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Editorial for Issue 2, 2018

Welcome to the 2nd issue of The PCMC Journal for 2018!

This issue showcases a good mix of the types of researches that our trainees carry out in the hospital, from meta-analyses, normative studies, clinical trials, prospective analytical studies, and a health policy study as well.

Of course, these papers were chosen for having won in the various research fora that the hospital organizes each year. But we also hope that these researches can stimulate policy changes at the level of the individual health practitioner, and the institution as well. Under the guidance of their research mentors, our trainees have produced relevant and meaningful researches that can have significant impact on our everyday practice. Thus we are proud to bring you and disseminate these outstanding research outputs!

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General Guidelines

1. One original and two duplicate manuscripts should be submitted. An electronic copy must also be submitted on a floppy or compact disc. The manuscript should be typed double-spaced throughout with 1 ¼ cm (½ inch) paragraph indentation, using only one side of each 22x28 cm (8 ½ x 11 inch) opaque bond paper with 3-cm margins (1 ¼ inch) all around. Preferred font styles and sizes are: Times New Roman 12, Arial 11, Tahoma 11, & Verdana 11.

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.

3. References should be selective and pertain directly to the work being reported.

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Title Page

1. The title should be as concise as possible. Include only the full names of the authors directly affiliated with the work starting with the first name, middle initial if any, and last name. The highest educational attainment or title of the authors should be included as an attachment whenever appropriate; name and location of no more than three institutional affiliations may be included.

2. If the paper has been presented in a scientific in a scientific program or convention, provide a footnote giving the name, location and the date of the meeting.

Abstract

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.

Text

1. Generally, the text should be organized consecutively as follows: Introduction, Materials and Methods, Results and Discussion (and Conclusion).
2. All References, tables, figures and illustrations should be cited in the text, in numerical order.
3. Even if commonly employed, all abbreviations should be spelled out once, the first time they are mentioned in the text, followed by the abbreviations enclosed in parentheses. Subsequently, the same abbreviations may be used instead of the long names.
4. All measurements and weights should be in System International (SI) units.
5. Acknowledgements to individuals/groups of persons, or institution/s should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

References

1. References in the text should be identified by Arabic Numerals in enclosed parentheses on the same line as the preceding sentence.
2. References should be typed double-spaced on a separate sheet. They should be numbered consecutively in the order by which they are mentioned in the text.
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5. A maximum of three authors per article can be cited; beyond that,"et al". is added
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Figures or graphs should be identified by Roman Numeral/s with titles and explanations underneath. The numbers should correspond to the order in which the figures/graphