, one point difference translates to a significant clinical implication (Table 3).

Table 3. Clinical Characteristics Of Patients With DKA

Parameter	Pre-pandemic (N=63) (2017-2019)	During Pandemic (N=73) (2020-2022)	p-value
Time interval between onset of symptoms and consult (Hours)	72	96	0.619
Severity of acidosis			
Mild	10	12	22
Moderate	9	12	21
Severe	44	49	93
Length of Hospital stay	6.0	7.0	0.366
Outcome			
Discharged	60	70	130
Mortality	3 (4.8%)	3 (4.1%)	6
Glycemic Control Based on HbA1c	12.7	13.2	0.075

Discussion

The absence of a significant difference between the age of children with diabetic ketoacidosis hospitalized in a tertiary pediatric hospital during the pre-pandemic and during the COVID-19 Pandemic is different from the findings of Vorgučin *et al.* (2022), where children aged 10 -14 years reflect the highest frequency rate of diabetic ketoacidosis observed during the pandemic.[17] This could be related to a difference in the health care system between countries and health-seeking behavior among parents.

Furthermore, pre-pandemic and during COVID-19 pandemic data show that there was also no significant association between sex and year of children with diabetic ketoacidosis hospitalized in a tertiary pediatric hospital. Similarly, the height of children with DKA reflects no statistically significant difference. These findings are in consonance with the findings of Mastromauro *et al.*, that while there is a remarkable increase in the prevalence of DKA among children during the pandemic, there is no consequential differences in terms of the sex, and height of children with diabetic ketoacidosis pre-pandemic and during the COVID-19 pandemic.

Meanwhile, as to the weight and the body mass index (BMI), the findings reflect a significant difference between the children with diabetic ketoacidosis hospitalized during the pre-pandemic period and during the COVID-19 pandemic Period. This is in consonance with the findings of Lange *et al.* which reported that the rate of weight and BMI increased among the pediatric population during the COVID-19 pandemic due to a more sedentary lifestyle, increased calorie intake, reduced access to physical activities, and increased social isolation as compared to the pre-pandemic period.

As to the incidence of DKA in children during pre-pandemic and pandemic between known and newly diagnosed T1DM children, results showed no statistically significant difference between the incidence of DKA and year of observation. This supports the findings of Rabbone *et al.* which shows that there were no differences in the incidence of DKA before and during the COVID-19 Pandemic.

This research also compared the characteristics of DKA in children hospitalized in a tertiary pediatric hospital during pre-pandemic and pandemic. In terms of the time interval between the onset of symptoms and consultation of children with DKA, the findings showed no statistically significant difference between the time interval during the pre-pandemic period and the COVID-19 pandemic period. However, the 24-day difference has significant clinical implications. Patients during pandemic could have been at greater risk for complications due to the delay in diagnosis The findings of Duncanson, *et al.* showed that the fear of COVID-19 transmission in hospitals resulted in a more delayed diagnosis and higher complication rates.

Data also revealed that there was no significant association between the severity of DKA during the pre-pandemic and during the COVID-19 pandemic period. This is consistent with the findings of Ordooei, *et al.* where the frequency of mild and moderate DKA cases was not significantly different between the pre -pandemic and during the COVID-19 Pandemic. However, their findings reflect that there are significantly more severe DKA cases found during the pandemic than the pre-pandemic period.

In terms of the length of hospitalization of children with DKA during the pre-pandemic and COVID-19 Pandemic, the absence of significant difference reflects a more aggressive and focused management during the COVID-19 as there were less consultations. This is in contrast to the study of Chambers, *et al.* (2022) where children in a tertiary care children's hospital with DKA after the pandemic onset had higher lengths of hospitalization.

In terms of the association between the outcome of Children with DKA during the pre-pandemic and the COVID-19 Pandemic period, analysis did not indicate a statistically

significant association between the two variables. This could be attributed to the standardized care that has been in place in the management of DKA patients in our institution. The findings provide a different view from the study of Kiral *et al.* and Chambers *et al.* which postulate that children who had COVID-19-unrelated diseases during the pandemic were more likely to experience negative outcomes.

In terms of glycemic control based on glycosylated HbA1c, the study revealed no significant difference but the slightly higher HbA1c among children during the pandemic period could be related to higher glucose levels with sedentary lifestyle as a contributory factor. While studies reflect that the global quarantine and health protocols brought by the COVID-19 Pandemic negatively affect the access to quality of care for children with T1DM diagnosed with diabetic ketoacidosis, the findings reflect that there was no significant difference between the established quality of care during the pre-pandemic for T1DM children diagnosed with diabetic ketoacidosis and during the COVID-19 pandemic. The sustained quality of care could be attributed to the established health intervention protocols amid the COVID-19 pandemic.

The implications of this study are multifaceted. The allocation of healthcare resources for DKA patients remained unchanged throughout the course of the two periods. Potential changes in health behaviors or access to healthcare services during the pandemic emphasizes the need for interventions to address weight management and overall health during crisis situations like the Covid-19 pandemic. The importance of continued monitoring and adaptation of healthcare practices could provide valuable insights to address emerging trends in diabetic ketoacidosis. These findings could provide clinical management strategies and patient education programs designed to target potential risk factors discovered during the pandemic period.

Conclusions and Recommendations

The incidence of DKA during the study periods offer important information despite not achieving statistical significance. The demographic and clinical characteristics of patients with DKA across two study periods indicate a degree of stability in patient profiles. Despite the unique circumstances of the pandemic, patient outcomes in terms of glycemic control and mortality were similar to those observed pre-pandemic. Meanwhile, the significant difference in weight and BMI emphasize how crucial it is to monitor and respond to modifications in the nutritional status and metabolic health of DKA patients during times of crisis, like the COVID-19 pandemic. Comprehending these changes can provide focused treatments aimed at promoting the best possible health outcomes for susceptible patient groups.

This pioneering study also has limitations due to the limited international and local literature on the impact of COVID-19 on children with DKA. The lack of existing data and registry also emphasizes the need to enhance measures and programs for an integrated, comprehensive, and optimal treatment for pediatric patients with diabetic ketoacidosis, this includes the establishment of a nationwide registry of pediatric patients with diabetic ketoacidosis to better assess the impact of the COVID-19 pandemic and its implications to the post-pandemic phase on the continuum of care for T1DM and its outcomes.

Given that the COVID-19 pandemic has also seen the potential of telemedicine and the relevance of the field of telehealth, there is also a need to recommend mechanisms that would enhance the scope of services and accessibility of telemedicine for pediatric patients with diabetic ketoacidosis and platforms for allied specialists to provide inputs on the continuum of care, especially in the underserved and geographically isolated and disadvantaged areas. Hand in hand with the need to sustain the efforts for the health sector to encourage screening for symptoms of DKA and T1DM among children and increase health campaigns on the awareness to the issue of delayed presentation and early intervention.

References

1. Al-Abdulrazzaq, D., Alkandari, A., Alhusaini, F., et al. (2022). Higher rates of diabetic ketoacidosis and admission to the paediatric intensive care unit among newly diagnosed children with type 1 diabetes in Kuwait during the COVID-19 pandemic. *Diabetes/metabolism research and reviews*, *38*(3), e3506. https://doi.org/10.1002/dmrr.3506

2. Birkebaek, N. H., Kamrath, C., Grimsmann, J. M., Aakesson, K., Cherubini, V., Dovc, K., de Beaufort, C., Alonso, G. T., Gregory, J. W., White, M., Skrivarhaug, T., Sumnik, Z., Jefferies, C., Hörtenhuber, T., Haynes, A., De Bock, M., Svensson, J., Warner, J. T., Gani, O., Gesuita, R., … Cinek, O. (2022). Impact of the COVID-19 pandemic on long-term trends in the prevalence of diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes: an international multicentre study based on data from 13 national diabetes registries. The lancet. Diabetes & endocrinology, 10(11), 786–794. https://doi.org/10.1016/S2213-8587(22)00246-7

3. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatrics. (2020) 174:882- 9. doi: 10.1001/jamapediatrics.2020.1467

4. Chambers, M. A., Mecham, C., Arreola, E. V., & Sinha, M. (2022). Increase in the Number of Pediatric New-Onset

diabetes and Diabetic Ketoacidosis Cases During the COVID-19 Pandemic. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 28(5), 479–485. https://doi.org/10.1016/j.eprac.2022.02.005

5. Duncanson, M., Wheeler, B., Jelleyman, T., Dalziel, S. & Mclntyre, P. (2021) Delayed access to care and late presentations in children during the COVID-19 pandemic New Zealand-wide lockdown: A New Zealand Paediatric Surveillance Unit study. J Paediatr Child Health. Oct;57(10):1600-1604. doi: 10.1111/jpc.15551.

6. Dżygało, K., Nowaczyk, J., Szwilling, A., & Kowalska, A. (2020). Increased frequency of severe diabetic ketoacidosis at type 1 diabetes onset among children during COVID-19 pandemic lockdown: an observational cohort study. Pediatric endocrinology, diabetes,andmetabolism, 26(4),167–175. https://doi.org/10.5114/pedm.2020.101003

7. Elgenidy, A., Awad, A.K., Saad, K. et al. Incidence of diabetic ketoacidosis during COVID-19 pandemic: a meta-analysis of 124,597 children with diabetes. Pediatr Res (2022). https://doi.org/10.1038/s41390-022-02241-2

8. Kamrath, C., Mönkemöller, K., Biester, T., Rohrer, T., Warncke, K., Hammersen, J. (2020). Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. Jama. 324(8):801–4. doi: 10.1001/jama.2020.13445

9. Kiral E, Kirel B, Havan M, et al. (2022). Increased Severe Cases and New-Onset Type 1 Diabetes Among Children Presenting with Diabetic Ketoacidosis During the First Year of COVID-19 Pandemic in Turkey. Front. Pediatr. 10:926013. doi: 10.3389/fped.2022.926013

10. Lange, S., Kompaniyets, L., Freedman, D., Kraus, E., Porter, R. (2021). Longitudinal Trends in Body Mass Index Before and During the COVID-19 Pandemic Among Persons Aged 2–19 Years — United States, 2018–2020. National Library of Medicine. 2021 Sep 17; 70(37): 1278–1283. https://doi.org/10.15585/mmwr.mm7037a3

11. Lavik, A. R., Ebekozien, O., Noor, N., Alonso, G. T., Polsky, S., Blackman, S. M., Chen, J., Corathers, S. D., Demeterco-Berggren, C., Gallagher, M. P., Greenfield, M., Garrity, A., Rompicherla, S., Rapaport, R., & Yayah Jones, N. H. (2022). Trends in Type 1 Diabetic Ketoacidosis During COVID-19 Surges at 7 US Centers: Highest Burden on non-Hispanic Black Patients. *The Journal of clinical*

endocrinology and metabolism, 107(7), 1948–1955. https://doi.org/10.1210/clinem/dgac158

12. Lee, Y., Kim, M., Oh, K.,et al. (2022). Comparison of Initial Presentation of Pediat:ric Diabetes Before and During the Coronavirus Disease 2019 Pandemic Era. Journal of Korean medical science, 37(22), e176.

13. Mastromauro, C., Blasetti, A., Primavera, M. (2022). Peculiar characteristics of new-onset Type 1 Diabetes during COVID-19 pandemic. Ital J Pediatr 48, 26. https://doi.org/10.1186/s13052-022-01223-8

14. Marks, B. E., Khilnani, A., Meyers, A., et al. (2021). Increase in the Diagnosis and Severity of Presentation of Pediatric Type 1 and Type 2 Diabetes during the COVID-19 Pandemic. Hormone research in paediatrics, 94(7-8), 275–284. https://doi.org/10.1159/000519797

15. Rahmati, M., Keshvari, M., Mirnasuri, S., et al. (2022). The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: A systematic review and meta-analysis. Journal of medical virology, 94(11), 5112–5127. https://doi.org/10.1002/jmv.27996

16. Rabbone, I., Schiaffini, R., Cherubini, V., Maffeis, C., Scaramuzza, A. (2020). Has COVID-19 Delayed the Diagnosis and Worsened the Presentation of Type 1 Diabetes in Children? Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Diabetes Care. 2020;43(11):2870–2. https://doi.org/10.2337/dc20-1321.

17. Vorgučin, I., Savin, S., Stanković, D., Miljković, D., Ilić, T., Simić, D., Vrebalov, M., Milanović, B., Barišić, N., Stojanović, V., Vijatov-Đurić, G., Koprivšek, K., Vilotijević-Dautović, G., & Antić, A. (2022). Incidence of Type 1 Diabetes Mellitus and Characteristics of Diabetic Ketoacidosis in Children and Adolescents during the First Two Years of the COVID-19 Pandemic in Vojvodina. Medicina. 2022; 58(8):1013. https://doi.org/10.3390/medicina58081013

ARTICLE

Effect of Pre-operative Isometric Exercise (PIE) on vascular caliber of stage 2-5D chronic kidney disease pediatric patients: a randomized controlled study

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OBJECTIVE: To determine the effect of pre-operative isometric exercise (PIE) on vascular caliber of pediatric chronic kidney disease (CKD) Stage 2-5D patients.

MATERIAL AND METHODS: This is a single-blind, randomized, single-center trial of 28 CKD patients. Fourteen participants allocated in the intervention group (PIE) were provided with a handgrip device and performed handgrip exercise consisting of two sets of 30 contractions daily while another 14 participants did not perform the exercise and were considered as controls (NE). For both groups, Duplex Ultrasonography was performed at baseline, four and eight weeks post-intervention.

RESULTS: Twenty-four CKD patients were included and analyzed. The mean age was 15.8 (+/- 1.9) years. There were 16 (66.7%) females and eight (33%) Males, 10 (41.7%) underweight (<18 kg/ m^2), 23 (95.8%) right-handed, 12 (50%) with Chronic Glomerulonephritis, and 10 (41.7%) with stage 2 CKD. Both the intervention and control group revealed a statistically significant increase in thecaliber of the non-dominant cephalic (ante-cubital) vein at four- and eight-weeks post-intervention.

CONCLUSION: PIE might not significantly impact vessel diameter in pediatric CKD population as compared to adult CKD patients. Further studies on reliability of ultrasonography of blood vessels utilizing a larger sample size and more controlled milieu are recommended.

KEYWORDS: *Pre-operative Isometric Exercise, Vascular Caliber, Chronic Kidney Disease*

INTRODUCTION

Chronic Kidney Disease (CKD) pertains to abnormalities of the kidney structure or function present for more than three months[1] and can eventually lead to End Stage Renal Disease (ESRD).[2] It is an emerging global public health concern with a high economic burden.[3] The information on the epidemiology of CKD in the pediatric population is limited. The only data available is derived from patients undergoing renal replacement therapy (RRT) which is estimated to be nine per million of age-related population.[1,2] Locally, based on the Philippine Pediatric Society (PPS) Disease registry program, there are a total of 1,720 cases of Chronic Kidney Disease in children reported in the past 16 years (from January 2006 – November 2022). Among these cases, 96 or 5.6% were seen and managed at the Philippine Children's Medical Center (PCMC). At present, there are 80 active CKD patients with regular follow-up in the PCMC Nephrology face-to-face and telemedicine clinic.

Forty-three percent (34 out of 80) of these cases are classified as End Stage Renal Disease (ESRD) and are maintained on renal replacement therapy. Chronic Kidney Disease has five stages based on Estimated Glomerular filtration rate (eGFR) wherein Stage 1 is defined as GFR of more than or equal 90ml/ min, Stage 2: 60-89ml/min; Stage 3 GFR 30-59 ml/min; Stage 4: GFR 15-29 ml/min and Stage 5: GFR <15ml/min. Stage 5 CKD is correspondingly referred to as End Stage Renal Disease (ESRD) whereas for patients who are on dialysis, the term CKD 5D is applied.

The gold standard in the management of ESRD is Kidney Transplantation (KT). Nevertheless, in instances where KT is unavailable or not yet feasible, renal replacement therapy is a life saving measure and a bridge in preparation for the definitive treatment. There are two modalities of renal replacement therapy which include Peritoneal Dialysis (PD) and Hemodialysis (HD). In patients requiring chronic hemodialysis, suitable vascular access is crucial in assuring adequate dialysis and more favorable long-term outcome.[5] There are three types of vascular access, namely the (1) Central venous catheters (CVC), (2) Arteriovenous grafts (AVG) and (3) Arteriovenous Fistula (AVF). In PCMC, CVCs are the most commonly used access due to their availability and less complicated surgical technique compared to permanent ones. A CVC is a temporary type of vascular access and is associated with high risk of catheter-related infection and thrombosis. The other two types are less common but act as long-term access with lesser impact on morbidity and mortality.[6,7] In PCMC, only three out of 16 HD patients or (19%) are currently utilizing AVF as access for hemodialysis. A functioning AVF is the preferred access due to less long-term vascular events including thrombosis, loss of primary patency and interventions.[8] Patients require suitable vessels for arteriovenous access creation.[5] A pre-requisite for optimal AVF is a vein diameter of more than or equal to 2.5mm.[9] This poses a challenge in the pediatric population who have smaller body weight and correspondingly with small vein diameter and weak arterial inflow.[11] Hence, any intervention that can increase the vein diameter remains of utmost importance. Previous evidence has demonstrated that Pre-operative Isometric exercise (PIE) can increase the vein diameter thereby enhancing the success rates of AVF creation and maturation. All these studies involved adult subjects who performed handgrip isometric contractions utilizing either a rubber ring, squeeze ball or a handgrip device.[12-16] To date, there is only one small case series of pediatric patients that has been done on this subject matter. Ramirez-Senent reported four cases of adolescents aged 13-19 years old requiring AVF but with unsuitable vessel sizes. All four patients underwent isometric exercise ranging from 9-30 months utilizing a handgrip device resulting in an increase in vessel diameter allowing AVF creation. They concluded that isometric exercise is a valuable option given its benefits including safety of the program and low cost.[17]

This study aims to determine the effect of Pre-operative Isometric exercise (PIE) on vascular caliber of pediatric chronic kidney disease (CKD) Stage 2-5D patients. Specifically, to describe the demographics and baseline characteristics of upper extremity vessels using duplex ultrasonography on pediatric CKD stage 2-5D patients; to evaluate the effect of PIE in the diameter of the radial, ulnar, brachial arteries as well as cephalic and basilic veins at four and eight weeks using Duplex Ultrasound and lastly to compare the mean change in diameter of the radial, ulnar, brachial arteries as well as cephalic and basilic veins between the control (no exercise) and the study groups (PIE) at zero and four weeks, and zero and eight weeks.

METHODOLOGY

A single-blind, randomized, controlled, single-centered trial with two treatment arms and a 1:1 allocation ratio was utilized in this study. Participants were recruited from the Nephrology outpatient clinic as well as the hemodialysis unit (HDU) and peritoneal dialysis unit (PDU) of the Philippine Children's Medical Center (PCMC). The primary investigator secured an informed consent/assent prior to the conduct of the study. The participants were CKD 2-5D patients aged 12 – 18 years old with signed informed consent/assent from a parent or legal guardian. Participants were excluded from the study if they had limitations in performing the exercise due to physical or mental disabilities or were unable to follow instructions.

Using OpenEpi version 3, the sample size was calculated using 95% confidence level, 80% power, ratio of 1:1 for the control and exercise group, and mean change in diameter of 0.39 (SD 0.06) for the control and 0.47 (SD 0.07) with the intervention group. [12] The computed sample size per group is 11 or total of 22 CKD pediatric patients. To account for 20% loss to follow-up, an additional three per group were recruited.

Participants were randomized into two groups, the intervention and control group using block randomization with sealed envelope method. The primary investigator who processed the data and the radiologist who measured the vessel diameter were blinded on the allocation of patients into the two groups. Only the patient, care giver and research assistant were informed of the group assignment whether in the intervention or control group. A thorough physical examination of all participants was done to ensure that the patient is physically and mentally fit to be in the study. A Duplex ultrasound at baseline was performed by one identified sonologist in both groups to measure the arteries including radial, ulnar and brachial as well as cephalic and basilic veins. Participants who were randomized in the PIE group underwent measurement of handgrip strength of the non-dominant hand using a hand grip dynamometer (Camry Digital

198lb/90kg Electronic Hand grip strength Dynamometer) (Figure 1). A physical therapist identified the level of resistance of the handgrip device based on the average handgrip strength for every patient which ranges from 10-100 kg. Additionally, a thorough instruction on pre-operative exercise protocol utilizing an instructional video was provided for the PIE group. The handgrip device (ATRONWA Hand Grip Exercise R-shape Adjustable 100kg) is a spring loader type, 200 grams in weight, equipped with a non-slip feature, an adjustable resistance knob with resistance level of 10kg-100kg and a digital counter (Figure 2).

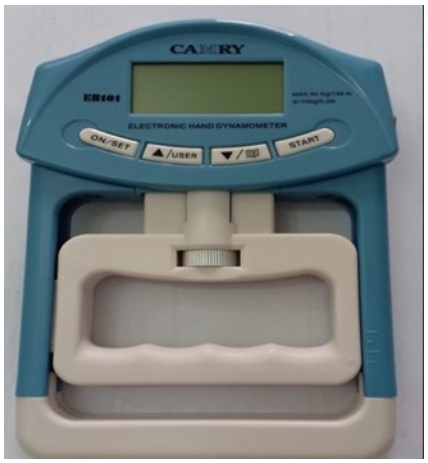


Figure 1: Handgrip Dynamometer

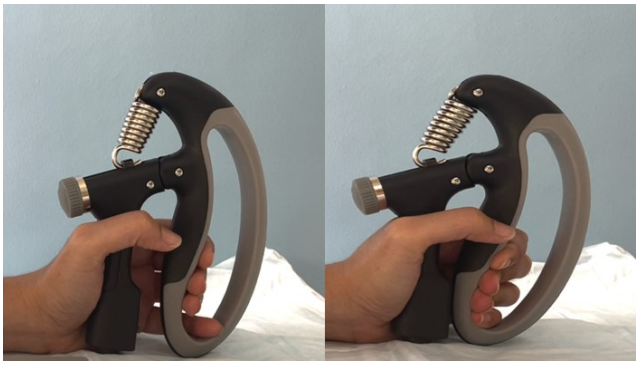


Figure 2: Handgrip Device

The participants in the PIE group performed daily handgrip exercise utilizing the non-dominant arm, to ensure that the outcome is less likely influenced by factors apart from the intervention. The exercise based on the study of Sauco et al consisted of two sets of 30 handgrip contractions per day using a handgrip device. Every handgrip contraction must be sustained for three to five seconds. Participants must do 10 contractions per cycle with a one-minute rest after each cycle. These handgrip exercises were done twice a day. Each patient was provided with their own handgrip device with strength adjusted to 30-40% of their maximum grip strength and as prescribed by the physical therapist. An instructional video was provided to all participants in the PIE group and served as their guide while performing the daily exercise. No other forms of exercise were performed during the entire study period. Clinical follow-up was done every four weeks to ensure that proper exercise protocol was performed.

Duplex Ultrasonography focusing on the identified arteries and veins were performed by the blinded sonologist on both groups at the initial visit, and at the fourth- and eighth-week visit. Veins and arteries of both upper extremities were measured twice with a tourniquet and recorded. The average of the two measurements was taken as the final measurement. To prevent inter-observer variability and bias, only one radiologist blinded to the group allocation performed the

vascular mapping and only one ultrasound machine was used throughout the study period. On the day of the imaging study, CKD 2-4 patients were advised to consume adequate amounts of fluids based on their maintenance requirements to prevent dehydration while patients on dialysis consumed their usual fluid limitation and underwent ultrasound pre-mid-week dialysis session. The temperature in the examining room was maintained at the same preset settings of 22-24 degree Celsius in every measurement.

To ensure compliance, a handgrip device with counter was provided to the participants. The caregivers were instructed to make an exercise diary by recording the cumulative number of handgrip contractions performed daily as reflected in the handgrip counter. The research assistant was in constant communication with the participants in the PIE group. A social media group chat was created to include all of the participants in PIE group with the research assistant as the administrator. The instructional video was sent twice daily as a reminder to all the PIE group participants to perform the handgrip exercise. The social media group likewise served as a tool to monitor the progress of the exercise regimen and to report if there were untoward symptoms experienced by the patient while performing the exercise.

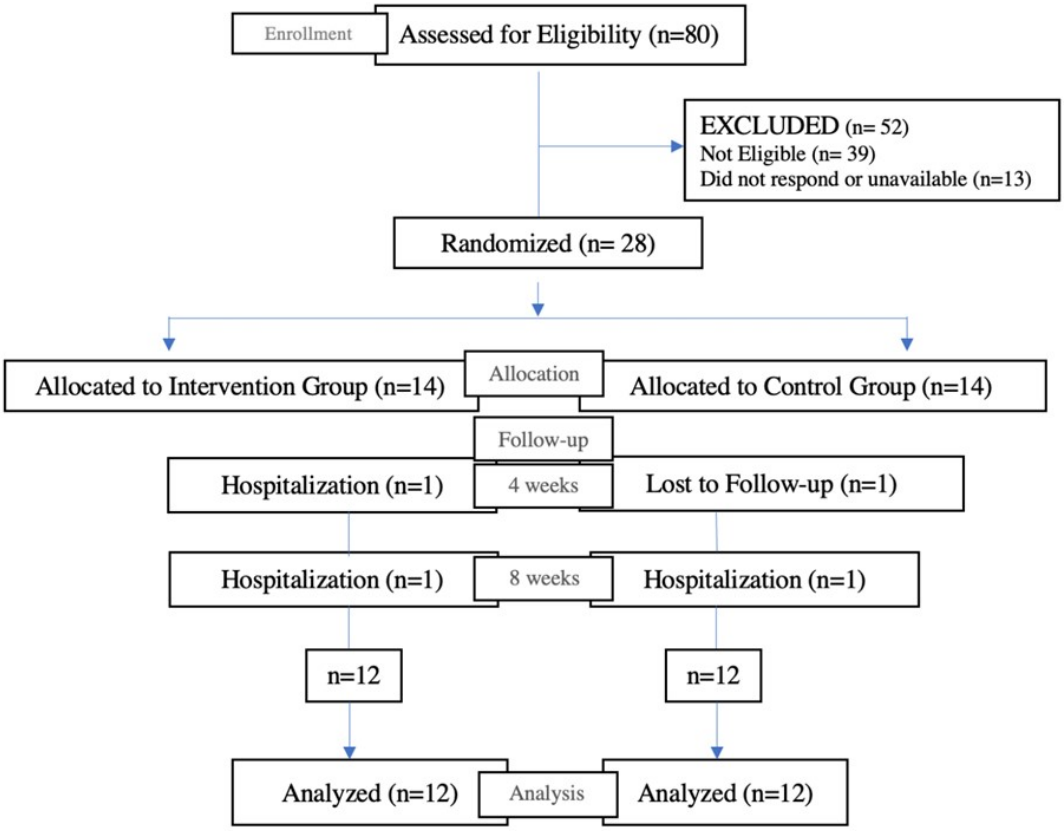
The primary outcome of this study was the mean change in the vascular diameter between the intervention and control group at zero and four weeks and zero and eight weeks. Ultrasound measurement of blood vessels was done on baseline, fourth week and eight weeks for both groups. Qualitative variables were described using frequency and proportion distribution while quantitative variables were described as mean and standard deviations. For the primary outcome, Fisher's exact test for categorical variables and independent *t*-test were used to compare the mean changes in the vein diameters from the baseline of the intervention and control groups at weeks four and eight. Paired t-test was used to compare the changes from baseline to four weeks and eight weeks in the two groups. A p-value of less than 0.05 is statistically significant. IBM SPSS Software Version 20 (IBM Corporation) was used in the analysis.

Implementation of this study was guided by the ethical principles stated in the Declaration of Helsinki, World Health Organization, International Conference on Harmonization – Good Clinical Practice and the National Ethics Guidelines for Research and the International Ethical Guidelines for Epidemiological Studies). The technical aspect of the study was presented for approval by the Clinical Trial and Research Division. The Institutional Research- Ethics Committee (IR-EC) approved the proposal last April 19, 2023. This trial was funded through a research grant from the Philippine Children's Medical Center (PCMC) and the Pediatric Nephrology Society of the Philippines (PNSP).

RESULTS

A total of 80 CKD patients were screened; 52 were excluded for non-eligibility or unavailability (Figure 3). The recruitment period started on May 23 until June 22, 2023, while follow-up ended last August 17, 2023. There were 28 CKD pediatric patients enrolled and randomized however, four dropped out of the study: one participant from the PIE group was admitted for bacterial peritonitis and one from the control group did not follow-up after four weeks of intervention because of schedule conflict. At the eighth week post intervention, an additional two participants were hospitalized: one from the PIE group had bacterial peritonitis while another from the control group had catheter related blood stream infection (CRBSI).

Figure 3: Enrollment Flowchart



A total of 24 CKD pediatric patients that were included and analyzed in the study. There were 12 CKD pediatric patients in the PIE and 12 CKD pediatric patients in control group. The mean age of CKD pediatric patients was 15.8 (+/- 1.9) years. The baseline characteristics are in Table 1.

Table 1. Demographics and clinical characteristics of pediatric CKD stage 2-5D patients

Characteristics	PIE n=12	NE n=12	p value	
Age (years +/- SD)	16.58 (1.31)	14.92 (2.15)		**0.032***
12-14yo	0 (0%)	5 (41.7%)	**.019***	
15-18yo	12 (100%)	7 (58.3%)		
Sex (%)			0.097	
Male	6 (50%)	2 (16.7%)		
Female	6 (50%)	10 (83.3%)		
BMI (kg/m2)	20.58 (3.370)	20.08 (5.518)		0.791
<18	4 (33.3%)	6 (50%)	0.301	
18-25	6 (50%)	2 (16.7%)		
>25	2 (16.7%)	4 (33.3%)		
Handedness (%)			0.5	
Left	1 (8.3%)	0 (0%)		
Right	11 (91.7%)	12 (100%)		
Etiology of CKD (%)			1	
CGN	6 (50%)	6 (50%)		
Lupus Nephritis	2 (16.7%)	3 (25%)		
Reflux Nephropathy	2 (16.7%)	1 (8.3%)		
Hypokalemic Nephropathy	2 (16.7%)	2 (16.7%)		
CKD Stage (%)				0.525
2	5 (41.7%)	5 (41.7%)		
3	4 (33.3%)	1 (8.3%)		
4	1 (8.3%)	2 (16.7%)		
5D	2 (16.7%)	4 (33.3%)		

Note. *p-value <0.05 is significant

The baseline characteristics of upper extremity vessels using the duplex ultrasound on pediatric CKD stage 2-5D patients showed that the diameter of the ulnar artery and cephalic (wrist) vein were significantly higher in PIE as compared to the control group with p-values < 0.05. The mean baseline measurements of radial artery and brachial artery as well as cephalic (antecubital) and basilic veins were comparable between the two groups. (Table 2).

Table 2. Baseline diameters of upper extremity vessels using the duplex ultrasonography on pediatric CKD stage 2-5D patients

Baseline	Non Dominant		p-value
	PIE n=12	NE n=12	
Artery	mm+/- SD		
Radial	2.08 (.289)	2.00 (.426)	0.581
Ulnar	1.92 (.289)	1.50 (.522)	**.024***
Brachial	3.33 (.492)	3.00 (.603)	0.152
Vein			
Cephalic (wrist)	2.33 (.651)	1.67 (.778)	**.033***
Cephalic (Antecubital)	3.08 (.996)	3.00 (.853)	0.828
Basilic	3.67 (1.073)	3.67 (.985)	1.00

Note. * p-value < 0.05 is significant

Based on the exercise diary, 10 out of 12 participants completed and performed the daily exercise. On the other hand, 2 (16.7%) patients had irregular compliance, and completed only 75-87.5% sessions of the prescribed exercise.

In the PIE group, the mean diameter from baseline to four weeks post-intervention was significant at cephalic (antecubital) vein with p-values < 0.05. The diameter of other arteries and veins were not significant with p-values > 0.05. In the control group, on the other hand, the mean diameter from baseline to four weeks post-intervention was significant at cephalic (antecubital) and cephalic (wrist) veins with p-values < 0.05. Other arteries and vein's diameter were not significant with p-values > 0.05. (Table 3)

Table 3. Pre and post intervention mean diameter of upper extremity vessels at four weeks in PIE intervention and control group

	PIE			CONTROL (NE)		
	Pre-intervention diameter (mm) mean (SD)	Post - intervention diameter at 4 weeks (mm) mean (SD)	p-value	Pre-intervention diameter (mm) mean (SD)	Post - intervention diameter at 4 weeks (mm) mean (SD)	p-value
Artery						
Radial	2.08 (.289)	2.08 (.289)	1.00	2.0 (.426)	2.17 (.389)	0.339
Ulnar	1.92 (.289)	1.83 (.389)	0.586	1.5 (.522)	1.83 (.389)	0.1034
Brachial	3.33 (.492)	3.58 (.515)	0.082	3.0 (.603)	3.25 (.754)	0.191
Vein						
Cephalic (wrist)	2.33 (.651)	2.50 (.674)	0.339	1.67 (.778)	2.25 (.866)	**0.027***
Cephalic (Antecubital)	3.08 (.996)	4.0 (1.128)	**0.009***	3.0 (.853)	3.67 (1.155)	**0.026***
Basilic	3.67 (1.073)	4.33 (1.155)	0.207	3.67 (.985)	4.42 (1.564)	0.120

Note. *p-value < 0.05 is significant

The mean change in blood vessel diameter for both the intervention and control group was not statistically significant with p values >0.05. Comparing both groups, the mean change in the diameter of the upper extremity vessels at four weeks in the control group was higher and more consistent as compared to the PIE group. (Table 4).

Table 4. Comparison of the mean change in diameter of upper extremity vessels between PIE and control group at four weeks

	PIE	CONTROL	
	diameter mean change (mm) mean (SD)	diameter mean change (mm) mean (SD)	p-value
Artery			
Radial	0.00 (.426)	+.167 (.577)	0.428
Ulnar	-.083 (.515)	+.333 (.651)	0.096
Brachial	+.250 (.452)	+.250 (.622)	>0.999
Vein			
Cephalic (wrist)	+.167 (.577)	+.583 (.793)	0.156
Cephalic (Antecubital)	+.917 (.996)	+.667 (.888)	0.523
Basilic	+.667 (1.723)	+.750 (1.545)	0.902

Note. *p-value < 0.05 is significant

The mean diameter from baseline to eight weeks post-intervention in PIE group was significant at cephalic (antecubital) vein with p-values < 0.05. The mean effect of PIE intervention at eight weeks in the diameter of other upper extremity arteries and veins was not significant. Meanwhile, in the control group, the mean diameter from baseline to eight weeks post-intervention was significant at brachial artery and cephalic (antecubital), cephalic (wrist) with p-values < 0.05 (Table 5). The increase in both arterial and venous diameters at eight weeks post intervention was comparable with four-weeks post intervention wherein there was variable and smaller increase in the PIE group as compared to the control group (Figure 4 and 5).

Table 5. Pre and post intervention mean diameter of upper extremity vessels at eight weeks in PIE intervention and control group

	PIE			**CONTROL**		
	Pre-intervention diameter (mm) mean (SD)	Post -intervention diameter at 8 weeks (mm) mean (SD)	p-value	Pre-intervention diameter (mm) mean (SD)	Post -intervention diameter at 8 weeks (mm) mean (SD)	p-value
Artery						
Radial	2.08 (.289)	2.17 (.389)	.586	2.0 (.426)	2.17 (.389)	.166
Ulnar	1.92 (.289)	1.92 (.289)	1.00	1.5 (.522)	1.83 (.389)	.104
Brachial	3.33 (.492)	3.58 (.515)	.082	3.0 (.603)	3.58 (.669)	**.027***
Vein						
Cephalic (wrist)	2.33 (.651)	2.33 (.778)	1.00	1.67 (.778)	2.17 (.835)	**.007***
Cephalic (Antecub	3.08 (.996)	4.0 (1.044)	**.005***	3.0 (.853)	4.00 (1.279)	**.032***
Basilic	3.67 (1.073)	4.17 (1.467)	.352	3.67 (.985)	4.50 (1.087)	.064

Note. *p-value < 0.05 is significant

Similar to the findings at four weeks, the mean change in the diameter of the upper extremity vessels at eight weeks post intervention in the control group was greater and more constant as compared to the PIE group. Only the mean change in diameter at cephalic (wrist) in control group was statistically significant with p-value <0.05. (Table 6).

Table 6. Comparison of the mean change in diameter of upper extremity vessels between PIE and control group at eight weeks

	PIE	**CONTROL**	
	diameter mean change (mm) mean (SD)	diameter mean change (mm) mean (SD)	p-value
Artery			
Radial	+.083 (.515)	+.167(.389)	0.656
Ulnar	0.00 (.426)	+.333(.651)	0.152
Brachial	+.250 (.452)	+.583(.793)	0.219
Vein			
Cephalic (wrist)	0.00 (.603)	+.500(.522)	**0.041***
Cephalic (Antecubital)	+.917 (.90)	+1.000(1.414)	0.865
Basilic	+.500 (1.784)	+.833(1.403)	0.616

Note. *p-value < 0.05 is significant

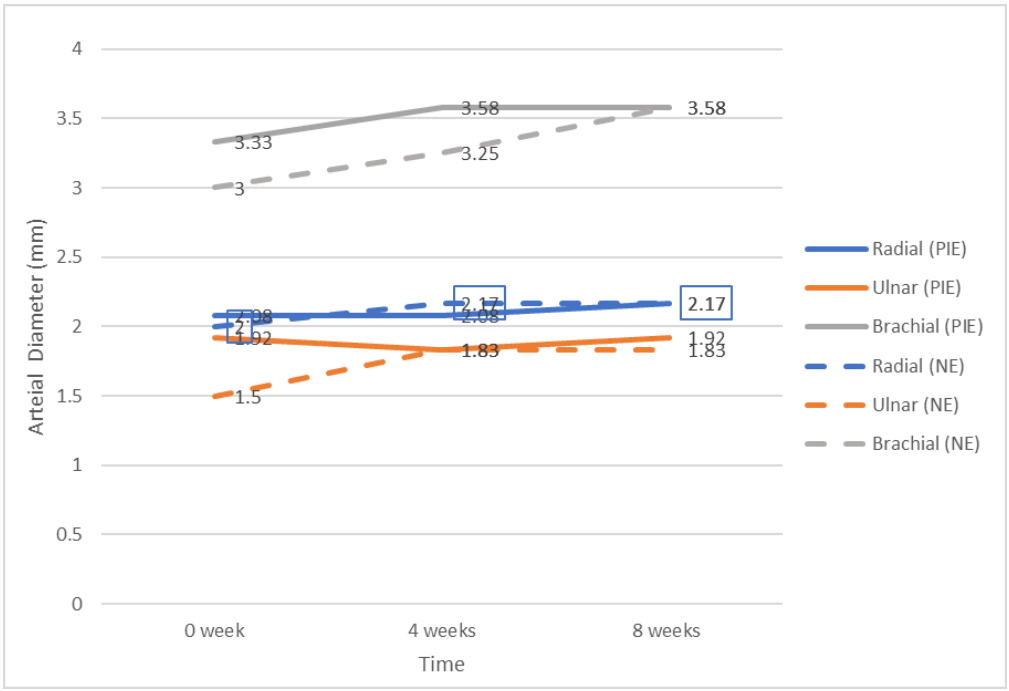


Figure 4. Line graph showing the mean arterial diameter of upper extremity of PIE and control Group (NE) at baseline, four- and eight-weeks post intervention

Figure 4 shows that from 0-4 as well as 0-8 weeks post intervention, most diameters did not show consistent improvement or increase. Only the brachial artery from the NE group had a consistent rise in the arterial diameter.

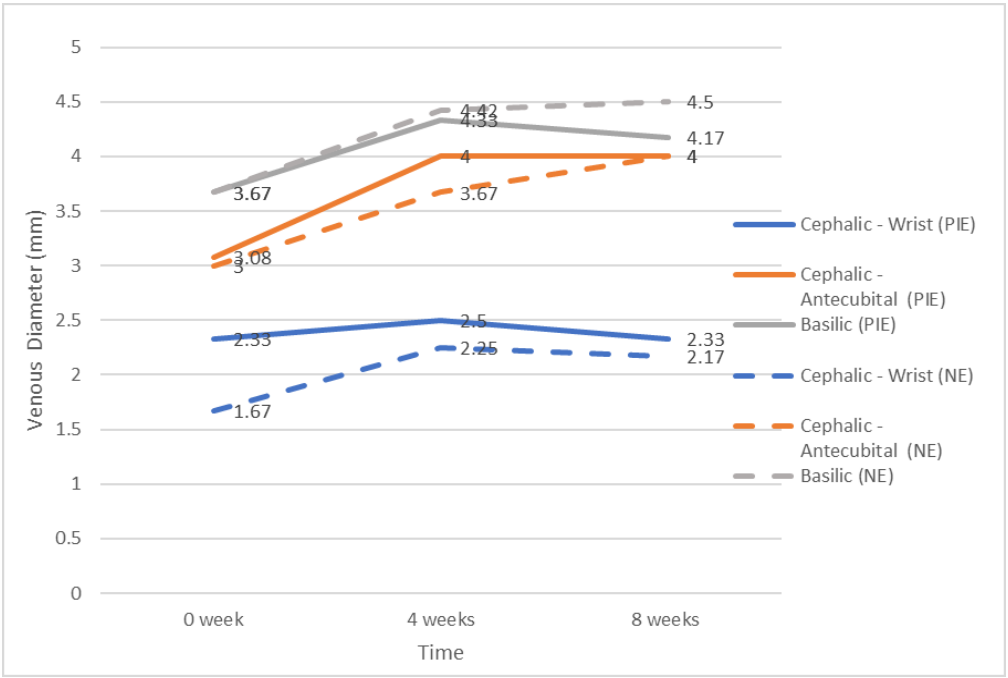


Figure 5. Line graph showing the mean venous diameter of upper extremity of PIE and control Group (NE) at baseline, four and eight-weeks post intervention

Figure 5 shows that from 0-4 and 0-8 weeks, the consistent increase in venous diameter was only appreciated in the cephalic (antecubital) and basilic vein of both PIE and NE group.

More than half (7 out of 12) of the participants did not report any symptoms experienced during handgrip exercise while a third (4 out of 12) reported tolerable pain on the fingers which was noted generally in the first few days of the exercise. A quarter (3 out of 12) of patients had numbness and or tightness noted in the fingers which resolved spontaneously.

Discussion

This study showed that PIE might not significantly impact vessel diameter in pediatric CKD population in contrast to adult CKD patients. There was a significant increase in the caliber of the non- dominant cephalic (ante-cubital) vein in the intervention group at four and eight weeks post intervention (4.0mm +/- 1.128 p 0.009; 4.0 mm +/- 1.04; p 0.005) though a substantial increase in diameter was also found in the cephalic vein of the control group at four and eight weeks (3.67 +- 1.15 p 0.024; 4.0+/- 1.3 p 0.032). Similar results were observed comparing the mean changes of cephalic vein diameter from baseline to four and eight weeks of both intervention and control groups. The participants in the control group were not provided with handgrip device nor instructed to perform any form of exercise. The increase in size of the cephalic vein in the exercise group may not exclusively be attributed to the PIE as an intervention but from other factors yet to be determined. Perhaps the most plausible explanation is that intra-observer variability contributed to the considerable change in the diameter of cephalic veins in both the intervention and control group. In this study, inter-observer variability during ultrasonography was mitigated by assigning only one radiologist to perform the measurement of the blood vessels.

Another possibility is natural occurrence of blood vessel enlargement corresponding to the physical growth and maturation experienced by a developing child. Vessels can dilate on a short term but can similarly undergo remodeling resulting to permanent vessel diameter changes.[18] According to Gifre-Renom et al, vessel enlargement postnatally is distinct compared to the embryo. The former occurs only when the vasculature is exposed to chronic change in flow resulting in vascular adaptation through either enlargement or inward remodeling to accommodate the altered blood flow. Blood vessels grow and regress in healthy tissues according to functional demands. Thus, spontaneous increase in vessel size in children might be a less likely consideration as a cause of the significant results observed in the control group of this study.

Two previous non-RCT studies in adults with CKD demonstrated an increase in vein diameter on the non-exercised or control arm[14-15.] The study of Leaf, 2003 and Uy, 2012 however utilized the contralateral arm as control and observed a concurrent statistically significant increase in the size of the cephalic vein.

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References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150
2. Harambat J, et al: Epidemiology of chronic kidney disease in children. Pediatr Nephrol 2012;27:363–373.
3. United States Renal Data System. 2020 *USRDS Annual Data Report: Epidemiology of kidney disease in the United States.*National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020.
4. Lok CE, Huber TS, Lee T, et al. KDOQI Vascular Access Guideline Work Group. KDOQI clinical practice guideline for vascular access: 2019 update. Am J Kidney Dis 2020; 75:S1–S164.
5. Lomonte, C., & Basile, C. (2015). Preoperative assessment and planning of haemodialysis vascular access. *CKJ*, *8* (3), 278–281. https://doi.org/10.1093/ckj/sfv022

6. Almasri J, Alsawas M, Mainou M, Mustafa RA, Wang Z, Woo K, Cull DL, Murad MH. Outcomes of vascular access for hemodialysis: A systematic review and meta-analysis. J Vasc Surg. 2016 Jul;64(1):236-43. doi: 10.1016/j.jvs.2016.01.053. PMID: 27345510

7. Arhuidese IJ, Orandi BJ, Nejim B, Malas M. Utilization, patency, and complications associated with vascular access for hemodialysis in the United States. J Vasc Surg. 2018 Oct;68(4):1166-1174. doi: 10.1016/j.jvs.2018.01.049. PMID: 30244924.

8. National Kidney Foundation (2020). KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update. *Am J Kidney Dis*, *75*(4), S1-S164. https://doi.org/10.1053/j.ajkd.2019.12.001

9. Lauvao LS, Ihnat DM, Goshima KR, Chavez L, Gruessner AC, Mills JL., Sr Vein diameter is the major predictor of fistula maturation. *J Vasc Surg*. 2009;49(6):1499-1504.

10. Wong V, Ward R, Taylor J, Selvakumar S, How TV, Bakran A. Factors associated with early failure of arterio- venous fistulae for haemodialysis access. Eur J Vasc End- ovasc Surg. 1996;12:207–213.

11. Kim, S. M., Min, S. K., Ahn, S., Min, S. I., & Ha, J. (2016). Outcomes of Arteriovenous Fistula for Hemodialysis in Pediatric and Adolescent Patients. *Vascular specialist international*, *32*(3), 113–118. https://doi.org/10.5758/vsi.2016.32.3.113

12. Kumar A/L S Katheraveloo K, Suryani Safri L, Guo Hou L, Hafiz Maliki A, Md Idris MA, Harunarashid H. Effect of isometric handgrip exercise on the size of cephalic veins in patients with stage 3 and 4 chronic kidney disease: A randomized controlled trial. *J Vasc Access*. 2020;21(3):372-378.

13. Aragoncillo Sauco I, Hevia C, Manzano Grossi S, Amezquita Y, Macias N, Caldes S, Ramirez Senent B, Hernandez Hernandez Y, Goicoechea M; Physicalfav Working Group. Effect of preoperative exercise on vascular caliber and maturation of arteriovenous fistula: the physicalfav trial, a randomized controlled study. J Nephrol. 2021 Jun;34(3):763-771. doi: 10.1007/s40620-020-00907-w. Epub 2021 Jan 2. PMID: 33387342.

14. Uy AL, Jindal RM, Herndon TW, Yuan CM, Abbott KC, Hurst FP. Impact of isometric handgrip exercises on cephalic vein diameter in non-AVF candidates, a pilot study. J Vasc Access. 2013 Apr-Jun;14(2):157-63. doi: 10.5301/jva.5000116. Epub 2012 Dec 12. PMID: 23258587.

15. Leaf DA, MacRae HS, Grant E, Kraut J. Isometric exercise increases the size of forearm veins in patients with chronic renal failure. Am J Med Sci. 2003 Mar;325(3):115-9. doi: 10.1097/00000441-200303000-00003. PMID: 12640286.

16. Rus RR, Ponikvar R, Kenda RB, Buturović-Ponikvar J. Effect of local physical training on the forearm arteries and veins in patients with end-stage renal disease. Blood Purif. 2003;21(6):389-94. doi: 10.1159/000073441. PMID: 14586181.: 14586181.

17. Ramírez-Senent B, Aragoncillo I, Ligero JM. Impact of Isometric Exercise in Adolescents With End Stage Kidney Disease and Unsuitable Vessels For An Autologous Arteriovenous Fistula. Vasc Endovascular Surg. 2022 Oct 4:15385744221131426. doi: 10.1177/15385744221131426. Epub ahead of print. PMID: 36194486.

18. Gifre-Renom L, Jones EAV. Vessel Enlargement in Development and Pathophysiology. Front Physiol. 2021 Feb 25;12:639645. doi: 10.3389/fphys.2021.639645. PMID: 33716786; PMCID: PMC7947306.

19. Edward M. Conway and others, Molecular mechanisms of blood vessel growth, *Cardiovascular Research*, Volume 49, Issue 3, February 2001, Pages 507–521, https://doi.org/10.1016/S0008-6363(00)00281-9

20. Adair TH, Montani JP. Angiogenesis. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. Chapter 1,Overview of Angiogenesis.https://www.ncbi.nlm.nih.gov/books/NBK53238/

21. Yasuda Y, M.M., Cross transfer effects of muscular training on blood flow in the ipsilateral and contralateral forearms. European journal of applied physiology and occupational physiology, 1983. 51(3): p. 321-322

ARTICLE

A systematic review on the effectiveness of N-acetylcysteine in children with dengue-associated liver injury

DJ G. Leaño, & Meadina G. Cruz

OBJECTIVE: This study aimed to determine the effectiveness of N-acetylcysteine (NAC) in reversal of liver enzyme abnormalities among pediatric patients with dengue induced liver injury.

MATERIALS AND METHODS: The preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P 2020) declaration was used to create this systematic review. The study population included children (<18 years old) diagnosed with dengue-associated Liver Injury and given NAC. The outcome of interest was full recovery. A search was performed in PubMed/MEDLINE, EMBASE, Google Scholar, HERDIN PLUS, WPRIM, clinicaltrials.gov, and Cochrane databases on March 2023. The New Castle-Ottawa Quality Assessment Scale was adapted for risk of bias assessment for cohort studies.

RESULTS: Three case series and one pre-post cohort study published from 2013 to 2022 were included. The studies were of acceptable quality. In two studies with overall 10 pediatric patients given NAC for dengue-related ALF, all recovered without adverse events. In one study with 4 patients given NAC, half survived with their liver function tests returning to normal values. Finally, in one comparative study, the durations of time before the liver function tests returned to normal levels, and the mortality rates between those treated with and without N-acetyl cysteine were not significantly different. All studies reported no occurrence of adverse drug reaction related to NAC.

CONCLUSION: *:* This systematic review shows limited evidence on the effectiveness of NAC in the reversal of liver enzymes among pediatric patients because of the low incidence of dengue induced liver injury seen in observational studies. Given that NAC is reported by all four studies to be accessible, effective, and with no attributable adverse events, its use can be considered. However, clinicians must still be cautioned given the limited available evidence.

KEYWORDS: *Dengue Associated Liver Injury; Dengue Hepatitis; N-acetylcysteine*

INTRODUCTION

Dengue virus is a vector borne disease transmitted by a day biting mosquito of the species Aedes aegypti and Aedes albopictus. Approximately fifty percent of the world's population is at risk of this infection, with 60-100 million symptomatic, and 20,000 deaths each year.[1-4]

In 2019, the Philippines had the highest cases ever recorded globally.[2,5] The incidence has increased dramatically, and the data has shown that dengue cases are more prevalent among children between 5-14 years old, while dengue related mortality was found among patients less than 20 years old.[1] Since then, national programs have been implemented to address the burden of disease, tailored on health promotion and advocacy, environmental control measures, and case and vector surveillance. However, the battle with dengue infection continues to challenge the public health until today.[5]

Dengue infection is a dynamic disease with levels of severity classified as: dengue with or without warning signs, and severe dengue based on clinical and laboratory parameters. The warning signs include abdominal pain or tenderness, persistent vomiting, clinical signs of fluid accumulation (ascites), mucosal bleeding, lethargy or restlessness, liver enlargement, increase in hematocrit and/or decreasing platelet count. Severe dengue is defined by at least one of the following: (a) plasma leakage that may lead to shock, (b) severe bleeding, and/or (c) severe organ impairment such as severe hepatitis (AST or ALT $\geq$ 1000); encephalitis (seizures, impaired consciousness), and myocarditis, among others.[2,6-8]

Dengue is also a multi-systemic infection, with liver involvement as the most common complication. Approximately 60-90% of patients with dengue may present with hepatitis. Elevation of liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) occur in 88% and 69% of cases respectively. The mechanisms that predispose dengue infection to liver pathology include hypoxic injury, direct viral invasion, immune mediated injury, and secondary bacterial sepsis. Liver injury is defined as an elevation of at least twice the upper limit of serum ALT, whereas the clinical practice guidelines on dengue in children defined liver failure based on laboratory findings of AST elevation of more than 200 u and INR of more than 1.3..[2,6,7]

There is no specific treatment for dengue, and no effective antiviral. Even though guidelines in disease management exist, management is only supportive in nature, with emphasis on early recognition and timely intervention.[2,10] Many drugs such as chloroquine, balapiravir, celgosivir, and lovastatin have been tried in dengue-induced acute hepatic failure but were later found ineffective in treating the infection.[3]

Newer medical treatment includes N-acetyl cysteine (NAC) which was postulated to improve antioxidant defense system, its free radical scavenging activity, and its vasodilatory activity that increases oxygen delivery to the liver.[11] NAC is used as mucolytic, antidote for paracetamol overdose, and ophthalmological. It acts both as a source of reduced glutathione and directly scavenging free radicals in the body.[10] In various studies, NAC has shown promising effect among patients with dengue- induced hepatic injury.[9]

At present, there are limited data on the use of NAC in dengue-induced acute liver injury. A study conducted in Pakistan by Ishtiaq et al. highlighted the hepatic involvement in dengue infection, and stated that NAC is among the current management strategies in their locality along with intravenous hydration and symptomatic management of complications.[12] A case report in Singapore by Lim et al. showed a favorable outcome of NAC in children with dengue-associated liver failure with suggested dose of 100 mg/kg/day.[11] A case series published by Dissanayake et al. showed statistically significant reduction in liver transaminases after NAC infusion among adult patients with dengue infection.[4] Furthermore, in the study done by Tafere, et al., various case reports and series (mostly among adults) and an animal study support the role of NAC in the treatment of dengue-induced liver failure.[9] These studies highlighted the potential benefit of NAC as a definitive therapy for dengue-associated liver injury.

Despite the presence of existing studies on use of NAC in Dengue infection, the number is still limited, especially its association among children. This study may help in decreasing the disease morbidity and mortality through providing evidence-based results. This study aims to determine the effectiveness and safety of N-acetylcysteine in reversal of liver enzymes among pediatric patients with dengue induced liver injury by synthesizing available published evidence.

METHODOLOGY

The preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P 2020) declaration was used to create this systematic review.

Eligibility criteria:

Types of studies. Randomized controlled trials and observational studies published until March 2023 were planned to be included. Posters, and conference abstracts were excluded. Only studies written in the English language were available.

Population. The study population included children (<18 years old) who were diagnosed with Dengue-Associated Liver Injury. Excluded are patients with other severe comorbidities.

Intervention/Exposure. N-acetyl cysteine given at any dose for the management of liver

injury.

Comparison. Standard treatment/ or no comparator group

Outcomes. In-hospital mortality, length of hospital stay, the incidence of encephalopathy post-treatment

Exclusion. Studies were excluded if outcomes were not reported clearly or cannot be computed/derived from results.

A search was performed in PubMed/ MEDLINE, EMBASE, Google Scholar, HERDIN PLUS, WPRIM, clinicaltrials.gov, and Cochrane databases on March 2023. The search terms used included: ("N-acetyl cysteine" OR NAC OR Acetylcysteine] MeSH]) AND (dengue]MeSH] OR "dengue fever" OR "dengue hemorrhagic fever") AND ("liver injury" OR hepatitis[MeSH]). Duplicate articles were removed and additional relevant articles were identified by scanning the reference lists of articles found from the original search.

Full-text articles for potential inclusion were saved in a Google drive. Extracted data were managed using Microsoft Excel and Microsoft Word. Two authors independently scanned the titles and abstracts found using the search approach described above. Papers by the same author were compared to reduce data duplication caused by duplicate reporting. The full-text articles were obtained for reports that were eligible based on the title or abstract. Full -text copies of potentially relevant papers selected by at least one author were retrieved and reviewed. Articles that met the inclusion requirements were evaluated independently by two authors, with any inconsistencies resolved through discussion. Following the PRISMA 2020 criteria, a flow diagram for the search and selection process was created.

Study name (along with first author's name and year of publication), definition of liver injury, country where the study was conducted, NAC dosage and comparison group, source from which patients or study participants were selected, study design, outcomes (mortality, length of hospital stay, rate of encephalopathy, and adverse events such as increase in prothrombin time, thrombocytopenia, and acidosis), study strengths, and limitations were extracted independently by two authors using a standardized extraction form. To ensure the correctness and consistency of the extracted data, the data extraction forms were cross-checked.

Two investigators independently assessed the studies' quality. The New Castle-Ottawa Quality Assessment Scale was adapted for risk of bias assessment for cohort studies. This scale has four dimensions: research group representativeness, suitable techniques for determining exposure, comparability of comparing analysis groups, and lower non-response bias. The quality score varied from 0 (low) to 4 (high).

The Joanna Briggs Institute quality assessment tool for case series was also used

with several indicators for inclusion criteria, definition of cases, reporting of outcomes, and follow-up of results. A score of at least 8 is considered as acceptable.

The studies were analyzed using a descriptive narrative approach wherein individual study findings were synthesized and describe the possible hypotheses on the effectiveness of NAC and its mechanism in dengue related liver injury. However, because there is heterogeneity in study design, methodology and population observed, a meta-analysis could not be performed.

RESULTS

A total of 216 articles were seen after database search and 17 duplicates were then removed. After title and abstract screening, 7 articles were determined to be for potential inclusion. After a full-text review, 3 were excluded because they were conducted on adult patients. Finally, 4 studies were included in the systematic literature review.

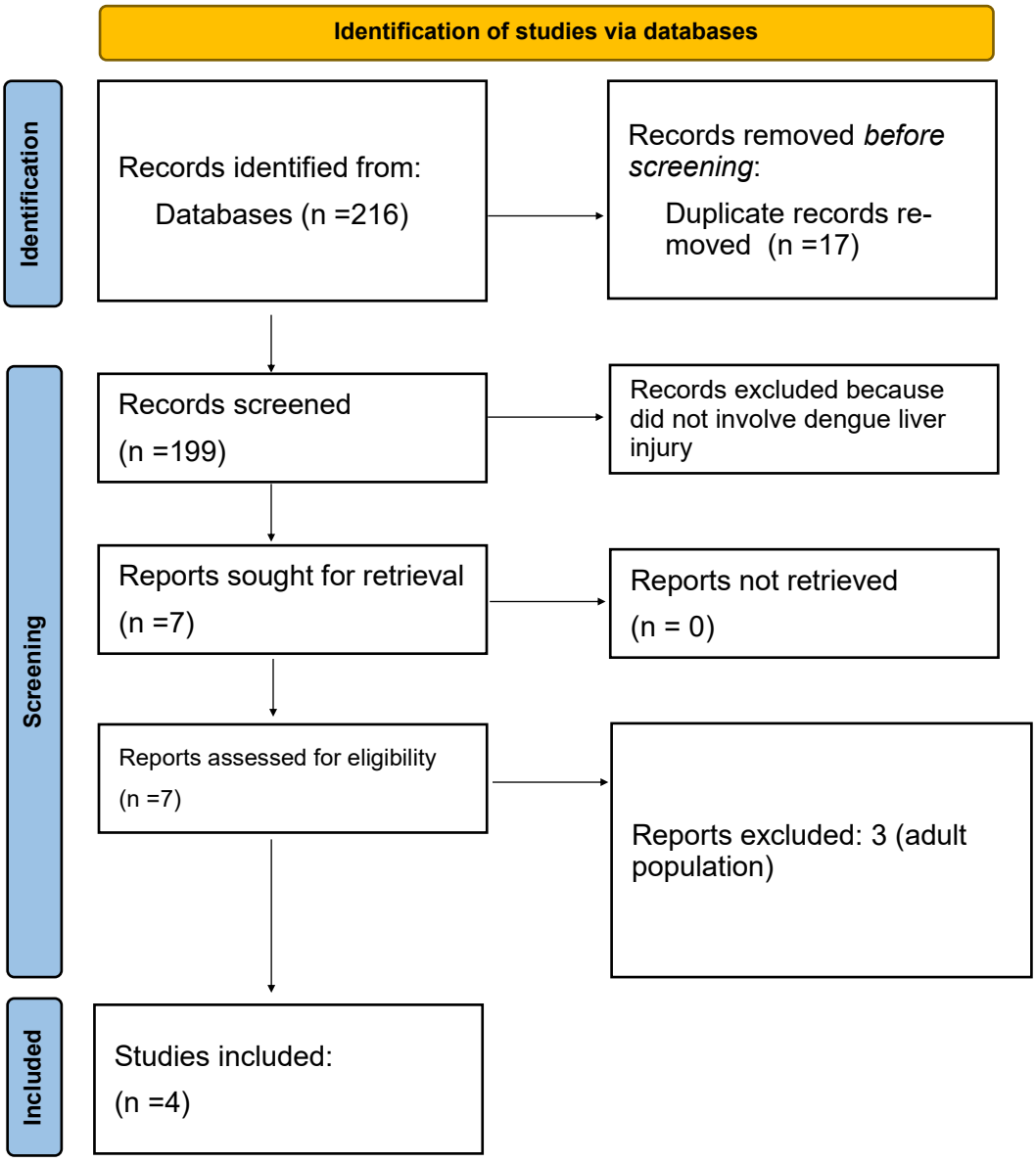

Figure 1. PRISMA Flowchart for study selection.

All four studies were conducted in Asia. Laoprasopwattana et al. (2022) was a cohort study with pre-post design while the three were case series. All studies have small sample size (3 to 23 patients given NAC). The age range in the included studies was between 6 months to 12 years. Acute liver injury was the indication for NAC use in all four studies. NAC treatment regimen was described in the study of Senanayake et al. (2013) only. Only one study was comparative in design (Laoprasopwattana et al., 2022). All studies reported on rates of complete recovery and adverse events.

Table 1. CHARACTERISTICS OF STUDIES INCLUDED IN THE STUDY

Author, year	Country	Study Design	Sample size	Sex ratio and mean age	Definition of liver injury	NAC regimen	Comparator	Outcomes
Senanayake et al. (2013)[5]	Sri Lanka	Case series	7	Not Reported, 6mo. to 12 years	Acute Liver Failure with the following signs: low GCS scores, raised transaminases and prolongedprothrombin/ INR.	NAC was administered at 100 mg/kg intravenously over 24 hours.	None	Adverse events Complete recovery
Laoprasopwattana et al. (2016)[8]	Thailand	Case series	41 with 4 given NAC	1M:3F 8 years	Rapid development of severe acute liver injury with impaired synthetic function (international normalized ratio≥1.5) and encephalopathy in a patient with no history of liver disease	Details of NAC treatment not provided	None	Survival Adverse events Complete recovery
Sharma et al. (2016) [13]	India	Case series	196 with 3 given NAC	2M: 1F 5 years	Not Reported	Details of NAC treatment not provided	None	Survival Adverse events Complete recovery
Laoprasopwattana et al. (2022) [14]	Thailand	Pre-post cohort	101 with 23 given NAC	Not Reported	Not Reported	Details of NAC treatment not provided	Standard Treatment with no NAC	Adverse events Time to complete recovery

As seen in Table 2, all studies are of good quality. However, all studies have low sample size which can be attributed to low incidence of ALF in dengue fever. Nonetheless, all studies had acceptable scores.

Table 2. RISK OF BIAS ASSESSMENT OF STUDY METHODOLOGY

Joanna Briggs Institute	Clear criteria for inclusion	Standard and reliable measurement of condition	Valid case definition	Consecutive or complete inclusion of participants	Clear reporting of demographics	Clear reporting of clinical information	Clear reporting of outcomes	Conduct of statistical analysis	Score
Senanayake et al. (2013)[5]	Yes (1)	Yes (1)	Yes (1)	Yes (2)	Yes (1)	Yes (1)	Yes (1)	No (0)	8 (acceptable)
Laoprasopwattana et al.	Yes (1)	Yes (1)	Yes (1)	Yes (2)	Yes (1)	Yes (1)	Yes (1)	No (0)	8 (acceptable)
Sharma et al. (2016)[13]	Yes (1)	Yes (1)	Yes (1)	Yes (2)	Yes (1)	Yes (1)	Yes (1)	No (0)	8 (acceptable)

Newcastle-Ottawa scale	Representativeness of the sample	Sample size	Comparability	Ascertainment of the exposure	Assessment of the outcome	Score
Laoprasopwattana et al. (2022)[14]	Representative of target population (1)	Small Sample size (0)	Pre-post design (1)	Record linkage (1)	Clinical diagnosis (1)	4 (Acceptable)

Four (4) studies published from 2013 to 2022 were included in this systematic review. The outcomes reported in these studies are summarized in Table 3. Senanayake et al. (2013) detailed the results of giving N-acetylcysteine (NAC) to children who had acute liver failure (ALF) complicated by dengue infection that was not caused by non-paracetamol. Retrospective analysis was done on the medical records of the patients (n=7, aged 6 months to 12 years) who had dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) exacerbated by ALF. As soon as ALF was identified based on low GCS scores, elevated transaminases, and delayed prothrombin/ INR, NAC infusion (100 mg/kg) was given. Four (4) patients showed rapid clinical improvement of their encephalopathy after receiving the first dosage of NAC (100 mg/ kg over 24 hours). After the second (n=2) and third (n=1) doses, the other 3 patients responded. In all cases, full clinical and biochemical recovery took place. NAC was found to have no adverse effects. The authors concluded that the early use of NAC to children with ALF complicating severe dengue infection resulted in a satisfactory outcome.[5]

The records of patients (n=41, aged 15 years) diagnosed with severe dengue virus infection and ALF were reviewed by Laoprasopwattana and colleagues (2016) to identify their clinical course and the outcomes of liver functions. With a death rate of 68.3%, all 41 patients with ALF experienced additional organ failure, such as acute respiratory failure (85.4%), acute kidney additional organ fail-ure, such as acute respiratory failure (85.4%), acute kidney injury (75.6%), and active bleeding (70.7%).

On the day the patient experienced ALF, the patient's aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were at their highest. Two (2) of the 4 patients who received NAC treatment survived, and in 4 and 12 days, their liver functions returned to normal. No patient developed adverse events. It was concluded that the key contributor to ALF in patients with dengue virus infects was a deep shock that caused microcirculatory disruption in liver cells.[8]

The study of Sharma et al. (2016) described the clinical experience and results of severe hepato-neurological dengue fever sequelae. In their hospital's pediatric critical care unit (PICU), all confirmed dengue cases were examined. Of the 196 confirmed dengue cases, 4 (median age: 5.33 years, range: 0.58 to 16 years) developed ALF. Results showed that encephalopathy started 4 days (1–5) following fever in these children. Three (3) of the patients had grade IV encephalopathy, and 1 patient initially had grade III encephalopathy before advancing to degree IV. One (1) patient appeared in shock, while 2 showed symptoms of capillary leaking (ascites and bilateral pleural effusion). At presentation, enzyme levels were noticeably raised although bilirubin levels were normal in all but 1 patient. All 4 patients were mechanically ventilated. Three (3) children received supportive treatment, fluconazole, NAC, and wide spectrum antibiotics. One (1) child passed away, three children recovered and were discharged without any complications. At presentation, the deceased child experienced shock and hypoalbuminemia (2.1 g/dl). Additionally, this child had significantly more fluid retention than the responders (36.8% vs mean 2. 6%), and NAC was started 48 hours later. It was concluded that the use of NAC in ALF was advantageous. No adverse events attributable to NAC were observed. According to the author's experience, effects are beneficial, but larger studies are still required investigate more.[13]

The most recent of the 4 studies was conducted by Laoprasopwattana et al. (2022) wherein they evaluated in their pre-post cohort study the severe dengue (SD) death rates before and after the 2016 introduction of a revised SD guideline.

The updated guidelines called for rigorous vital sign and intra-abdominal pressure monitoring, the release of intra-abdominal pressure in cases of abdominal compartment syndrome (ACS), and the administration of NAC in situations when the liver has failed suddenly. Review of SD patients' (age of <15 years old) medical records was done. Between 78 and 23 patients treated in the pre- and post-revised guideline periods, respectively, there were no appreciable differences in organ failure at initial admission, including severe bleeding, acute respiratory failure, acute renal injury, and acute liver failure. Following hospitalization, there was no statistically significant difference between the pre- revised guidelines (n=78) and post-revised guideline (n=23) periods in the percentage of patients who experienced multiorgan failures (60.4% vs. 73.3%) and fatal outcomes (33.3% vs. 13.0%). The mortality rates for patients with multiorgan failure (44.1% vs. 15.8%) considerably higher in the pre-than in the post-revised guideline periods, according to subgroup analysis. In patients with acute liver failure treated with or without NAC, there were no significant differences in the lengths of time before the liver function tests returned to normal levels or the fatality rates. No NAC side effects were reported in any patient. The authors concluded that although it was determined that the updated recommendations, which call for the administration of NAC, did not prevent organ failure, doing so considerably reduced the mortality rates of patients with multiorgan failure.[14]

Table 3. OUTCOMES REPORTED IN THE INCLUDED STUDIES

Author, year	Outcomes
Senanayake et al. (2013)	No incidence of adverse events 100% of patients showed complete recovery without residual hepatic or neuro-developmental damage
Laoprasop-wattana et al. (2016)	Of the four patients treated with n-acetyl cysteine, two survived and their liver functions returned to normal levels in 4 and 12 days. No incidence of adverse events
Sharma et al. (2016)	All three recovered with no encephalopathy post-treatment and no adverse events
Laoprasop-wattana et al. (2022)	The durations of time before the liver function tests returned to normal levels, and the mortality rates in acute liver failure patients treated with and without N-acetyl cysteine were not significantly different. No incidence of adverse events

DISCUSSION

The use of NAC as a safe and efficient treatment for dengue-induced liver impairment was endorsed by all four studies. NAC was seen to be beneficial in some pediatric patients. Specifically, in one study, NAC has been shown to be beneficial for children who have non-paracetamol-induced liver failure.[5] Its effective usage in individuals with severe dengue infection and ALF has been documented.[23]

Its effective treatment in a child with fulminant liver failure complicating dengue illness is described in a single case report.[7] According to the review of Tafere et al. (2020), N-acetylcysteine (NAC) could be utilized as a curative treatment for ALF caused by the dengue virus. However, the majority of their evidence comes from adults.[9]

Currently, dengue is recognized as the most significant virus spread by mosquitoes.[13] Although mild to moderate increases in serum aminotransferase levels are typical with dengue infections, acute liver failure (ALF) is a potentially fatal complication for which there is no specific medication and which is generally treated with supportive care.[5] The literature reports a mortality rate from dengue ALF of 0–60%, but the data are too small for statistical significance.[15]

Direct viral damage, a dysfunctional host immune response, or hypoxia damage are thought to be the causes of ALF in dengue infection. Previous research has revealed that the dengue virus may promote the production of Fas ligand on hepatocytes, leading to immune-mediated hepatocytic damage and cell death.[17,18] The clinical observation of circulatory collapse, a frequent comorbidity with ALF, supports hypoxic damage. While liver enzymes like aspartate transferase (AST) and alanine transferase (ALT) are high after acute dengue virus infection, the level of antioxidants like glutathione peroxidase and glutathione reductase is decreased. This suggests that the dengue virus has caused oxidative stress.[19] Additionally, as explored in a mouse model, the production of inflammatory cytokines, particularly interleukin-22 (IL-22) and interleukin-17 (IL-17), may result in dengue-induced acute liver failure.[20] Interleukin-5 (IL-5) and interleukin-10 (IL-10) were increased later. Tumor necrosis factor (TNF) alpha, interleukin 2 (IL-2), interleukin-6 (IL-6) and interleukin-8 (IL-8) levels are also enhanced in early dengue virus infection.[21] Unknown variables may predispose certain people to developing ALF. Several histologic alterations, such as fatty change, hepatocyte necrosis, hyperplasia, and degeneration of Kupffer cells, Councilman bodies, and mononuclear cell infiltrates at the portal tract, were seen in dengue-induced liver failure.[4] Also, a study found that acetaminophen/ paracetamol overdose can be a significant factor in the development of acute liver failure in dengue patients.[22] NAC is essential for the treatment of acute liver damage brought on by dengue, presumably through lowering oxidative stress, acting directly against viruses, and improving blood flow to the liver. The potential of NAC to boost antioxidant defense, its free radical scavenging activity, and its vasodilatory activity, which increases blood flow to the liver, may be associated to its mechanism of action in patients who recovered from dengue-induced ALF.[23,24]

The antioxidant enzymes glutathione reductase and glutathione peroxidase are decreased during acute dengue infection, according to Chandrasena et al (2019). Thus, the antioxidant action of NAC may be brought on by a rise in plasma levels of antioxidants such glutathione peroxidase and glutathione reductase, which lowers oxidative stress.[19]

Published evidence shown in this systematic review shows that NAC can be a promising treatment to dengue-induced ALF in children. It is also considered safe as none of the four studies observed adverse events in any of their patients. However, three of four of the included studies lack comparison groups and have small number of patients given NAC. The lack of comparison group makes it impossible to estimate an effect size such as risk ratio or odds ratio. On the other hand, small sample size limits the extent to which findings can be generalized in a bigger population. Further investigations, especially of randomized controlled trials with larger sample size, should still be conducted. Furthermore, other basic and advanced medications, treatments and life-saving interventions to ALF and other dengue-induced complications should be taken into account. Other comorbidities, as well as complications, also play vital role in the prognosis of children diagnosed with severe dengue. advanced medications, treatments and life-saving interventions to ALF and other dengue-induced complications should be taken into account. Other comorbidities, as well as complications, also play vital role in the prognosis of children diagnosed with severe dengue.

Conclusion and Recommendations

This systematic review shows limited evidence on the effectiveness of N-acetylcysteine in the reversal of liver enzymes among pediatric patients because of the low incidence of dengue induced liver injury seen in observational studies. Given that NAC is reported by all four studies to be accessible, effective, and with no attributable adverse events, its use can be considered. However, clinicians must still be cautioned given the limited available evidence. Large-scale randomized controlled trials are recommended to verify these findings and provide better level of evidence.

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REFERENCES

1. Undurraga EA, Edillo FE, Erasmo JN, Alera MT, Yoon IK, Largo FM, Shepard DS. Disease burden of dengue in the Philippines: adjusting for underreporting by comparing active and passive dengue surveillance in Punta Princesa, Cebu City. Am. J. Trop. Med. Hyg. 2017 Apr 4;96(4):887.

2. Dengue and severe dengue [Internet]. World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue

3. Schaefer TJ, Panda PK, Wolford RW. Dengue fever [Internet]. 2022.

4. Samanta J, Sharma V. Dengue and its effects on liver. World J Clin Cases. 2015 Feb 16;3(2):125-31. doi: 10.12998/wjcc.v3.i2.125. PMID: 25685758; PMCID: PMC4317605.

5. Senanayake MP, Jayamanne MD, Kankananarachchi I. N-acetylcysteine in children with acute liver failure complicating dengue viral infection. Ceylon Med J. 2013 Jun;58(2):80-2. doi: 10.4038/cmj.v58i2.5684. PMID: 23817939.

6. Dissanayake DMDIB, Gunaratne WMSN, Kumarihamy KWMPP, Kularatne SAM, Kumarasiri PVR. Use of intravenous N-acetylcysteine in acute severe hepatitis due to severe dengue infection: a case series. BMC Infect Dis. 2021 Sep 20;21(1):978. doi: 10.1186/s12879-021-06681-9. PMID: 34544380; PMCID: PMC8454086.

7. Lim G, Lee JH. N-acetylcysteine in children with dengue-associated liver failure: a case report. J Trop Pediatr. 2012 Oct;58(5):409-13. doi: 10.1093/tropej/fmr108. Epub 2011 Dec 23. PMID: 22199018.

8. Tafere GG, Wondafrash DZ, Demoz FB. Repurposing of N-Acetylcysteine for the Treatment of Dengue Virus-Induced Acute Liver Failure. Hepat Med. 2020 Nov 3;12:173-178. doi: 10.2147/HMER.S263840. PMID: 33177895; PMCID: PMC7650016.

9. Tan JM, Tan NW, Ong C, Thoon KC, Chong CY. Dengue Fever Associated Liver Failure. Pediatric Infect Dis. 2016;1(31):2573-0282.

10. Laoprasopwattana K, Jundee P, Pruekprasert P, Geater A. Outcome of Severe Dengue Viral Infection-caused Acute Liver Failure in Thai Children. J Trop Pediatr. 2016 Jun;62(3):200-5. doi: 10.1093/tropej/fmv099. Epub 2016 Feb 6. PMID: 26851434.

11. Medimarketing Inc. Search Drug Information, Interactions, Images, Dosage & Side Effects. MIMS Philippine [Internet]. 2023/ Available from: https://www.mims.com/philippines/

12. Ong EP, Obeles AJT, Ong BAG, Tantengco OAG. Perspectives and lessons from the Philippines' decades-long battle with dengue. Lancet Reg Health West Pac. 2022 Jun 24;24:100505. doi: 10.1016/j.lanwpc.2022.100505. PMID: 35789734; PMCID: PMC9249805.

13. Sharma PK, Kumar M, Sahani A, Goyal R, Aggarwal GK, Kumar V. Severe hepatic-neurological complications of dengue fever in children from a tertiary care center in North India. Age (years). 2016 May 1;5:0-75.

14. Laoprasopwattana K, Khantee P, Saelim K, Geater A. Mortality Rates of Severe Dengue Viral Infection Before and After Implementation of a Revised Guideline for Severe Dengue. Pediatr Infect Dis J. 2022 Mar 1;41(3):211-216. doi: 10.1097/INF.0000000000003411. PMID: 34840312.

15. Chongsrisawat V, Hutagalung Y, Poovorawan Y. Liver function test results and outcomes in children with acute liver failure due to dengue infection. Southeast Asian J Trop Med Public Health. 2009 Jan;40(1):47-53. PMID: 19323033.

16. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. Trans R Soc Trop Med Hyg. 2006 Jul;100 (7):608-14. doi: 10.1016/j.trstmh.2005.10.007. Epub 2006 Feb 17. PMID: 16483623.

17. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. Trans R Soc Trop Med Hyg. 2006 Jul;100 (7):608-14. doi: 10.1016/j.trstmh.2005.10.007. Epub 2006 Feb 17. PMID: 16483623.

18. Marianneau P, Cardona A, Edelman L, Deubel V, Desprès P. Dengue virus replication in human hepatoma cells activates NF-kappaB which in turn induces apoptotic cell death. J Virol. 1997 Apr;71(4):3244-9. doi: 10.1128/JVI.71.4.3244-3249.1997. PMID: 9060688; PMCID: PMC191457.

19. Pagliari C, Quaresma JA, Fernandes ER, Stegun FW, Brasil RA, de Andrade HF Jr, Barros V, Vasconcelos PF, Duarte MI. Immunopathogenesis of dengue hemorrhagic fever: contribution to the study of human liver lesions. J Med Virol. 2014 Jul;86(7):1193-7. doi: 10.1002/jmv.23758. Epub 2013 Sep 23. PMID: 24114877.

20. Chandrasena L, De Silva A, De Mel C, Peiris H, Abesuriya V, De Mel S, Seneviratne S, Bandara S. Glutathione enzymes and liver injury in acute dengue viral infection. J.Biosci. 2019 Oct 18;7 (10):61.

21. Guabiraba R, Besnard AG, Marques RE, Maillet I, Fagundes CT, Conceição TM, Rust NM, Charreau S, Paris I, Lecron JC, Renauld JC, Quesniaux V, Da Poian AT, Arruda LB, Souza DG, Ryffel B, Teixeira MM. IL-22 modulates IL-17A production and controls inflammation and tissue damage in experimental dengue infection. Eur J Immunol. 2013 Jun;43(6):1529-44. doi: 10.1002/ eji.201243229. Epub 2013 Apr 17. PMID: 23505056.

22. Chia PY, Thein TL, Ong SWX, Lye DC, Leo YS. Severe dengue and liver involvement: an overview and review of the literature. Expert Rev Anti Infect Ther. 2020 Mar;18(3):181-189. doi: 10.1080/14787210.2020.1720652. Epub 2020 Feb 3. PMID: 31971031.

23. World Health Organization. Global strategy for dengue prevention and control 2012-2020.

24. Kumarasena RS, Mananjala Senanayake S, Sivaraman K, de Silva AP, Dassanayake AS, Premaratna R, Wijesiriwardena B, de Silva HJ. Intravenous N-acetylcysteine in dengue-associated acute liver failure. Hepatol Int. 2010 May 28;4(2):533-4. doi: 10.1007/s12072-010-9176-4. PMID: 20827413; PMCID: PMC2900558.

25. Abeysekera RA, Illangasekera U, Jayalath T, Sandeepana AG, Kularatne SA. Successful use of intravenous N-acetylcysteine in dengue haemorrhagic fever with acute liver failure. Ceylon Med J. 2012 Dec;57(4):166-7. doi: 10.4038/cmj.v57i4.5085. PMID: 23292059.

ARTICLE

Sleep disturbances among 4 to 12-year-old Filipino children with drug resistant epilepsy in a pediatric tertiary hospital

Cherise Andrea E. Llaneta, & Mel Michel Villaluz

OBJECTIVE: To perform a pilot study on the frequency of sleep-disturbance (Total sleep Disturbance Score (TSD) of > 41) in children diagnosed with Drug Resistant Epilepsy aged 4 to 12 years, using the Children's Sleep Habits Questionnaire (CSHQ).

METHODOLOGY: The Children's Sleep Habits Questionnaire (CSHQ) was used to screen for sleep disturbances among 73 patients aged 4 to 12 years old with drug-resistant epilepsy seen at the Seizure Clinic of Philippine Children's Medical Center. Descriptive statistics were used to characterize sociodemographic variables, and sleep and epilepsy-related variables. Continuous data were presented as mean ± standard deviation (SD), and categorical data as frequencies (percentages).

RESULTS: Sleep disturbances were common and severe in children with drug-resistant epilepsy. Out of the seventy-three participants, 61 patients had a TSD score of greater than 41 (84%) and 12 (16%) had TSD scores below 41 with a mean CSHQ score of 58. The most frequently occurring sleep disturbances involve the domains of bedtime resistance (29%), night wakings (28%), and daytime sleepiness (23%). Meanwhile, the least frequently occurring sleep disturbances involve the domains of sleep disordered breathing (76%), parasomnias (65%), and sleep anxiety (56%).

CONCLUSION: Majority of the children with drug-resistant epilepsy are sleep disturbed exhibiting high TSD scores (>41) using the Children's Sleep Habits Questionnaire. We recommend to actively evaluate and screen for sleep and behavioral problems concurrently in children with epilepsy.

KEYWORDS: *Epilepsy, Sleep Disturbance, Seizure Recurrence, Pediatrics*

INTRODUCTION

Sleep disturbances – ranging from bedtime resistance and frequent night wakings to obstructive sleep apnea and narcolepsy – affect approximately 25 to 40% of the pediatric population worldwide. [1] Regardless of the type of sleep disturbance, each can have a significant impact on daytime functioning and development – that is learning, growth, behavior, and emotion regulation – of the child, and will most likely persist if left untreated.[2]

Among the different populations of children, those with epilepsy, developmental disabilities, chronic health conditions, and psychiatric disorders have the most reported cases. Sleep plays a crucial role in modulating seizure occurrence and or interictal epileptiform discharges and at the same time sleep disturbances worsen epileptic symptoms. Hence, epilepsy with the added sleep disturbances exacerbates a child's health and functioning.[4] In the past years, studies have been conducted to investigate the use of appropriate antiepileptic drugs (AED) to eliminate seizures. However, a fraction of these patients still suffer from seizures despite taking AEDs in adequate doses. The three main categories to consider for the management of refractory epilepsy are: (1) pharmacotherapy, (2) epilepsy surgery and (3) lifestyle changes.[5] In terms of lifestyle, sleep disturbances in children with drug resistant epilepsy are found to cause increasing seizure frequency. Screening for factors such as sleep disturbance that may be contributory to the recurrence of seizures despite being adequately treated with anti-epileptic drugs can help in finding a more holistic approach in managing patients with drug resistant epilepsy.

One of the lifestyle factors that contribute to the intractability of seizures include the sleeping habits of children with epilepsy. In young children, virtually all problems including bedtime problems and night waking are defined by their caregivers and its definition is influenced by a host of variables such as parent education level, parental psychopathology, family dynamics, household composition, and parenting styles. The definition of these sleep disturbances may also be developmentally based, namely transient problems that can be understood in the context of normal physical, cognitive, and emotional changes occurring at various developmental stages.[3] However, there has been an effort to categorize sleep disturbances into 8 domains, as suggested by Owens, Spirito, and McGuinn[1] in their development of the Children's Sleep Habits Questionnaire (CSHQ). The eight domains are the (1) bedtime resistance, (2) sleep onset delay, (3) sleep duration, (4) sleep anxiety, (5) night waking, (6) parasomnias, (7) sleep disordered breathing, (8) daytime sleepiness. A study on the relationship between Sleep disturbances and behavioral problems in children with epilepsy using the CSHQ showed that higher seizure frequency was related to higher scores for excessive sleepiness.[4] Children on polytherapy presented with worse sleep problems than children on monotherapy. Findings on previous studies that used the CSHQ showed that children with epilepsy with sleep disturbances presented with higher emotional symptoms, conduct problems, hyperactivity/ attention, and peer relationship problems than those without.

The Children's Sleep Habits Questionnaire (CSHQ) is a parent-report

screening tool designed for school-aged children (4-12 years). In the Philippines, the validated Filipino version created by Mabilangan and Moral-Valencia[6] have been used in 3 local studies that utilized the tool in screening for sleep disturbances in various populations – Autism Spectrum Disorder, Asthmatic Children, and School-aged Children. While the CSHQ has already been used in screening for sleep disturbances in children with drug resistant epilepsy in other Asian countries, there is no available local study yet that used this tool in this specific population in the Philippines. This pilot study aims to determine the frequency of sleep-disturbance (TSD score of > 41) in children diagnosed with Drug Resistant Epilepsy, consulting at the outpatient department of the Philippine Children's Medical Center, using the CSHQ. Also, this study intends to describe the demographic characteristics of children with Drug Resistant Epilepsy (Age and Gender), describe the seizure medications, seizure frequency, seizure pattern, and seizure duration in sleep disturbed children with Drug Resistant Epilepsy. Findings of this study can be used as baseline data for further studies such as, but not limited to, validation and modification of the CSHQ for children with drug resistant epilepsy. Creation of a screening tool for this specific population can help clinicians in recognizing sleep disturbances. Addressing sleep problems in this specific population can lead to better seizure control.

METHODOLOGY

The present research is a cross-sectional study using a self-administered questionnaire to be completed by the parents and/or caregivers of children with: (1) drug-resistant epilepsy who are on two or more antiepileptic drugs and, (2) Aged 4 to 12 years old. Children with drug-resistant epilepsy must have previously received a clinical diagnosis of drug-resistant epilepsy from a neurologist and are currently being seen at the outpatient department of Philippine Children's Medical Center.

The study excluded the following: (1) children taking other medications that are not anti-epileptic drugs that may have an effect on sleep such as psychostimulants (methylphenidate), atypical antipsychotics (risperidone), and antihistamines (diphenhydramine)[4] (2) children with intake of stimulants such as but not limited to caffeine and nicotine.

The Children's Sleep Habits Questionnaire (CSHQ) is a parent-report screening tool designed for school-aged children (4-12 years). It was developed by by Owens, Spirito, and McGuinn[1] while the validated Filipino version was created by Mabilangan and Moral-Valencia.[6] The CSHQ is comprised of 33 items representing eight sleep disturbance subscales: 1) bedtime resistance, 2) sleep onset delay, 3) sleep duration, 4) sleep anxiety, 5) night wakings, 6) parasomnias, 7) sleep-disordered breathing, and 8) daytime sleepiness. [1]

[1] The parents are asked to recall their child's sleep habits in a recent typical week. Items are rated on a 3-point Likert scale (rarely = 0-1 night per week; sometimes = 2-4 nights per week; usually = 5-7 nights per week) and each item is evaluated if the sleep behavior represented a problem or not.

The total sleep disturbance score is equivalent to the sum of all 33 subscale items. The cut-off score is 41 with 0.80 sensitivity and 0.72 specificity, implying this score correctly identifies 80% of the clinical sample.[1]

In addition to the above assessment, parents also reported patient characteristics including age, sex, and their children's seizure history.

The sample size was computed using the sample size for frequency in a population formula via the Epi_info/STATCALC EXE online software. With a confidence interval of 90%, a minimum of 72 patients should be included in this study.

Data Analysis

Descriptive statistics were used to characterize sociodemographic variables, and sleep and epilepsy-related variables. Continuous data were presented as mean ± standard deviation (SD), and categorical data as frequencies (percentages).

Results

Seventy-three (73) parents from the out-patient department of Philippine Childre's Medical Center were surveyed to assess the sleep habits of their children with drug resistant epilepsy (4-12 years old). Findings from this research indicate that sleep disturbances were more prevalent among male children, with an average age of 7.42 years old.

Table 1 below shows the frequencies of how many parents rated each sleep habit or item as occurring usually (5 to 7 times in a week), sometimes (2 to 4 times), and rarely (0 to 1 time). The most frequently occurring sleep disturbances involve the domains of bedtime resistance (29%), night wakings (28%), and daytime sleepiness (23%).

In the domain of bedtime resistance, the most frequently occurring sleep habits were: falls asleep in other's bed (51%), needs a parent in the room before being able to sleep (44%), and afraid of sleeping alone (41%). Sleep onset delay was reported in 19% of children with drug resistant epilepsy and 16% of the parents reported that their children sleep too little. In terms of night wakings, 44% of the parents reported that their children usually wake up once during the night while 38% reported that their children usually wakes up more than once per night. Meanwhile, the most commonly occurring sleep disturbance under the domain of daytime sleepiness were: children looking tired the whole day (36%), children having a hard time getting out of bed (32%), and falling asleep while watching the television (30%).

Table 1. *Frequencies and Percentages of the Sleep Habit of Children with Drug Resistant Epilepsy*

DOMAIN	Usually %	Sometimes %	Rarely %
BEDTIME RESISTANCE	29%	21%	50%
SLEEP ONSET DELAY	19%	53%	27%
SLEEP DURATION	14%	26%	50%
SLEEP ANXIETY	22%	23%	56%
NIGHT WAKINGS	28%	26%	47%
PARASOMNIAS	11%	24%	65%
SLEEP DISORDERED BREATHING	6%	18%	76%
DAYTIME SLEEPINESS	23%	36%	41%
TOTAL	19%	30%	51%

Note: Percentages may not total to 100% due to rounding

On the other hand, the least frequently occurring sleep disturbances involve the domains of sleep disordered breathing (76%), parasomnias (65%), and sleep anxiety (56%). Only 18% of the parents reported that their children usually snore loudly at night. Meanwhile, 92% of the respondents reported that their children rarely experience gasping and stopping of breathing during their sleep. In terms of anxiety, respondents reported that 44% of their children needs a parent in the room before being able to sleep and 41% are afraid to sleep alone. On the other hand, 58% of the parents reported that their children rarely get afraid of sleeping in the dark.

In terms of TSD scores, a TSD score of greater than 41 is the cut-off for determining sleep disturbed children. Table 2 summarizes the demographic characteristics of children with drug resistant epilepsy. Based on the table, out of the seventy-three participants, 61 patients had a TSD score of greater than 41 (84); on the other hand, only 12 (16%) had TSD scores 41 or lower. The average age of children TSD scores greater than 41 is 7.62 ± 2.23 while there is a lower average age of 6.42 ± 1.78 in those children who scored lower than 41. Meanwhile, both groups differ by only 3% in terms of the average age at seizure onset. Sleep disturbance is also found to be more common in males (63%) than in females (37%).

Table 2. *Demographic Characteristics of Sleep Disturbed (CHSQ>41) Children with Epilepsy compared to Non-Sleep Disturbed (CHSQ <41) Children with Epilepsy*

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
Age, years	7.42 ± 2.19	7.62 ± 2.23	6.42 ± 1.78
Age at seizure onset, years	3.89 ± 1.25	3.9 ± 1.33	3.8 ± 0.83
Duration of epilepsy, months	42.41 ± 21.73	44.66 ± 20.57	31.05 ± 24.78
Gender			
Male	45 (61%)	39 (63%)	6 (50%)
Female	28 (39%)	22 (37%)	6 (50%)

Note: Data are presented as mean ± standard deviation (SD) or n (%)

As shown in Table 3, those who are sleep disturbed have a shorter average sleeping time of 8.11 ± 1.98 as compared to the non-sleep disturbed group with an average sleeping time of 10.72 ± 1.60.

Table 3. *Average Sleep time of Children with Drug Resistant Epilepsy*

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
Total sleep time per 24h (hours)	8.42 ± 2.04	8.11 ± 1.98	10.72 ± 1.60

Table 4 shows the distribution of patients according to seizure frequency in the last 6 months. Majority of the patients (56%) had monthly seizure recurrence. 32 (52%) of the 61 patients with TSD scores higher than 41 experienced monthly seizures; while only 10 (83%) of the 12 patients with TSD scores lower than 41 experienced monthly seizure recurrence. The three (4%) patients who were reported to have daily seizure episodes had TSD scores greater than 41. Majority of the patients in the sleep disturbed group had weekly (34%) and monthly (52%) seizure recurrences; while in the other group, majority of the patients had monthly (83%) or less than 1 seizure episode per month (17%).

Table 4. *Distribution of Patients According to Seizure Frequency in the last 6 months*

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
Seizure frequency in the last 6 months			
Daily	3 (4%)	3 (5%)	0 (0%)
Weekly	22 (30%)	21 (34%)	1 (8%)
Monthly	41 (56%)	32 (52%)	10 (83%)
Less than 1 per month	7 (10%)	5 (8%)	2 (17%)

Figure 1 shows that higher TSD scores were observed in patients with higher seizure frequency, with those having once a month seizure averaging a score of 43.29 on the CSHQ and those with daily seizures averaging a score of 57.33.

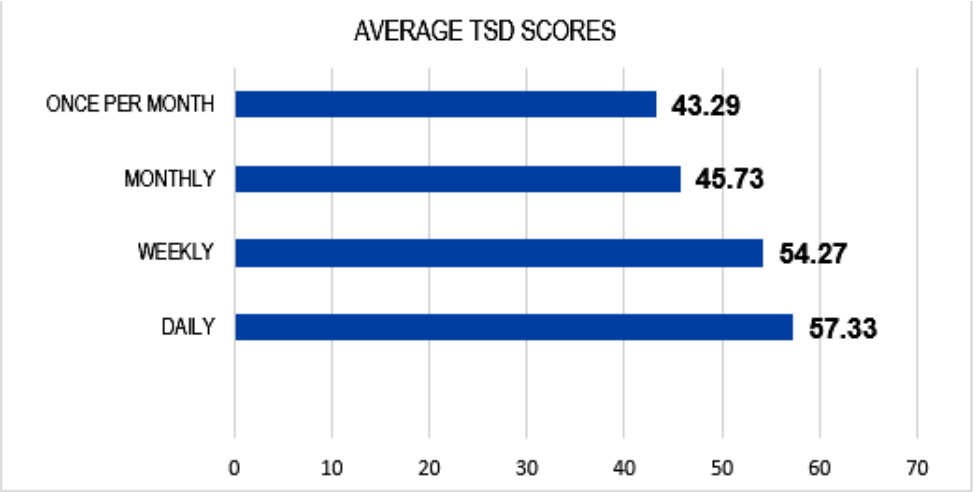

Figure 1. *Seizure frequency and Average TSD Scores of Children with Drug Resistant Epilepsy*

As shown in Table 5, majority of the patients had focal epilepsy (82%), while only 18% had generalized epilepsy. Regarding diurnal patterns, 52 patients (71%) experienced seizures during the daytime, while 12 patients (16%) had more frequent seizures at night. Among the patients with significant TSD scores, 50 (82%) had focal epilepsy, and 46 patients (75%) experienced seizure episodes during the day. Concerning seizure duration, 57 patients (78%) reported seizure episodes lasting for 5 minutes. Additionally, 13 patients (18%) out of 73 experienced seizure episodes lasting from 5 to 15 minutes, while 3 patients (4%) reported seizures lasting from 16 to 30 minutes, resulting in hospitalization in the past 6 months.

Table 5. *Distribution of Patients According to Seizure Type, Pattern, and Duration*

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
Seizure Type			
Focal	60 (82%)	50 (82%)	10 (83%)
Generalized	13 (18%)	11 (18%)	2 (17%)
Unclassified	0 (0%)	0 (0%)	0 (0%)
Seizure Diurnal Pattern			
Day	52 (71%)	46 (75%)	4 (34%)
Night	12 (16%)	8 (13%)	2 (16%)
Both	9 (12%)	7 (12%)	6 (50%)
Seizure Duration (min) in the last 6 months			
< 5	57 (78%)	48 (79%)	9 (75%)
5-15	13 (18%)	10 (16%)	3 (25%)
16-30	3 (4%)	3 (5%)	0 (0%)
>30	0 (0%)	0 (0%)	0 (0%)

Table 6 shows the breakdown of patients according to their anti-epileptic medications. The most frequently prescribed drug among the patients in this study is Levetiracetam, utilized by 93% of them. Following closely are Phenobarbital (46%) and Oxcarbazepine (39%). Conversely, Valproic acid (36%) and Topiramate (32%) were less commonly prescribed. Interestingly, these medication trends were consistent across both groups.

Table 6. *Distribution of Patients According to Anti-Epileptic Medications*

Characteristics	Total Sample (n = 73)	CSHQ >41 (n = 61)	CSHQ < 41 (n = 12)
Levetiracetam	68 (93%)	57 (93%)	12 (100%)
Phenobarbital	34 (46%)	30 (49%)	4 (33%)
Oxcarbazepine	29 (39%)	25 (40%)	4 (33%)
Topiramate	24 (32%)	24 (39%)	1 (8%)
Valproic acid	26 (36%)	24 (39%)	2 (17%)

DISCUSSION

Sleep disturbances are among the most prevalent comorbidities of epilepsy, with prevalence ranging 45–95% among children with epilepsy, as compared with 25–40% among typically developing children. The current study showed that sleep disturbances were common and severe in children with drug resistant epilepsy, with a frequency of 84% and a mean CSHQ total score of 58. In China, CSHQ total score of was 45.92 from a sample of children with epilepsy aged 4 to 12 years old with prevalence of 73.7%. A study among Hong Kong children with epilepsy aged 4 to 12 years old CSHQ total and a study among American children with epilepsy aged 2 to 10 years reported a CSHQ total score of 48.25.[4]

The average age of children TSD scores greater than 41 is 7.62 ± 2.23 while there is a lower average age of 6.42 ± 1.78 in those children who scored lower than 41. Meanwhile, both groups differ by only 3% in terms of the average age at seizure onset. Sleep disturbance is also found to be more common in males (63%) than in females (37%). Men are generally more prone to excitability episodes and epileptic seizures than women. While the exact molecular mechanisms behind this difference are not fully understood, variations in the brain's structure and neural pathways between men and women may help explain why men are more vulnerable to seizures and epileptic events. Changes in sensitivity to seizures can be attributed to steroid hormones, including fluctuations in neurosteroids and alterations in how their receptors signal.[8]

Sleep Habits in Children with Epilepsy

One of the identified lifestyle factors that contribute to the intractability of seizures include the sleeping habits of children with epilepsy. A study on the relationship between Sleep disturbances and behavioral problems in children with epilepsy showed that higher seizure frequency was related to higher scores for excessive sleepiness.[4] Data gathered from this study showed that higher seizure frequency is seen in patients with higher TSD scores as previously described in Figure 1. There were 3 patients who was reported to have daily seizures and their average TSD score is 57.33. This is 20% higher than the average TSD score of those patients with monthly seizure recurrence (Average score: 45.73). Sleep plays a crucial role in modulating seizure occurrence and or interictal epileptiform discharges and at the same time sleep disturbances worsen epileptic symptoms. Sleep and epilepsy has a bidirectional relationship where in epileptic discharges have also been shown to disrupt sleep-wake cycles. Children with poorly controlled seizures had even worse sleep habits compared with children with better control of seizures. Hence, epilepsy with the added sleep disturbances exacerbates a child's health and functioning.[4]

The interaction between sleep and epilepsy is complex with children with epilepsy having poorer sleep with clinically defined sleep disorders than their healthy counterparts.[5] In another study, it was found that the most common sleep disturbances in children with epilepsy include excessive daytime sleepiness (76%), sleep disordered breathing (65%), and parasomnia (53%).[4] Data gathered from this study showed that the most frequently occurring sleep disturbances involve the domains of bedtime resistance (29%), night wakings (28%), and daytime sleepiness (23%). On the contrary, disordered breathing (76%), parasomnias (65%), along with sleep anxiety (56%) were found to be the least frequently occurring sleep disturbances among the studied participants. Obstructive Sleep Apnea is the most common form of sleep-disordered breathing. Although this condition is highly prevalent in children with epilepsy, it is usually an underrecognized and underdiagnosed condition due to lack of parental awareness. unrecognized by the parents due to lack and is highly prevalent and grossly underdiagnosed.[9] Only 18% of the parents reported that their children usually snore loudly at night. Meanwhile, 92% of the respondents reported that their children rarely experience gasping and stopping of breathing during their sleep.

Results of this study showed that in the domain of bedtime resistance, the most frequently occurring sleep habits were: falls asleep in other's bed (51%), needs a parent in the room before being able to sleep (44%), and afraid of sleeping alone (41%). Sleep onset delay was reported in 19% of children with drug resistant epilepsy and 16% of the parents reported that their children would sleep too little. In terms of night wakings, 44% of the parents reported that their children usually wake up once during the night while 38% reported that their children usually wakes up more than once per night. Meanwhile, the most commonly occurring sleep disturbance under the domain of daytime sleepiness were: children looking tired the whole day (36%), children having a hard time getting out of bed (32%), and falling asleep while watching the television (30%). This coincides with the findings in another study that lack of a bedtime routine, having irregular bedtimes and risetimes, and frequent daytime napping are among the most common sleep problems identified in this specific population.[10]

Sleep duration

In terms of sleep duration, results show that patients with significantly higher TSD scores have a shorter average sleeping time of 8.11 ± 1.98 as compared to the non-sleep disturbed group with an average sleeping time of 10.72 ± 1.60. Children aged 3 to 5 years of age should sleep 10 to 13 hours per 24 hours (including naps) on a regular basis to promote optimal health while children 6 to 12 years of age should sleep 9 to 12 hours per 24 hours.[11]

Given this data, it can be said that majority of the children with significantly higher TSD scores are not getting the appropriate length of sleep that is recommended for their age and this may contribute further to seizure recurrence. Majority participants with low TSD scores (<41) reach the optimal length of sleep per age and thus the data also showed a lower seizure recurrence rate and shorter seizure duration wherein only 8% of the patients have weekly seizure episodes compared to the 34% of the participants with significant TSD scores. A case-control study conducted in Hong Kong reported that 50 minutes less sleep during weekdays compared with weekends in 63 epileptic preschool- and school-aged children led to increasing seizure recurrence.[12]

Effects of Anti-Epileptic Medications

It is important to consider how antiepileptic medications can impact sleep. Results of this study showed that the most common drug used by 98% of all the patients surveyed is Levetiracetam. This was followed by Phenobarbital (46%) and Oxcarbazepine (39%). The least commonly used drugs include Valproic acid (36%) and Topiramate (32%). All of the patients included in this study are taking multiple antiepileptic medications (polytherapy) and among those patients with significantly higher TSD scores, the most commonly used AED used include: Levetiracetam (93%), Phenobarbital (49%), and Oxcarbazepine (40%). Only 4 patients (33%) use Phenobarbital among those patients with low TSD scores. Benzodiazepines and barbiturates are known to affect sleep by reducing the time it takes to fall asleep, valproate increases the duration of the first stage of sleep, and Lamotrigine reduces slow wave sleep, which can lead to insomnia.[4] Moreover, children who are on multiple antiepileptic medications (polytherapy) tend to experience more sleep-related issues compared to those on a single medication (monotherapy). Data gathered from this study showed that sleep onset delay was seen in 19% of children with drug resistant epilepsy. `

Our study's strength lies in the use of validated tools that cover a broad spectrum of relevant factors. However, it's essential to interpret our findings cautiously considering the following limitations: (1) Our sample was drawn exclusively from a single site and the generalizability of our findings may be limited. Future research should aim to replicate and extend our results by involving larger samples from multiple locations; (2) The study did not utilize objective sleep assessments, such as actigraphy or polysomnography, potentially introducing reporting bias. Nonetheless, the Child Sleep Habits Questionnaire (CSHQ) is a well-established tool for screening sleep issues in children with neurodevelopmental disorders and offers measurements that reasonably align with objective data. The study could benefit from clinical evaluations of sleep disorders, psychopathology, and neurodevelopmental

disorders by experienced psychiatrists or developmental and behavioral pediatricians; (3) Due to the cross-sectional design of our study, we cannot establish causal relationships. Longitudinal studies and intervention research can be utilized to comprehensively explore the connections among sleep disturbances and seizure recurrence among children with drug-resistant epilepsy.

Conclusion and Recommendation

In conclusion, the findings of this study align with previous research indicating that majority of the children with drug resistant epilepsy are sleep disturbed exhibiting high TSD scores (>41) when examined using the Children's Sleep Habits Questionnaire. The CSHQ is a parent-report screening tool designed for school-aged children (4-12 years). The current study showed that sleep disturbances were common and severe in children with drug resistant epilepsy, with a frequency of 84% and a mean CSHQ total score of 58. Sleep disturbances in children with drug resistant epilepsy is found to cause increasing seizure frequency hence screening for factors such as sleep that may be contributory to the recurrence of seizures de-spite being adequately treated with anti-epileptic drugs can help in finding a more holistic approach in managing patients with drug resistant epilepsy. Furthermore, children with epilepsy with sleep disturbances demonstrated more behavioral problems and lower quality of life compared to those without sleep disturbances. Findings of this study recommends the need to actively evaluate and screen for sleep and behavioral problems concurrently when seeing children with epilepsy.

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References

1. Owens, J. A., Spirito, A., & McGuinn, M. (2000). The children's sleep habits questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. *Sleep, 23*(8), 1043-1051.

2. Mindell JA & Owens JA (2003). A clinical guide to pediatric sleep: diagnosis and management of sleep problems. XPhiladelphia: Lippincott, Williams &Wilkins.

3. Mindell, J. A., Kuhn, B., Lewin, D. S., Meltzer, L., & Sadeh, A. (2006). Behavioral treatment of bedtime problems and night wakings in infants and young children. *SLEEP, 29*(10).

4. Zhao, F., Sun, X., Wang, Y., Zhou, Y., He, Y., Wang, C., Han, F., Liu, J., Tsai, S.-Y., Wang, G., & Wang, J. (2022). Sleep disturbances in Chinese children with epilepsy: Associations with behavioral problems and quality of life. *Nature and Science of Sleep*, *Volume 14*, 1225–1236. https://doi.org/10.2147/nss.s367900

5. Tang, H Liu, Z., Wang, G.,., Wen, F., & Li, N. (2014, July). Reliability and validity of the Children's Sleep Habits Questionnaire in preschool-aged Chinese children. *Sleep and Biological Rhythms*, *12*(3), 187–193. https://doi.org/10.1111/sbr.12061

6. Mabilangan, K. & Moral-Valencia, M.A. (2015). Validation study of the Filipino version of the Children's Sleep Habits Questionnaire. *Sleep Medicine, 16*, S61-62.

7. [7] Kharod P, Mishra D, Juneja M. Drug-resistant epilepsy in Indian children at a tertiary-care public hospital. 2019:5-8.

8. Reddy DS, Thompson W, Calderara G. Molecular mechanisms of sex differences in epilepsy and seizure susceptibility in chemical, genetic and acquired epileptogenesis. Neurosci Lett. 2021 Apr 17;750:135753. doi: 10.1016/j.neulet.2021.135753. Epub 2021 Feb 18. PMID: 33610673; PMCID: PMC7994197.

9. Foldvary-Schaefer NR, Waters TE. Sleep -Disordered Breathing. Continuum (Minneap Minn). 2017 Aug;23(4, Sleep Neurology):1093-1116. doi: 10.1212/01.CON.0000522245.13784.f6. PMID: 28777178.

10. Batista BH, Nunes ML. Evaluation of sleep habits in children with epilepsy. Epilepsy Behav. 2007 Aug;11(1):60-4. doi: 10.1016/j.yebeh.2007.03.016. Epub 2007 May 11. PMID: 17499554.

11. Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, Malow BA, Maski K, Nichols C, Quan SF, Rosen CL, Troester MM, Wise MS. Consensus Statement of the American Academy of Sleep Medicine on the Recommended Amount of Sleep for Healthy Children: Methodology and Discussion. J Clin Sleep Med. 2016 Nov 15;12(11):1549-1561. doi: 10.5664/jcsm.6288. PMID: 27707447; PMCID: PMC5078711.

12. Chan B, Cheong EY, Ng SF, Chan YC, Lee QU, Chan KY. Evaluation of sleep disturbances in children with epilepsy: a questionnaire-based case-control study. Epilepsy Behav. 2011 Aug;21(4):437-40.

13. Bill F, Foundation MG. Global, regional , and national burden of epilepsy , 1990 – 2016 : a systematic analysis for the Global Burden of Disease Study 2016. 2019. doi:10.1016/S1474-4422(18)30454-X

14. Carter, K., Hathaway, N., & Lettieri, C. (2014). Common sleep disorders in children. *Am Fam Physician, 89* (5):368-377

15. Gavino M. & Pacifico, R. (2008). Sleep patterns of patients ages 4-12 with pervasive developmental disorder enrolled at the neurodevelopmental center in a Tertiary Teaching Hospital. (Unpublished).

16. Gutter, T., Brouwer, O. F., & de Weerd, A. W. (2013). Subjective sleep disturbances in children with partial epilepsy and their effects on quality of life. *Epilepsy & Behavior*, *28*(3), 481–488. https://doi.org/10.1016/j.yebeh.2013.06.022

17. Khalil M. Risk Factors for Intractable Epilepsy in Children Risk Factors for Intractable Epilepsy in Children. 2018; (April). doi:10.12816/0038475

18. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE OFFICIAL REPORT A practical clinical definition of epilepsy. 2014:475-482. doi:10.1111/epi.12550

19. Madulara, G. (2017) A Survey On Sleep Behaviors And Sleep-Related Problems Among Asthmatic Children Ages 6 – 12 Years Old In University of Santo Tomas Hospital – Outpatient Division Using The Filipino Version Of The Children's Sleep Habits Questionnaire (CSHQ) https://www.em-consulte.com/article/1200291/article/a-survey-on-sleep-behaviors-and-sleep-related-prob

20. Pedraza AJD, Cerdá JMM. Drug-resistant epilepsy: Definition and treatment alternatives. 2015;30(7). doi:10.1016/j.nrleng.2014.04.002

21. Tigistu M, Azale T, Kebebe H, Yihunie T. Frequency of seizure attack and associated factors among patients with epilepsy at University of Gondar Referral Hospital: A cross-sectional study, Gondar, North West Ethiopia, 2017. *BMC Res Notes*. 2018;11(1):2-7. doi:10.1186/s13104-018-3761-3

22. Tsui, S.-Y., Lee, W.-T., Lee, C.-C., & Weng, W. C. (2018). *Sleep and Behavior Problems in Children With Epilepsy*. https://doi.org/https://doi.org/10.1016/j.pedhc.2018.07.004

23. Viteva, E. I. (2014). Seizure frequency and severity: How really important are they for the quality of life of patients with refractory epilepsy. *Annals of Indian Academy of Neurology*, *17*(1), 35. https://doi.org/10.4103/0972-2327.128544

ARTICLE

A ten-year review of Congenital Pulmonary Airway Malformation cases in a Pediatric tertiary hospital

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OBJECTIVE: A retrospective study of the demographic, clinical and diagnostic profile, intervention and outcomes of children with Congenital Pulmonary Airway Malformation (CPAM) in Philippine Children's Medical Center (PCMC) from January 2011 to December 2021 was presented.

METHODOLOGY: Medical charts of identified patients were reviewed. Data obtained included demographic profile, clinical history, diagnostic procedures, intervention, and outcomes. The findings were analyzed and correlated with the synthesized findings from relevant studies about CPAM.

RESULTS: Twenty-three cases (n=23) were included in the study. Most of the patients were diagnosed at 1 to 11 months of age, accounting for 43.48% while there is a minimal disparity in terms of gender distribution. Seventy-five percent of neonates presented with respiratory distress while recurrent pneumonia occurred more frequently beyond the neonatal period. Four patients at 17.39% had incidental findings of CPAM on prenatal ultrasound. All cases were confirmed using a Chest CT scan and only six patients at 26.09% had Chest X-ray results consistent with CPAM. Eight cases were confirmed using biopsy wherein results were mainly Type I seen in 87.5% of cases. Lobectomy is the procedure of choice with 92.86% success rate. Overall, patients who underwent surgical intervention had a low complication rate at 6.25%.

CONCLUSION: CPAM is most common in patients aged 1 to 11 months and has no gender predilection. Neonates often present with respiratory distress while recurrent pneumonia is the most common clinical manifestation beyond neonatal period. CPAM can be detected using ultrasound prenatally and CT scan can confirm CPAM postnatally. Surgical intervention particularly lobectomy is the preferred option over conservative management which showed a favorable outcome. CPAM has an overall good prognosis. Findings of this research may guide clinicians in the diagnosis and management of CPAM in the Philippines.

KEYWORDS: *Congenital Cystic Adenomatoid Malformation, Congenital Pulmonary Airway Malformation, Congenital Cystic Lung*

INTRODUCTION

Congenital Pulmonary Airway Malformation (CPAM), formerly known as Congenital Cystic Adenomatoid Malformation (CCAM), is a rare developmental malformation of the lower respiratory tract characterized by the formation of hamartomatous or dysplastic lung tissue.[1,2] Despite its rarity, CPAM has been recognized internationally with an incidence ranging from 1 in 25,000 to 35,000 births and a prevalence of 1 to 4 in 100,000 births.[3,4,5] In the Philippines, although data on CPAM are limited, the Philippine Pediatric Society (PPS) has reported 84 cases of unspecified congenital lung malformations and 194 cases of congenital cystic lung disease since 2006. Out of these cases, 29 cases were recorded at the Philippine Children's Medical Center (PCMC) as of 2021. Despite the significant number of CPAM cases, limited Philippine literature exists and there has been no reviews made on the cases of CPAM in PCMC. The findings of this study will therefore provide evidence-based data on the local clinico-demographic profile and current local practice in diagnosing and managing CPAM along with its outcomes. It will also highlight the comparison of these findings with the international findings. These data may guide the management of CPAM in hopes of improving patient health care. In addition, it will contribute to the limited number of literatures on CPAM in the Philippines.

Almost all reported CPAM cases are from whites however there is no evidence for racial predilection, neither is it associated with age, sex, weight, gestational age, parity nor intrauterine maternal exposures.[2,3] This can be attributed by the fact that most of the available data were from international journals. The etiology of CPAM remains uncertain, but it is believed to result from embryologic injury before the 35th day of gestation during lung development.[1,3] CPAM can be classified into different types based on embryologic origin and histologic features, which may influence prognosis and malignant potential.[5] Clinical presentation varies from asymptomatic to respiratory distress, and diagnosis can be made prenatally or postnatally using various imaging modalities such as ultrasonography, MRI, X-ray, CT scan.[2,6,7] With the increasing diagnosis of CPAM in utero, conservative management were made including steroid therapy and thoracoamniotic shunts.[5] On the other hand, invasive CPAM resection has already been performed in a 29 week old fetus.[5] In the postnatal period, surgery is indicated for symptomatic patients either by lobectomy, segmentectomy or wedge-resection via thoracotomy or thoracoscopy whereas the timing of surgery for asymptomatic cases is controversial, with advocates for early intervention citing the risk of complications such as recurrent infection, impaired lung growth, growth from mass effect of the lesion, repeated exposure to imaging radiation on

on lesion monitoring and malignant potential.[2,3,6,7] The contrary opinion is that the risk of surgery outweighs the risk of these complications.[6] Furthermore, despite advancements in understanding and managing CPAMs, there remains to be lack of clarity regarding nomenclature, classification, pathogenesis, natural history, diagnosis, and management of CPAM.[6] Continued research efforts are essential to address these gaps and guide clinical practice of CPAM.

The general objective of this study is to provide an evidence-based profile of patients diagnosed with CPAM in PCMC from January 2011 to December 2021. Specifically, it aims to determine the demographic profile, clinical and diagnostic profile, intervention, and outcomes of patients diagnosed with CPAM admitted in PCMC from January 2011 to December 2021.

Methodology

This is a retrospective descriptive study that identified and reviewed all confirmed cases of CPAM in PCMC from January 2011 to December 2021 and correlated it with the synthesized findings from relevant studies about CPAM.

The target population of this study were patients diagnosed with CPAM and admitted at PCMC from January 2011 to December 2021. The basis of the diagnosis is made by confirmed Chest CT scan, Chest MRI, or pathology findings.

Secondary data collection method was used in this study. Medical charts of the confirmed cases of CPAM were retrieved and reviewed. From these medical records, the following data were obtained: demographic data such as patient's age and sex, clinical history, and physical examination, diagnostic procedures, intervention, and outcomes during admission. The collected data was tabulated and presented in graphs. This study utilized descriptive statistics such as measures of frequency, central tendency, and dispersion or variation and position.

Results

Twenty-three patients (n=23) diagnosed with CPAM or CCAM were identified and studied. At the time of diagnosis, the patients' age ranged from 0 to 11 years old, with the majority of the patients presenting at 1 month to 11 months of age, accounting for 43.48% (10 out of 23) of total cases as presented in table 1. All the neonates were born full-term. In terms of gender distribution, there is minimal disparity regardless of age at presentation (Males: 11; Females: 12) (Table 1).

Table 2. Clinical Manifestation Profile of Patients Diagnosed with CPAM Admitted in PCMC from January 2011 to December 2021

Age at presentation	Clinical Manifestation				Total
	Respiratory distress	Recurrent Pneumonia	Feeding difficulties	Asymptomatic	
0- 28 days	3	0	0	1	4
1 month to 11 months	2	6	0	2	10
1 year to 9-year-old	0	6	0	1	7
10 year- 18 years	0	2	0	0	2
Total	5	14	0	4	23

Table 3 shows that during the prenatal period, four patients at 17.39% had incidental findings of CPAM on prenatal ultrasound. The median gestational age at diagnosis was 20 weeks. All four patients were born alive and lesions persisted until birth which were confirmed via Chest CT scan. One was symptomatic while the rest were asymptomatic. Three of them underwent lobectomy which all improved while the remaining one was observed. All of the diagnosed CPAM cases were confirmed using a Chest CT scan, comprising 100% (23 out of 23) of cases. Only six patients at 26.09% had Chest X-ray results consistent with CPAM. Eight cases at 34.78% were confirmed via biopsy with the majority classified as type 1 seen at 87.5% (7 out of 8) of cases. The biopsy of one patient who underwent lobectomy revealed bronchogenic cyst. In PCMC, there were no records of MRI being used to diagnose CPAM cases.

Table 3. Diagnostic Procedure Profile of Patients Diagnosed with CPAM Admitted in PCMC from January 2011 to December 2021

Diagnostic procedure	CCAM/CPAM	Others	Total
Antenatal Ultrasound	4	0	4
Chest X-ray	6	17	23
Chest CT Scan	23	0	23
Biopsy	8	1	9
Chest MRI	0	0	0

In Table 4, only postnatal intervention was employed in PCMC including cyst excision, blebectomy, and lobectomy, wherein most of the patients at 87.5% (14 out of 16) underwent lobectomy. Notably, positive outcomes were observed with most of the patients improved and had no complications postoperatively at 92.86% (13 out of 14); however, there was a mortality rate of 7.14% (1 out of 14) associated with the said procedure. In addition, among the surgical procedures performed, there was one case of cyst excision and one case of blebectomy, both of which also resulted in improved statuses with no complications. Overall, most patients who underwent surgical intervention at 93.75% (15 out of 16) improved with unremarkable postoperative course. Observation and close monitoring methods were chosen for three patients however this study did not include an outpatient follow-up review hence the outcomes were unknown. The four other patients were either lost to follow-up, coordinated to other hospitals, or sent home against medical advice. The average hospitalization day was nine days.

Table 4. Descriptive Comparison of Outcomes According to Management Performed to Patients Diagnosed CPAM Admitted in PCMC from January 2011 to December 2021

Intervention	**Outcome**						
Surgical	**Improved**	**Residual cyst**	**Pneumo-thorax**	**Readmis-sion**	**Mortali-ty**	**Un-known**	**Total**
Cyst Excision	1	0	0	0	0	0	1
Blebectomy	1	0	0	0	0	0	1
Segmental resection	0	0	0	0	0	0	0
Lobectomy	13	0	0	0	1	0	14
Total	15	0	0	0	1	0	16
Medical	**Improved**	**Residual cyst**	**Pneumo-thorax**	**Readmis-sion**	**Mortali-ty**	**Un-known**	**Total**
Observation	0	0	0	0	0	3	3
Others	0	0	0	0	0	4	4
Total	0	0	0	0	0	7	7
						Total	23

DISCUSSION

Congenital Pulmonary Airway Malformation (CPAM), formerly known as Congenital Cystic Adenomatoid Malformation (CCAM), is a developmental malformation of the lower respiratory tract causing formation of hamartomatous or dysplastic lung tissue.[1,2] It belongs to the heterogeneous group of embryologically-related malformations of the lung along with pulmonary agenesis, aplasia, hypoplasia, and sequestration, and bronchogenic cyst.[1,3] It is a rare but well-known congenital lung lesion with an international incidence of 1 in 25,000 to 35, 0000 births and a prevalence of 1 to 4 in 100,000 births.[3,4,5] In the Philippines, 84 cases of unspecified congenital malformation of the lung and 194 cases of congenital

cystic lung were reported by the Philippine Pediatric Society (PPS) since 2006. Out of these recorded cases, 29 were found in Philippine Children's Medical Center as of 2021. According to studies, CPAM has no racial predilection neither is it associated with age, sex, weight, gestational age, parity, nor intrauterine maternal exposures. This coincides with our findings wherein CPAM has no gender predilection. Although some studies state that it is more common in whites and males, and most are diagnosed before two years of age.[2,3,8] This is also congruent with our findings as majority of the CPAM patients were diagnosed at 1 month to 11 months of age.

The exact pathogenesis of CPAM is still uncertain however it is believed to have resulted from an embryologic injury before the 35th day of gestation during the various stages of lung development commonly during the pseudoglandular stage causing maldevelopment of the tracheobronchial tree and formation of cysts.[1,3] Typical histologic findings reveal few normal lung tissues and many glandular elements wherein cysts are very common and the presence of cartilage is rare indicating that the embryological insult occurred later in the 10th to 24th week.[1] CPAM was classified into 3 types by Stocker et. al in 1977 and expanded into 5 types by Stocker in 2002 which differ based on the embryologic level of origin and histologic features subsequently leading to distinct prognosis and malignant potential.[5] The first type is Type 0 which is the least common type (<3%) arising from the trachea and proximal bronchus and consists of microcystic (<5mm) lesions involving all lobes hence has the poorest prognosis and is incompatible with life while Type 1 is the most common type (60%) which arises from the distal bronchus or proximal bronchioles and consists of single or multiple macrocysts (>5mm) lesions lined with ciliated pseudostratified epithelium with one-third of cases characterized with mucus-secreting cells. This lesion involves only a part of one lobe and hence has a good prognosis for survival. Type 2 (20%) arises from terminal bronchioles and consists of multiple microcyst with histology similar to that of the type 1 however carries a poor prognosis since majority of the CPAM cases associated with congenital anomalies including cardiac, renal, gastrointestinal and skeletal anomalies were classified as Type 2 lesions. Another type is Type 3 (<10%) which arises all the way down to alveolus and is characterized with a mixture of microcysts and solid tissue with bronchiole-like structures lined with cuboidal ciliated epithelium separated by areas of nonciliated cuboidal epithelium. This type also carries a poor prognosis. The last type is Type 4 (10%) which arises in the alveoli and is commonly macrocystic and lacks mucus cells. It is the lesion that has been associated with malignancy (pleuropulmonary blastoma).[1,3,8,9] In PCMC, eight cases were confirmed by biopsy wherein the majority were classified as CPAM type 1 seen in 87.5% (7 out of 8) of cases which is consistent with the existing

of cases which is consistent with the existing studies.

The presentation of CPAM ranges from asymptomatic to respiratory distress. Two thirds of affected patients are diagnosed during neonatal period.[2] Approximately 75% of these patients are asymptomatic at birth while the remaining 25% of patients are symptomatic.[2] Affected neonates with expanding cystic lung mass may present with respiratory distress while those with small lesions may remain asymptomatic.[2] Only one-third of CPAMs are diagnosed beyond the neonatal period due to associated cough, decreased breath sounds on physical examination, incidental findings on imaging, and recurrent respiratory infections.[2,3,8] A common presentation in older children is recurrent pneumonia. In contrary to our data, most patients with CPAM were diagnosed beyond the neonatal period and diagnosed neonates often had respiratory distress at 75% (3 out of 4) of cases. Similarly, recurrent pneumonia is the most common presentation after the neonatal period at 60.87% (14 out of 23) of cases.[2]

With the advent of ultrasonographic technology, a more frequent and earlier prenatal diagnosis of CPAM is made with most cases diagnosed at 18-22 weeks age of gestation with a median gestational age of 21 weeks.[1,7] Prenatal diagnosis of CPAM using ultrasound has already been employed in PCMC with most cases diagnosed at 20 weeks age of gestation which was nearly congruent with previous studies. When ultrasound findings are equivocal such as in late pregnancy where there is loss of fluid-tissue interface or inaccessible fetal position, MRI can be used for morphological and volumetric evaluation of this lung lesion.[3,6] However in PCMC, there were no records of MRI being used to diagnose CPAM prenatally. Spontaneous regression of CPAM prenatally on serial fetal ultrasonography which occurs in approximately 50% of cases between 28-37 weeks age of gestation has also been observed.[2,6,7] Among lesions persisted in the postnatal period, spontaneous resolution has also been reported in a small number of cases.[2] Since prenatal ultrasound becomes less sensitive in detecting lung cysts as the pregnancy advances, involution of the lesion can be misleading hence true resolution must be documented using a postnatal Chest CT scan.[6,10] Based on the algorithm of CPAM postulated by Oermann et. Al (2021), all infants with prenatal diagnosis of CPAM should have a Chest X-ray in the neonatal period. However, some studies showed that thin-walled cystic lesions are difficult to see in Chest X-ray hence CT Scan is strongly recommended for definitive diagnosis. In PCMC, CPAM lesions found on fetal ultrasound of four patients persisted until birth which were confirmed using Chest CT scan. On the other hand, Chest X-ray, CT scan, and MRI are used to evaluate for CPAM postnatally.[6,7] According to a study by Shamas and Bohara (2016), CT scan is superior to Chest X-ray in detecting lesions in cases of

CPAM with sensitivity of 100% and 88%, respectively and positive predictive value of 95% and 78%, respectively. This is also true in a case report by Disu et. Al (2019) wherein a 13-day old neonate presented with tachypnea on the third day of life and had a chest X-ray finding consistent with congenital lobar emphysema or congenital pneumonia while CT scan findings was suggestive of CPAM. A similar report was presented by Atalabi et al. (2006) wherein an initial diagnosis of congenital diaphragmatic hernia was suspected based on the Chest X-ray, but chest CT findings revealed CPAM type 2. This was evident in our findings as all the CPAM patients were diagnosed using a Chest CT scan in 100% (23 out of 23) of cases and only six patients at 26.09% had Chest X-ray results consistent with CPAM. MRI could be an alternative to a CT scan but there is no evidence showing which one is the best modality.[6,8] In PCMC, there were no records of MRI being used to diagnose CPAM postnatally. Furthermore, since the signs and symptoms of CPAM are constitutional, the differential diagnosis can be broad, hence imaging studies play a crucial role in distinguishing CPAM from other diseases. Bronchopulmonary sequestration (BPS), congenital lobar emphysema, and bronchogenic cyst are some of the diseases that causes pulmonary cystic changes while congenital diaphragmatic hernia (CDH) can mimic cystic lung changes.[4,8,9] Colour Doppler ultrasound which is a tool that evaluates the arterial and venous blood flows allows differentiation between CPAM and BPS since CPAM is supplied and drained through the pulmonary circulation whereas BPS is supplied through the systemic circulation.[6,9] However, this diagnostic procedure was not yet employed in PCMC hence for one case, the Chest CT scan result was suggestive of CPAM but biopsy result turned out to be BPS.

With the increasing diagnosis of CPAM in utero, conservative managements were made to decrease morbidity and mortality including steroid therapy and thoracoamniotic shunts.[5] On the other hand, a study by Fan et. Al (2017) demonstrated an invasive antenatal procedure performed in case of CPAM wherein the uterine of a 22-year-old at 29 2/7 weeks of gestation was incised and the fetal CPAM lesion was resected through thoracotomy then the fetus was returned back to the uterine cavity. In the postnatal period, surgery is indicated for symptomatic patients either by lobectomy, segmentectomy or wedge-resection via thoracotomy or thoracoscopy.[1,3] Whereas postnatal management of asymptomatic CPAM remains controversial.[6] Only postnatal interventions were employed in PCMC including cyst excision, blebectomy, and lobectomy, wherein majority of the patients at 87.5% (14 out of 16) underwent lobectomy. Although surgery may be delayed for asymptomatic infants because postnatal resolution has been reported, advocates of elective postnatal surgery cite the risk of

recurrent infection, impaired lung growth from mass effect of the lesion, repeated exposure to imaging radiation on lesion monitoring and malignant potential which has been described for some cases, thus surgical resection by one year of age is recommended.[6,7] The contrary opinion is that the risk of surgery outweighs the risk of these complications.[6] Notably in our findings, positive outcomes were observed for patients who underwent lobectomy with majority of them improved and had no complications post operatively at 92.86% (13 out of 14); however, there was a mortality rate of 7.14% (1 out of 14) associated with the said procedure. In addition, among the surgical procedures performed, there was one case of cyst excision and one case of blebectomy, both of which also resulted in improved statuses with no complications. Overall, most patients who underwent surgical intervention at 93.75% (15 out of 16) improved with unremarkable postoperative course.

A consensus was made regarding the management of CPAM presented in the study of Oermann et. Al. (2021). In symptomatic cases, immediate advance thoracic imaging such as CT scan or MRI is required to further define the type and extent of lesion as part of preoperative planning and patient should undergo early surgical resection while in asymptomatic patient, close monitoring and simple chest radiograph should be done due to the possibility of becoming symptomatic and the risk of recurrent infection and malignant transformation. If during monitoring the patient is tagged as high risk which is defined as having large lesion (>20% of hemithorax), bilateral and multifocal cysts, and malignant risk factors then immediate advance thoracic imaging should be done to confirm the diagnosis and surgical intervention is suggested while if patient is low risk with none of the high risk features outlined above, the decision will primarily come from the family after a detailed discussion of the advantages and disadvantages of each approach. If observation is chosen, advance thoracic imaging is done after 6 months and close follow up for development of signs and symptoms with routine annual imaging should be done while if surgical intervention is chosen, elective surgical procedure should be done by one year old.[2] This was apparent in our findings as three patients were observed but since this study did not include out-patient follow up review thus the outcomes were unknown. The prevention of recurrent infection and potential malignancy, the improved restoration of lung volume, and fewer complications favor early elective surgery in asymptomatic patients.

Conclusion

In conclusion, CPAM is most common in patients aged 1 month to 11 months and has no gender predilection. Neonates often present with respiratory distress while recurrent pneumonia is the most common clinical manifestation beyond neonatal period. CPAM can be detected using ultrasound prenatally and CT scan can confirm CPAM postnatally.

Surgical intervention particularly lobectomy was the preferred option over conservative management which showed a favorable outcome. CPAM has an overall good prognosis. The involvement of a multidisciplinary team in the management of these patients is of utmost importance.

As the research aims only to review in-patient cases of CPAM in PCMC over a ten -year period, there is limited population size and short-term evaluation of outcomes. The study as well, was conducted through review of medical charts and some of these records had incomplete documentation therefore were not included in the study.

Due to limited population size, a longer period may be reviewed to account for more CPAM cases. A follow-up review is also recommended to evaluate for the long-term complications. For future study, a review on the profile of pathologic findings and associated anomalies in CPAM cases can also be beneficial.

REFERENCES

1. Kliegman RM, Stanton BF, Geme JW, Schor, NF. Nelson Textbook of Pediatrics. Canada. Elsevier Inc. 2020. Chapter 423, Congenital Disorders of the Lung; part XVIII; p. 2229-2233

2. Oermann C. Congenital Pulmonary Airway Malformation [Internet]. 2021 [2023 Feb]. Available from: https://www.uptodate.com/contents/congenital-pulmonary-airway-malformation

3. Disu EA, Kehinde OA, Anga AL, Ubuane PO, Itiola A, Akinola IJ, Et Al. Congenital Pulmonary Airway Malformation: A Case Report of A Rare Cause Of Neonatal Respiratory Distress And Review Of The Literature [Internet]. 2019 Nov [2023 Feb]; 22 (11):p 1621-1625. Available from: https://journals.lww.com/njcp/Fulltext/2019/22110/Congeni-tal_Pulmonary_Airway_Malformation__A_Case.23.aspx. DOI: 10.4103/njcp.njcp_20_19

4. Iavazzo C, Eleftheriades M, Bacanu AM, Hassiakos D, Botsis, D. Congenital Cystic Adenomatoid Malformation: Is There a Need for Pregnancy Termina-tion? [Internet]. 2012 Mar [2023 Feb]; Available from: https://www.hindawi.com/journals/crim/2012/397508/ doi:10.1155/2012/397508

5. Fan D, Wu S, Wang R, Huang Y, Yao F, Wen A, et al. Successfully Treated Congenital Cystic Adenomatoid Malformation By Open Fetal Surgery A Care-Compliant Case Report Of A 5-Year Follow-Up And Review Of The Literature [Internet].

6. David, M, Pinheiro, R, Coelho, T. Prenatal and Postnatal Management of Congenital Pulmonary Airway Malformation [Internet]. 2016 April [2023 Feb];110 (2): 101–115. Available from: https://karger.com/neo/article/110/2/101/231375/Prenatal-and-Postnatal-Management-of-Congenital. DOI: 10.1159/000440894

7. Gallegos S, Sibaja MJ, Gaona JM, Calvo JA, Torrez BV, Cabrera DM. Congenital Adenomatoid Cystic Malformation: Expectant Management Outcomes [Internet]. 2018 Sep [2023 Feb] 5 (5). Available from: https://www.omicsonline.org/open-access/congenital-adenomatoid-cystic-malformation-expectant-management-outcomes.pdf. DOI: 10.4172/2376-127X.1000387

8. Carias MB, Orillaza M. Congenital Cystic Adenomatoid Malformation Type II With Associated Cardiac Anomalies [Internet]. 2007 May [2023 Feb]; 13 (2):161-167 Available from: https://www.phc.gov.ph/about-phc/journals/pdf/carias.pdf

9. Sfakianaki, AK. and Copel, JA. Congenital Cystic Lesions of the Lung: Congenital Cystic Adenomatoid Malformation and Bronchopulmonary Sequestration [Internet]. 2012 [2023 Feb];5(2):85-93. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3410507/pdf/RIOG005002_0085.pdf. doi: 10.3909/riog0183a

10. Shamas AG, Bohara K. 2016. Congenital Cystic Adenomatoid Malformation Of The Lung (CCAM), A Retrospective Clinical Audit And Literature Review In A Tertiary Centre In Scotland Over A Period Of 14 Years [Internet]. 2017 Jan [2023 Feb];37(1):19-24. Available from: https://pubmed.ncbi.nlm.nih.gov/27666113/ doi: 10.1080/01443615.2016.1196480

ARTICLE

Efficacy of intranasal Dexmedetomidine in combination with Ketamine as premedication and sedation in pediatric patients: a systematic review and meta-analysis

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OBJECTIVE: To compare the efficacy and safety of the combination of Dexmedetomidine (Dex) and Ketamine (Ket) administered via the intranasal (IN) route on sedation of children aged 0 to 12 years old prior to elective surgery or procedural sedation as compared to Intranasal Dexmedetomidine.

METHOD: Relevant studies were identified after a literature search on electronic databases as PubMed, Cochrane Library, Google Scholar and Science Direct. Meta-analyses of mean differences were performed to examine differences in sedation onset and recovery times between IN Dex-Ket and IN Dex. Meta-analyses of proportions were performed to estimate the incidence of sedation success, satisfactory sedation at parental separation and mask induction, and incidence of adverse events. Review Manager 5.4.1 was used for statistical analysis.

RESULT: Six articles (388 patients) were included. The overall incidence of sedation success was higher among children premedicated with IN Dex-Ket (RR = 1.05; 95%CI = 0.97,1.13; P = 0.27, I^2 = 20%) however was not statistically significant. Children given IN Dex-Ket had faster sedation onset time (WMD = -7.17; 95%CI = -12.44, -1.89; P=0.008) with greater incidence of satisfactory sedation at mask induction (RR = 0.71; 95%CI = 0.53, 0.94; P = 0.02). There was no significant difference as to recovery time and incidence of adverse events among the groups.

CONCLUSION: Premedication with IN Dex-Ket is as safe as IN Dex but of better efficacy as evidenced by faster sedation onset time and smoother inhalational induction without increasing clinically relevant adverse events.

KEYWORDS: *Dexmedetomidine, ketamine, premedication, intranasal, pediatric*

INTRODUCTION

The preoperative period can be a stressful and traumatic time for children undergoing surgery and worrisome for the anesthesiologist and caregiver [1]. Anesthesiologists therefore must adopt strategies to reduce potential psychological trauma to children induced by forced inhalational induction of anesthesia. Premedication in children is helpful for both separating the

of anesthesia. A variety of pharmacological or behavioral interventions have been proposed as preoperative anxiolytics to minimize the distress of children in the operating room, however, no technique or pharmacologic agent has been found to be completely satisfactory in children. Despite its high bioavailability and rapid onset, the disadvantage of intravenous premedication is the requisite for cannulation. Intranasal administration is easy, non-invasive and usually well tolerated. Among children, it avoids the necessity of injections or bitter tasting oral drugs. Pooled studies on effective premedication via the intranasal route may foster increase in its use with a consequent decrease in observed parental separation anxiety, stormy inhalational induction and postoperative delirium and agitation.

Dexmedetomidine (Dex) is a highly selective a2-agonist that provides sedation which parallels natural sleep, anxiolysis, sympatholysis and an anesthetic-sparing effect without clinically significant respiratory depression; however, it is associated with modest reductions in heart rate and blood pressure [2,3]. Currently, dexmedetomidine is not approved for use in children in any country. As an off-label medication, it has been administered as an adjunct to anesthesia, both general and regional, in and out of the operating room for both surgical and medical procedures in children and for sedation in the pediatric ICU (PICU) with beneficial results [4]. A study by Li et al on the bioavailability of dexmedetomidine, revealed a marked difference between the nasal (40.7%), buccal (81%) and oral (16%) route [5,6]. A recent meta-analysis by Tervonen and colleagues on intranasal dexmedetomidine premedication in children concluded that it provided a more satisfactory sedation at parent separation and reduced the need for rescue analgesics compared with intranasal ketamine and oral midazolam [7]. As with intravenous dexmedetomidine, the intranasal route has the additional benefit of reduced postoperative nausea and vomiting and need for rescue analgesics[8]. However, there are some disadvantages of dexmedetomidine when it is used alone. First, the sedative effects of dexmedetomidine are concentration dependent. When the plasma concentration of dexmedetomidine is between 0.2 and 0.3 ng/ mL, the patients may be of arousable sedation, at a concentration above 1.9 ng/mL, the patients will be in deep sedation and difficult to arouse [9]. Similarly, dexmedetomidine has a dose dependent effect on mean arterial pressure (MAP) and heart rate. Where intravenous dexmedetomidine was used as a sole sedative for children undergoing procedural sedation, the incidence of bradycardia given intravenously and intranasally was 16% and 14% respectively [10,11]. Given the concentration dependent effects of dexmedetomidine on hemodynamics and arousal, it may be more effective to combine dexmedetomidine with another drug to compensate for the disadvantages of dexmedetomidine sedation rather than to simply increase the dose. Ketamine (Ket),

a racemic nonbarbiturate cyclohexamine derivative that exerts its effects via noncompetitive antagonism to N-methyl-D-aspartate (NMDA) receptors, is one of the most widely used drugs in pediatric anesthesia. In subanesthetic doses, Ketamine has sedative and analgesic properties with the benefit of retaining airway reflexes and can be given via several routes, including intranasally [12,13]. In children, sedation takes effect after approximately 5-10 minutes with peak plasma concentration in 20 minutes. Its undesirable effects include nausea and vomiting, increased salivation, excitatory behavior and its hemodynamic effects namely high blood pressure, tachycardia, and high cardiac output [14-16]. Recent literature supports that dexmedetomidine provides a synergy with ketamine, which would be advantageous in enabling a decrease in dosing of both sedatives. A retrospective analysis by Yang et al., on pediatric patients undergoing procedural sedation with a combination of intranasal dexmedetomidine and ketamine, showed a sedation success rate of 93% with onset time of 15 minutes, lower rates of adverse effects, in particular, bradycardia or hypotension than those in previous studies of dexmedetomidine as sole sedative [17]. In 2019, Oriby compared the effects of combined intranasal dexmedetomidine and oral ketamine versus intranasal midazolam as sedative premedication for children undergoing dental procedures, the study results revealed the combination had significantly more satisfactory and rapid onset of sedation, with more postoperative analgesia and less postoperative shivering in comparison to midazolam [18]. The potential of dexmedetomidine to attenuate the sympathetic response, provide sedation and decrease emergence agitation are properties that may be favorable in its combination with ketamine. The combination of dexmedetomidine with ketamine has a pharmacologic rationale, as the two medications exhibit complementary pharmacologic effects. Though there have been reviews on the combined usage of Dexmedetomidine and Ketamine as premedication for procedural sedation, none have been published to date on its efficacy and safety with combined use solely via the intranasal route.

The general objective of this study is to compare the efficacy and safety of the combination of Dexmedetomidine and Ketamine administered via the intranasal route on sedation of children aged 0 to 12 years old prior to elective surgery or procedural sedation as compared to Intranasal Dexmedetomidine. The specific objectives are to determine differences in sedation onset time, incidence of satisfactory sedation at parent separation, incidence of satisfactory sedation at mask induction, recovery time and incidence of adverse events such as bradycardia, hypotension, hypoxemia, postoperative nausea and vomiting (PONV), nasal irritation and emergence agitation using combination of Dexmedetomidine and Ketamine administered

via intranasal route as compared to intranasal Dexmedetomidine.

METHODOLOGY

A systematic approach was used to identify publications that evaluated the efficacy and safety of a combination of intranasal dexmedetomidine and ketamine premedication in children. This systematic review and meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 and the Cochrane Review Methods [19]. Articles were lifted from the electronic databases of PubMed, Cochrane Library, Clinical Trials, Science Direct, Google Scholar and local databases such as Herdin Plus from its establishment until August 2023 and restricted only to studies written in English language. The search was conducted using the following MeSH terms: ("dexmedetomidine", AND "ketamine" OR "Ketodex") AND ("premedication" OR "sedation") AND ("intranasal" or "intranasally") AND ("pediatric" OR "child" OR "children) AND ("anesthesia") AND ("randomized trial" OR "randomized controlled trial" OR "RCT"). Additional articles were obtained via cross-referencing from selected articles.

Two reviewers independently identified all the studies using predefined selection criteria. A third reviewer arbitrated disagreements that occurred in the primary study selection. Studies were included in this meta-analysis if they satisfied the following criteria: (1) full text randomized controlled trials, (2) children aged 0 to 12 years old, (3) American Society of Anesthesiologists (ASA) physical status classification I-III, (4) scheduled for elective surgery or procedural sedation, (5) received as premedication a combination of dexmedetomidine and ketamine via the intranasal route. Exclusion criteria include (1) children over 12 years old, (2) ASA IV-V, (3) observational studies, case series, commentaries.

Studies derived from the different electronic databases were screened and checked for duplicates. After which, two researchers independently reviewed each of the titles and abstracts. In case of disagreements between two researchers, this was resolved by discussion. If the disagreement was not resolved, a third researcher was called in to serve as arbitrator. Full-text of all journals that met the eligibility criteria were retrieved for full-text review. Data collection was performed independently by two researchers using a data collection form in Microsoft Excel 2021.

The primary outcome measure of this study was the incidence of sedation success of a combination of intranasal dexmedetomidine and ketamine as compared to intranasal dexmedetomidine given alone. Secondary outcomes include sedation onset time, incidence of satisfactory sedation at parental separation, incidence of satisfactory sedation

sedation at parental separation, incidence of satisfactory sedation at mask induction, recovery time and the incidence of adverse events namely, bradycardia, hypotension, hypoxemia, nasal irritation, PONV and emergence agitation.

The risk of bias among included studies was performed independently by two researchers using the Cochrane risk of bias (RoB 2.0) tool, which considers the methods of random sequence generation, allocation concealment, blinding of participants and the outcome estimator, incomplete reporting of outcome data, selective reporting of outcomes and other sources of bias risk. Studies with more than one area of unclear or high risk of bias were excluded from the analysis.

All statistical analyses were conducted using the Cochrane Collaboration Review Manager Software (RevMan version 5.4.1). The study reports continuous data as mean differences and their associated 95% confidence intervals (CIs) with analyses using weighted mean differences (WMDs) determined via the inverse variance method. Binary outcomes are reported as risk ratio (RR) with 95% CI. Heterogeneity testing was performed using the □2 test and the I^2 statistic. In this study, an I^2 statistic >50% and a □2 test with P value <0.10 was considered significant to indicate statistical heterogeneity. Random effects model was used due to clinical heterogeneity among study variables of included researches, as population (cardiac vs non-cardiac patients) and procedure (e.g. surgical, diagnostic procedures) despite minimal statistical heterogeneity. Subgroup and sensitivity analysis was performed to account for other possible sources of heterogeneity, such as the results of included studies.

The protocol was submitted to PCMC Institutional Review – Ethics Committee for expedited approval prior to proceeding, which was granted exemption from ethics review last August 23, 2023. Data confidentiality was observed throughout the process of this analysis.

RESULTS

Initial search identified 443 articles, with 27 publications from research databases, 33 from online registries, 381 records from website search engines and 2 from citation searching. Among those derived from research databases and registries, 15 full manuscripts were screened after removing 18 duplicated articles and an additional 19 records after screening their titles and abstracts. Among these, 5 publications were identified as potentially relevant studies. Nine studies were excluded due to the following reasons: 4 had a different control group and 5 studies utilized different methods of drug administration. As to publications derived via a website search engine (i.e., Google Scholar), only 3 publications were deemed acceptable after screening for eligibility and duplicates.

Two of these, one of which was a proposal for an ongoing clinical trial, were not retrieved despite attempts to contact its study authors. Thus, only 1 study was included using this search strategy. In total, six studies were included in the meta-analysis (Figure 1). Risk of bias analysis for each included study are shown in Figure 2. Four studies were assessed as having low risk of bias and two studies were assessed as having unclear risk due to unspecified information on allocation concealment. Publication bias was not assessed as the funnel plots derived may be inaccurate due to the low number (i.e., <10) of included studies.

A total of 388 patients, with ages ranging from 1 month to 7 years old, scheduled for elective surgery or procedural sedation with American Society of Anesthesiologists (ASA) classification scores I-III were included in the study. All of the patients received as premedication via the intranasal route either a combination of dexmedetomidine and ketamine or dexmedetomidine alone. The characteristics of the included studies are summarized in Table 1.

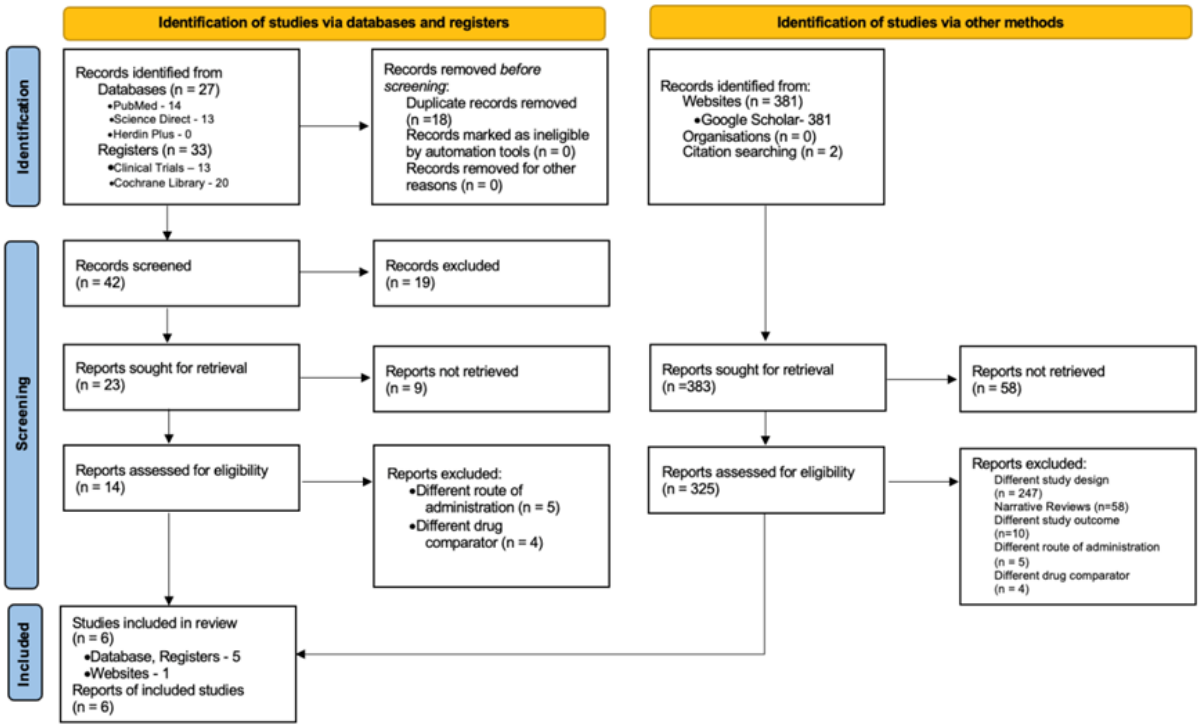
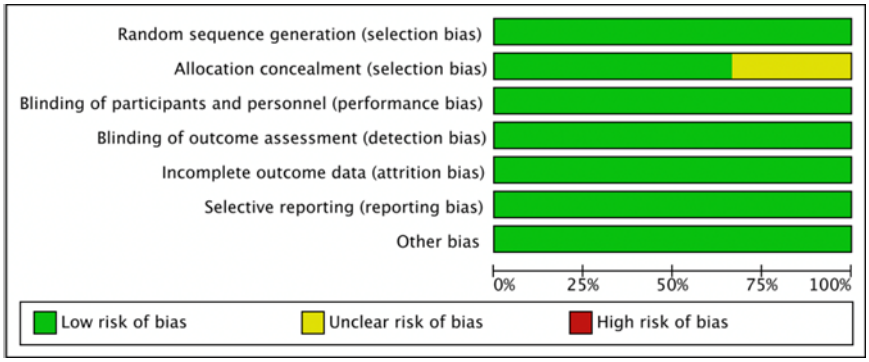


Figure 1. Flow Diagram of the literature search strategy



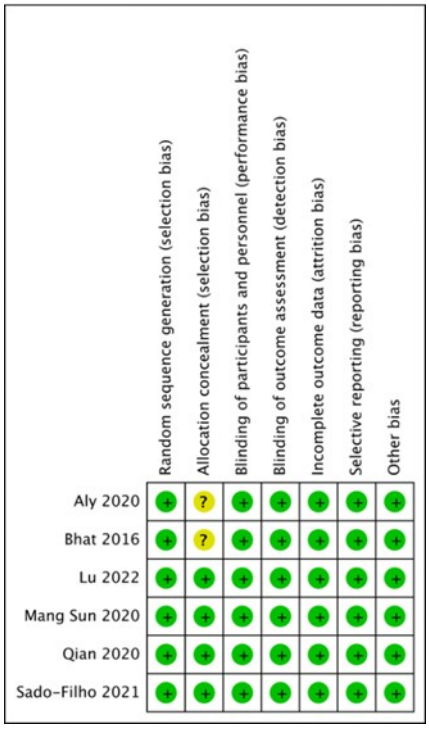


Figure 2. Cochrane Risk of Bias Assessment

Table 1. Characteristics of included studies

Primary Author	Year	N	Type of study	Age , ASA status, type of surgery	Inter-vention (Dose)	Com-parator	Primary Outcome	Secondary Outcome
Aly, A	2020	60	RCT	2-4 yrs. old, ASA I-III, for interven-tional cardi-ac catheter-ization	IN Dex (1mcg/ kg) + Ket (3mg/ kg)	IN Dex (2mcg/ kg)	Sedation success measured by child's behavior during venous cannulation	Onset of sedation, behavior at parental separation, propofol consumption during procedure, recovery time, incidence of postoperative agitation, adverse events
Bhat, R	2016	54	RCT	1-6 yrs. old, ASA I-II, for elective minor sur-gery	IN Dex (1mcg/ kg) + Ket (2mg/ kg)	IN Dex (1 mcg/ kg)	Level of sedation measured via 5 point sedation score	parental separation, mask acceptance, postoperative recovery, incidence of emergence agitation
Mang Sun, MM	2020	60	RCT	1 to 36 mos. old, ASA I-II, for transthorac-ic echocar-diography	IN Dex (2mcg/ kg) + Ket (1mg/ kg)	IN Dex (2mcg/ kg)	Change in hemodynamics (MAP, HR)	sedation success measured via MOAA/S. onset time, wake up time, discharge time, adverse events
Qian, B	2020	66	RCT	3 to 7 yrs. old, ASA I-II, for ton-sillectomy	IN Dex (2mcg/ kg) + Ket (2mg/ kg)	IN Dex (2mcg/ kg)	Sedation level assessed by Modified Observer Assessment of Alertness and Sedation (MOAA/ S) scale	sedation onset time, parental separation anxiety, acceptance of mask induction, emergence time, emergence delirium, postoperative pain intensity, length of PACU stay, adverse events

Table 1. Characteristics of included studies								
Sado-Filho, J	2021	88	RCT	1-7 yrs. old, ASA I-II, for dental restoration	IN Dex (2 mcg/kg) + Ket (1mg/kg)	IN Dex (2.5 mcg/kg)	Sedation success measured by children's behavior using OSUBRS	parental and dentist satisfaction, adverse events, recovery time
Lu, X	2022	60	RCT	1-6 yrs. old, ASA I-II, for lower abdominal or perineal surgery	IN Dex (1mcg/kg) + Ket (0.5mg/kg)	IN Dex (2mcg/kg)	Sedation success measured via Induction Compliance Checklist (ICC) scale	sedation success rate, preoperative anxiety scale score, time of reaching 2 points on the UMSS, parental separation anxiety scale, anesthesiologist satisfaction with induction based on VAS, emergence agitation scale, adverse effects

Of the six studies [20-25], five had available data on sedation success. There were a total of 319 patients with 159 in the intranasal dexmedetomidine – ketamine group and 160 in the intranasal dexmedetomidine group. Forest plot depicted as Figure 3 showed no difference in sedation success among patients premedicated with intranasal dexmedetomidine and ketamine as compared to intranasal dexmedetomidine alone (RR = 1.05; 95%CI = 0.97,1.13; P = 0.27, I^2 = 20%). As to sedation onset time, only two studies had available data. As depicted in figure 4, patients given a combination of intranasal dexmedetomidine and ketamine had faster sedation onset time compared to dexmedetomidine given alone (WMD = -7.17; 95%CI = -12.44, -1.89; P=0.008). Though substantial heterogeneity was noted to be significant (□2 = 7.56, I^2 = 87%, P=0.006), subgroup analysis was not performed due to the number of involved studies.

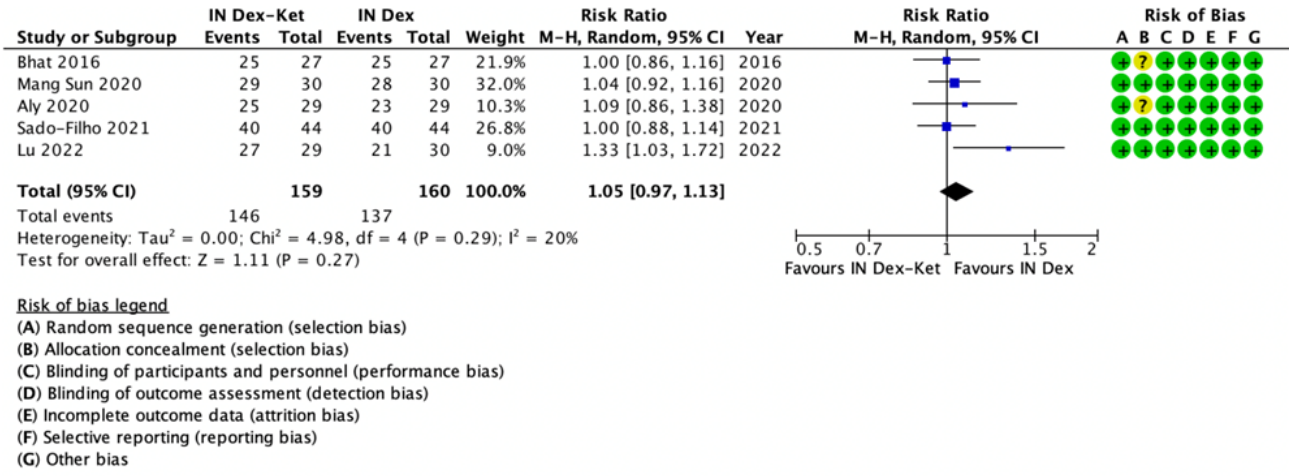


Figure 3. Incidence of sedation success

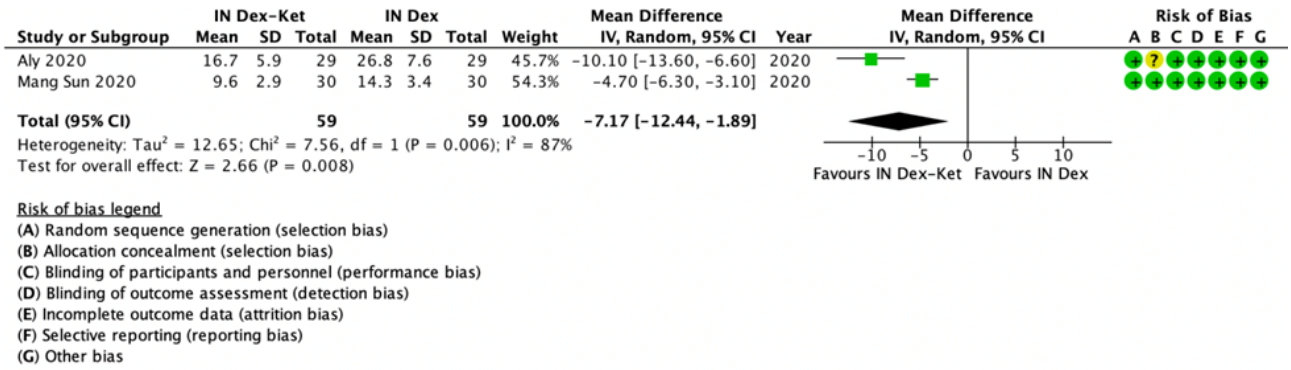


Figure 4. Sedation onset time

Satisfactory sedation at patient separation was reported in only 2 randomized controlled trials utilizing the Patient Separation Anxiety Score (PSAS). The study found no differences in satisfactory sedation at parent separation between intranasal dexmedetomidine and ketamine and dexmedetomidine alone (RR = 1.06; 95%CI = 0.97,1.15; P = 0.19) (Figure 5A). Similar to satisfactory sedation at parent separation, sedation status at mask induction was assessed using a 4 point Mask Acceptance Scale (MAS). Synthesis of data revealed patients premedicated with a combination of intranasal dexmedetomidine and ketamine were significantly sedated at mask induction as compared to those given dexmedetomidine alone (RR = 0.71; 95%CI = 0.53, 0.94; P = 0.02) (Figure 5B).

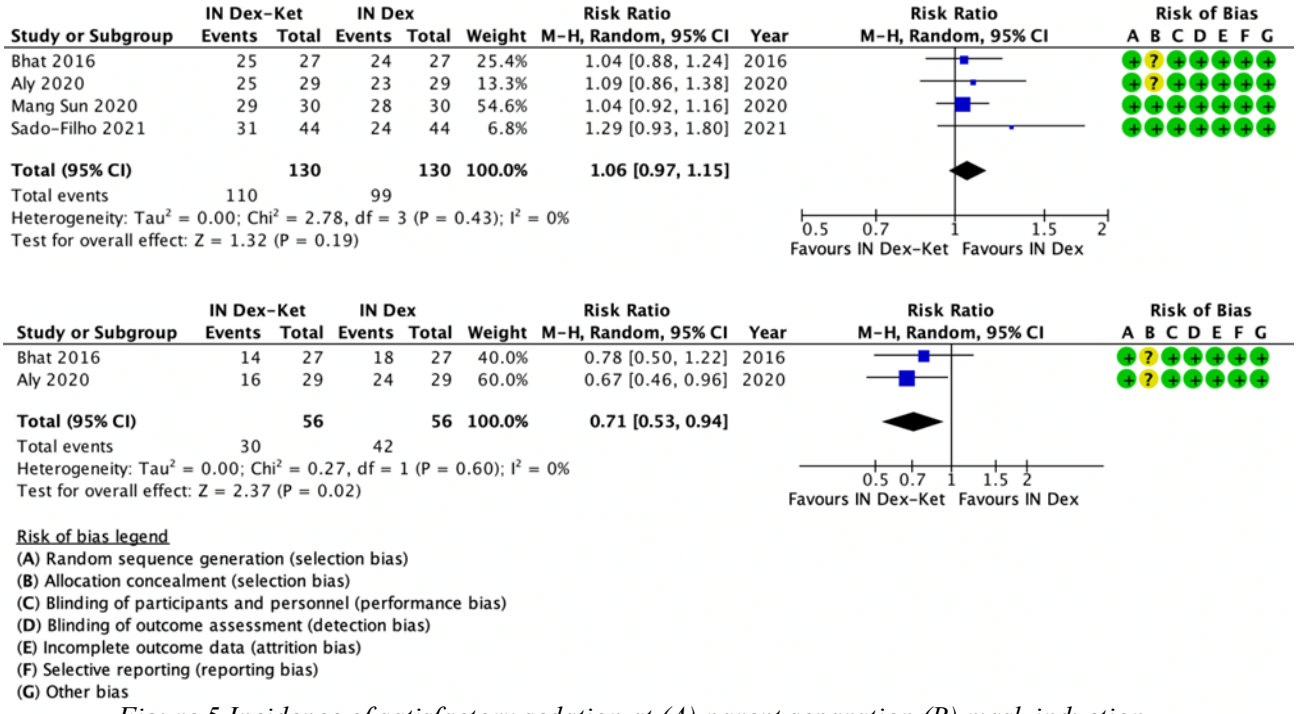


Figure 5 Incidence of satisfactory sedation at (A) parent separation (B) mask induction

Four trials reported the recovery time from premedication administration, however only 2 studies fulfilled this study's operational definition. Patients premedicated with intranasal dexmedetomidine and ketamine had faster recovery time compared to those given dexmedetomidine alone, however was not statistically significant (WMD = -0.84; 95% CI = -2.15,0.48; P=0.21; I^2 = 0%) (Figure 6).

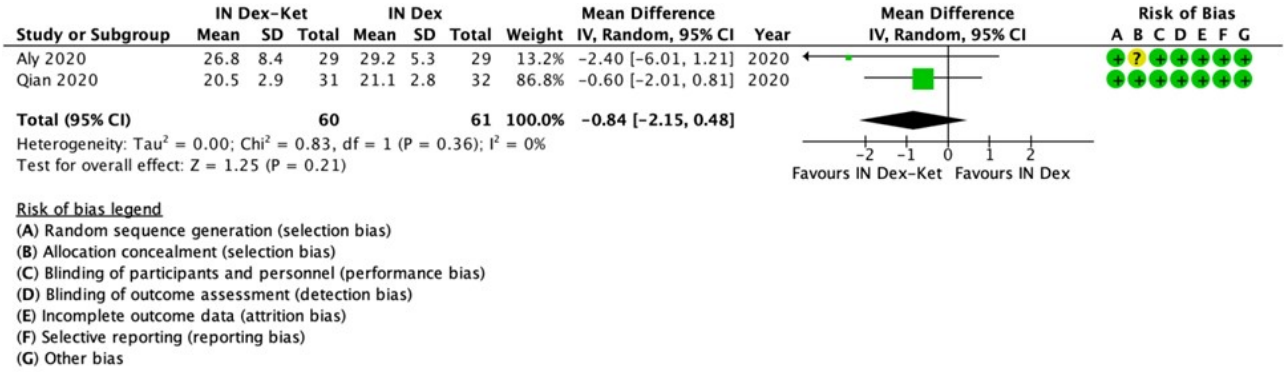
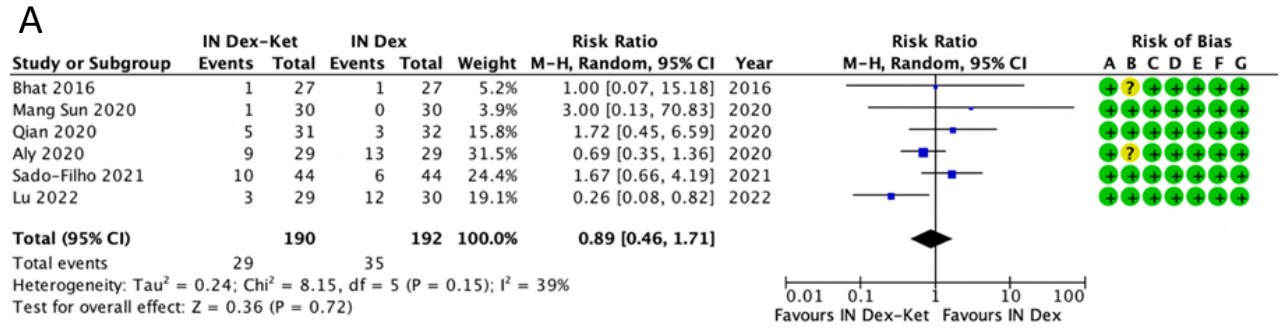


Figure 6. Recovery time

All six of the studies revealed the incidence of adverse effects of a combination of intranasal dexmedetomidine and ketamine as premedication as compared to intranasal dexmedetomidine alone. The forest plot in Figure 7A shows there is no difference on the likelihood of adverse events between intranasal dexmedetomidine and intranasal dexmedetomidine and ketamine given in combination (RR = 0.89; 95%CI = 0.46, 1.7; P=0.72; I^2 = 39%). A subgroup analysis of the different adverse effects associated with dexmedetomidine and ketamine use are shown in Figure 7B. There were no observed differences among both study groups as to the incidence of emergence agitation with the use of a combination of dexmedetomidine and ketamine (RR = 0.57; 95%CI = 0.22, 1.48; P=0.25; I^2=12%), and occurrence of postoperative nausea and vomiting (RR = 2.21; 95%CI = 0.51; 9.61; P = 0.29; I2=0%). All of the six included studies in the meta-analysis, noted no occurrence of bradycardia, hypoxemia, hypotension and nasal irritation, among all the study participants.



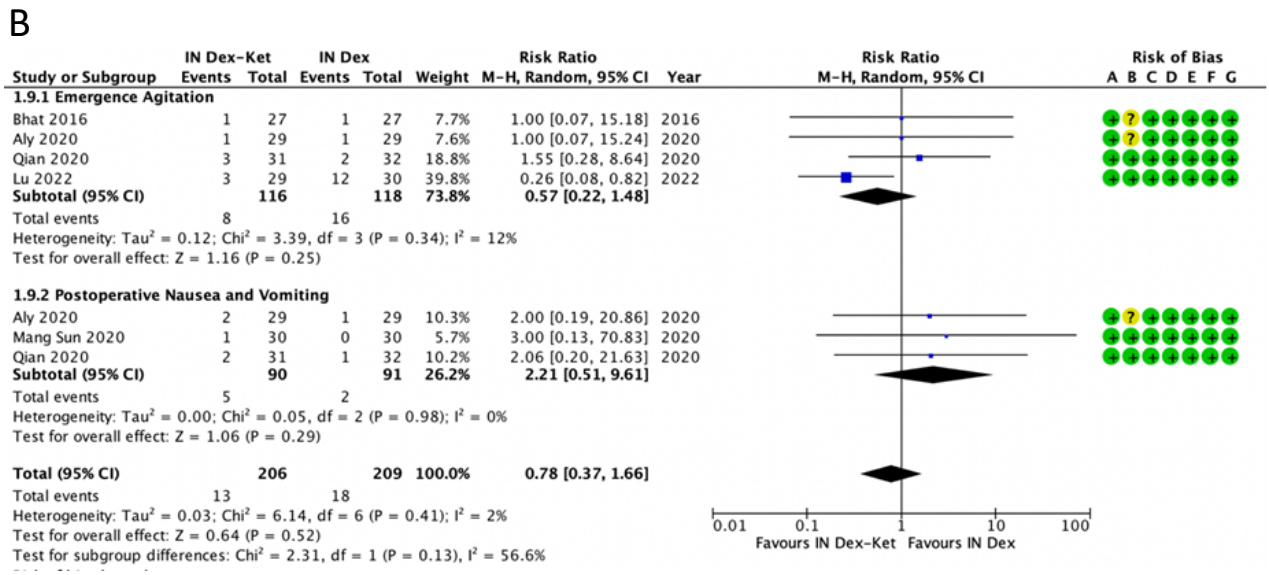


Figure 7. (A) Incidence of Adverse Events (B) Subgroup Analysis of Adverse Event

DISCUSSION

This meta-analysis showed that premedication for pediatric patients via the intranasal administration of a combination of ketamine and dexmedetomidine is as safe and efficacious as intranasal dexmedetomidine alone. Patients who were administered the combination drug achieved faster sedation onset time and smoother inhalational induction than intranasal dexmedetomidine alone without significantly prolonging recovery time or increasing clinically relevant adverse events.

Dexmedetomidine has been advocated as an alternative premedication in the field of pediatric anesthesia, given its sedative properties paralleling those of natural sleep, analgesia, and an anesthetic sparing effect with minimal respiratory depression [26,27]. As it leads to sympatholysis, it attenuates the cardiovascular and metabolic response in in response to surgical trauma. Despite its robust benefits, attention should be paid to the hemodynamic effects of the drug, among which, depending on dose administered and age group result in bradycardia and either hypotension (low doses with effect on presynaptic a2-a that generate vasodilation) or hypertension (use of high doses that activate postsynaptic a2-b receptors generating vasoconstriction) [28]. Yuen et al's studies on intranasal dexmedetomidine on the pediatric population reveal dexmedetomidine at a dose of 1 to 1.5 mcg/kg produced sedation in 45-60 minutes with median onset time of sedation 25 minutes and peaks in 90-105 minutes, with bioavailability as high as 82% [29,30].

Ketamine at subanesthetic doses, in addition to its ability to provide nearly all the requirements of anesthesia namely analgesia, immobility, amnesia and hypnosis, also has the beneficial qualities of producing bronchodilation, the ability to maintain airway reflexes and the sympathetic nervous system tone. When given intranasally among children it is safe and fast acting with sedation onset time after approximately 5-10 minutes and peak plasma concentration within 18± 13 minutes [31-33]. Ketamine interacts with multiple binding areas, including NMDA and non-NMDA glutamate receptors; nicotinic, muscarinic, cholinergic, adrenergic and opioid receptors. Due to its adrenergic effect, it leads to tachycardia, increasing cardiac output and blood pressure except in cases of catecholamine depletion, when it can cause a negative inotropic effect. Other potentially worrying effects are sialorrhea, nausea and psychomimetic effects [34-36].

When used together, dexmedetomidine can limit tachycardia, hypertension, salivation and restlessness on ketamine awakening. While the latter can prevent dexmedetomidine induced hypotension and bradycardia, in addition to speeding up the onset of sedation and maintaining airway patency. Several studies have shown similar results of increased sedation success, translatable to decreased parental separation anxiety and increased mask acceptance on induction with use of intranasal dexmedetomidine combined with ketamine. Yang et al did a retrospective analysis on the use of dexmedetomidine 2 mcg/kg combined with ketamine 1mg/kg intranasally for procedural sedation with a success rate of 93% [17]. Zanaty et al. compared nebulized ketamine, nebulized dexmedetomidine and their combination and reported more satisfactory sedation at venipuncture when combining the two drugs than using either drug alone [37]. Similarly, Qiao reported that adding oral ketamine 3 mg/ kg to intranasal dexemedetomidine 2mcg/kg resulted in successful sedation at venous cannulation in 80.5% of patients given the combination drug 30 minutes prior to eye surgery as compared to dexmedetomidine (47%) alone [38].

Of the studies included in this meta-analysis, only 2 had relevant study values on sedation onset time, coincidentally involving children diagnosed with acyanotic congenital heart disease (CHD). Though the rapid onset of action via the intranasal route is attributed to direct nose to brain delivery by bypassing the blood-brain barrier via the olfactory and trigeminal nerve pathways, a third route is via a peripheral pathway, where drugs enter the systemic circulation via vascular absorption and subsequently cross the blood-brain barrier [39]. The study populations on RCTs done by Aly and Mang Sun et al., could explain faster sedation onset as the shunting of blood among children with CHD affects drug pharmacokinetics [21,25]. In patients whose lesions are characterized by left to right shunting and increased pulmonary

pulmonary blood flow, drug reaches the brain at the same time as it would if no shunt existed. In lesions with right to left shunting, where systemic venous blood bypasses the pulmonary circulation, the drug reaches the brain sooner than predicted [40]. In part, the age of the patient population of both studies done by Aly (2.9±0.8 yrs old) and Mang Sun et al (10.6 ± 8.05 months old) may also explain the difference in sedation onset time as children do not follow a simple linear growth process with drug distribution dependent upon body composition. Lipophilic drugs, as with dexmedetomidine and ketamine, have a relatively larger volume of distribution in infants compared with older children owing to their higher comparative levels of fat (22.4% at 12 months vs 13% at 15 years) [41].

Increased sedation success at mask induction in patients premedicated with a combination of intranasal dexmedetomidine and ketamine may be attributed to the higher dose of ketamine used in the involved RCTs study population. In this meta-analysis, included studies assessing mask acceptance score involved patients who underwent procedures where greater patient stimulation is expected namely interventional cardiac catheterization, minor surgery and tonsillectomy. This may explain the choice of larger ketamine dose, as several studies support though dexmedetomidine is effective as a sole premedicant, the application of a face mask or attempts at venipuncture have resulted in patients waking and resulting in difficulties with anesthesia induction [42].

The faster recovery time of children in the dexmedetomidine-ketamine group is noteworthy, though had no statistical significance in the study. Dexmedetomidine has a rapid distribution phase with a distribution half-life of six minutes. In children under 2 years of age, the volume of distribution in the stable phase is high indicating that higher doses are required to obtain the stable phase; but its elimination half-life is prolonged, which can lead to high drug accumulation over time [21]. The use of ketamine as an adjunct, decreases the dose of dexmedetomidine necessary to produce its sedative effects. The difference impacts scheduling, efficiency and finances especially in the office -based or outpatient setting. Though the efficacy of the two sedative regimens in managing the patient's behavior is similar, a single drug which can provide satisfactory and better length of recovery is desirable for the patient and the institution.

The incidence of adverse events are decreased when children are premedicated with a combination of dexmedetomidine and ketamine, though the synthesis of studies revealed no significant differences among study groups. Emergence agitation (EA) with sevoflurane has been found in 18-80% of patients in previous studies [36]. Emergence Agitation after inhalational anesthesia, as was done on all 4 studies who included this outcome in this meta-analysis, can be due to inadequate pain relief,

preoperative anxiety, the type of postoperative environment and type of surgery. Ketamine, used solely, has been associated with dysphoria and hallucinations too. A study by Kim et al found that low dose infusion of dexmedetomidine reduces EA after desflurane anesthesia [43]. This may explain the negligible risk of EA among patients premedicated with a combination of dexmedetomidine and ketamine. The likelihood of PONV is decreased due to the potentially anti-emetic effect of dexmedetomidine as a-2 receptors are found in gastric and intestinal mucosa, although this outcome requires further investigation [44,45]. The absence of hemodynamic instability (bradycardia, hypotension) and hypoxemia in all the included studies may well be explained by the complementary effects of dexmedetomidine and ketamine. Those results are in accordance with the results of Tammam who used a combination of intramuscular dexmedetomidine and ketamine and Qiao et al, who used a combination of intranasal dexmedetomidine and oral ketamine [30].

There are some limitations of the present study. First, clinical heterogeneity among studies such as premedication dose, type of procedure, comorbidities and different age ranges were identified. Varying measurements and scales precluded further synthesis of data, which was compounded by the small number of patients in this study, significantly affecting weight and outcomes. The intervention effects of small clinical trials with incomplete allocation concealment are at risk of being overestimated. Although all the studies in the meta-analysis used a random allocation method and objectively measured outcome date, caution is needed when interpreting these results.

No local studies on dexmedetomidine or ketamine premedication in children were found on literature search, understandably due to the absence of FDA approval among the pediatric population for the former. With increasing use though off-label and its safety and efficacy established as evidenced by numerous studies, in future, once approved by requisite authorities, high quality RCTs, favorably those with large sample sizes are still needed to evaluate the safety of a combination of intranasal dexmedetomidine and ketamine premedication.

Conclusion

This meta-analysis demonstrates that premedication via intranasal administration of a combination of ketamine and dexmedetomidine is as safe as intranasal dexmedetomidine alone. The combination of dexmedetomidine and ketamine achieved faster sedation onset time and smoother inhalational induction than intranasal dexmedetomidine alone without increasing clinically relevant adverse events. Prudence in selection of patient population and procedure type should be exercised in application of drug doses due to the paucity of data to standardize such intervention.

REFERENCES

1. Kain Z, Caldwell-Andrews A, Maranets I, Mcclain B, Mayes LC, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg 2004; 99:1648 -1654

2. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015 Aug;115(2):171-82. doi: 10.1093/bja/aev226. PMID: 26170346.

3. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; **93**: 382– 94.

4. Lin R, Ansermino JM. Dexmedetomidine in paediatric anaesthesia. BJA Educ. 2020 Oct;20(10):348-353.

5. Li A., Yuen V.M., Goulay-Dufaÿ S. Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine. Br J Anaesth. 2018;120:960–968.

6. Anntila M, Penttila J, Helminen A, Vuorilehto L, Scheinin H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. Br J Clin Pharmacol 2003; 56:69-3.

7. Tervonen M, Pokka T, Kallio M, Peltoniemi O. Systematic review and meta-analysis found that intranasal dexmedetomidine was a safe and effective sedative drug during paediatric procedural sedation. Acta Paediatr. 2020 Oct;109 (10):2008-2016

8. Jun J.H., Kim K.N., Kim J.Y., Song S.M. The effects of intranasal dexmedetomidine premedication in children: a systematic review and meta-analysis. Can J Anesth. 2017;64:947–961.

9. Ebert TJ, Hall JE, Barney JA, et al. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000;93:382–394

10. Mason K.P., Zurakowski D., Zgleszewski S.E. High dose dexmedetomidine as the sole sedative for pediatric MRI. Paediatr Anaesth. 2008;18:403–411

11. Miller, J.W., Divanovic, A.A., Hossain, M.M. et al. Dosing and efficacy of intranasal dexmedetomidine sedation for pediatric transthoracic echocardiography: a retrospective study. Can J Anesth/J Can Anesth **63**, 834–841 (2016).

12. Tsze, D.S., Steele D.W., Machan, J.T.,Akhlaghi, F. and Linakis, J.G.Intranasal Ketamine for Procedural Sedation in Pediatric Laceration Repair: A Preliminary Report. Pediatr. Emerg. Care 2012; 28(8): 767-770

13. Scheier, E, Siman A and Balla . Intranasal Ketamine Proved Feasible for Pain Control in Paediatric Care and parental Support was High.Acta Paediatr. 2017; 106:1702

14. Diaz JH. Intranasal ketamine preinduction of paediatric outpatients. Paediatr Anaesth1997;7:273-8.

15. White PF, Way WL, Trevor AJ. Ketamine–its pharmacology and therapeutic uses.Anesthesiology 1982;56:119-36.

16. Liu J, Du M, Liu L, et al. Sedation effects of intranasal dexmedetomidine combined with ketamine and risk factors for sedation failure in young children during transthoracic echocardiography. Paediatr Anaesth 2019;29:77-84.

17. Yang F, Liu Y, Yu Q, et al. Analysis of 17 948 pediatric patients undergoing procedural sedation with a combination of intranasal dexmedetomidine and ketamine. Paediatr Anaesth 2019;29:85-91.

18. Oriby ME. Comparison of Intranasal Dexmedetomidine and Oral Ketamine Versus Intranasal Midazolam Premedication for Children Undergoing Dental Rehabilitation.Anesth Pain Med 2019;9:e85227.

19. Moher D, Liberati A, et.al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PLos Med 6(6): e1000097. Doi:10.1371/journal.pmed1000097

20. Bhat R, Santhosh MC, Annigeri VM, Rao RP. Comparison of intranasal dexmedetomidine and dexmedetomidine-ketamine for premedication in pediatrics patients: A randomized double-blind study. Anesth Essays Res. 2016 May-Aug;10(2):349-55.

21. Aly AA. A Comparison of intranasal ketamine, intranasal dexmedetomidine, and their combination as premeication in pediatric patients undergoing cardiac catheterization. Res Opin Anesth Intensive Care. 2020;7:232-40.

22. Qian B, Zheng W, Shi J, Chen Z, Guo Y, Yao Y. Ketamine Enhances Intranasal Dexmedetomidine-Induced Sedation in Children: A Randomized Double- Blind Trial. Drug Des Devel and Ther. 2020;14:3559-65.

23. Sado-Filho J, Correa-Faria P, et al. Dexmedetomidine compared to a Combination of Intranasal Dexmedetomidine with Ketamine for Sedation of Children Requiring Dental Treatment: A Randomized Clinical Trial. Journal of Clinical Medicine 2021;10:2840.

24. Lu X, Tang L, Lan H, Li C, Lin H. A Comparison of Intranasal Dexmedetomidine, Esketamine or a Dexmedetomidine-Esketamine Combination for Induction of Anaesthesia in Children: A Randomized Controlled Double-Blind Trial. Frontiers in Pharmacology 2021;12:808930.

25. Sun M, Liu H, Yu, Q, Liu Y, Zhang J, Lei, Y, et al. A Comparison of Intranasal Dexmedetomidine and Dexmedetomidine-Ketamine Combination Sedation for Transthoracic Echocradiography in Pediatric Patients with Congenital Heart Disease: A Randomized Controlled Trial. Cardiothorac Vasc Anesth 2020;000:1-6.

26. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015; 115: 171-182.

27. Hsu YW, Cortinez LI, Robertson KM, et al. Dexmedetomidine pharmacodynamics: Part I: crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology. 2004; 101: 1066-1076.

28. Hammer GB, Drover DR, Cao H, et al. The effects of dexmedetomidine on cardiac elec- trophysiology in children. Anesth Analg. 2008; 106: 79-83.

29. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in paediatric anaesthesia: A double-blinded randomized controlled trial. *Anesth Analg.* 2008;106:1715–21.

30. Yuen VM, Hui TW, Irwin MG, Yao TJ, Wong GL, Yuen MK. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. *Anaesthesia.* 2010;65:922–9.

31. Jaume Canet, Jorge Castillo. Ketamine: A Familiar Drug We Trust. Anesthesiology. 2012; 116: 6-8.

32. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain and critical care. Anesth Essays Res. 2014; 8: 283-290.

33. Diaz JH. Intranasal ketaminepreinduction of paediatric outpatients. *Paediatr Anaesth*. 1997; **7**: 273-278.

34. Malinovsky JM, Servin F, Cozian A, et al. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. *Br J Anaesth.* 1996; **77**: 203-207.

35. Hustveit O, Maurset A, Oye I. Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. Pharmacol Toxicol. 1995; 77: 355-359.

36. Kress HG. Actions of ketamine not related to NMDA and opiate receptors. Anaesthesist. 1994; 43: 15-24.

37. Zanaty OM, El Metainy SA. A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. Anesth Analg. 2015 Jul;121(1):167-171.

25. Sun M, Liu H, Yu, Q, Liu Y, Zhang J, Lei, Y, et al. A Comparison of Intranasal Dexmedetomidine and Dexmedetomidine-Ketamine Combination Sedation for Transthoracic Echocradiography in Pediatric Patients with Congenital Heart Disease: A Randomized Controlled Trial. Cardiothorac Vasc Anesth 2020;000:1-6.

26. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015; 115: 171-182.

27. Hsu YW, Cortinez LI, Robertson KM, et al. Dexmedetomidine pharmacodynamics: Part I: crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology. 2004; 101: 1066-1076.

28. Hammer GB, Drover DR, Cao H, et al. The effects of dexmedetomidine on cardiac elec- trophysiology in children. Anesth Analg. 2008; 106: 79-83.

29. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in paediatric anaesthesia: A double-blinded randomized controlled trial. *Anesth Analg.* 2008;106:1715–21.

30. Yuen VM, Hui TW, Irwin MG, Yao TJ, Wong GL, Yuen MK. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. *Anaesthesia.* 2010;65:922–9.

31. Jaume Canet, Jorge Castillo. Ketamine: A Familiar Drug We Trust. Anesthesiology. 2012; 116: 6-8.

32. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain and critical care. Anesth Essays Res. 2014; 8: 283-290.

33. Diaz JH. Intranasal ketaminepreinduction of paediatric outpatients. *Paediatr Anaesth*. 1997; **7**: 273-278.

34. Malinovsky JM, Servin F, Cozian A, et al. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. *Br J Anaesth.* 1996; **77**: 203-207.

35. Hustveit O, Maurset A, Oye I. Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. Pharmacol Toxicol. 1995; 77: 355-359.

36. Kress HG. Actions of ketamine not related to NMDA and opiate receptors. Anaesthesist. 1994; 43: 15-24.

37. Zanaty OM, El Metainy SA. A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. Anesth Analg. 2015 Jul;121(1):167-171.

38. Qiao H, Xie Z, Jia J. Pediatric premedication: a double-blind randomized trial of dexmedetomidine or ketamine alone versus a combination of dexmedetomidine and ketamine. BMC Anesthesiol. 2017 Nov 29;17(1):158.

39. Tai J, Han M, Lee D, Park IH, Lee SH, Kim TH. Different Methods and Formulations of Drugs and Vaccines for Nasal Administration. Pharmaceutics. 2022 May 17;14(5):1073.

40. ST Verghese & RS Hannallah (2008) A nesthesia for non-cardiac surgery in children with congenital heart disease, Southern African Journal of Anaesthesia and Analgesia, 14:1, 84-86,

41. Tobias JD, Berkenbosch JW. Initial experience with dexmedetomidine in paediatric-aged patients. *Pediatric Anesthesia* 2002; **12**: 171–5.

42. Tazeroualti N, De Groote F, De Hert S, De Villé A, Dierick A, Van der Linden P. Oral clonidine vs midazolam in the prevention of sevoflurane-induced agitation in children. A prospective, randomized, controlled trial. *Br J Anaesth.* 2007;98:667–71

43. Kim J, Kim SY, Lee JH, Kang YR, Koo BN. Low-dose dexmedetomidine reduces emergence agitation after desflurane anaesthesia in children undergoing strabismus surgery. *Yonsei Med J.* 2014;55:508–16.

44. Vutskits L, Sall JW. Reproducibility of science and developmental anaesthesia neurotoxicity: a tale of two cities. Br J Anaesth. 2017; 119: 451-452.

45. Duan X, Li Y, Zhou C, et al. Dexmede- to- midine provides neuroprotection: impact on ketamine-induced neuroapoptosis in the developing rat brain. Acta Anaesthesiol Scand. 2014; 58: 1121-1126.

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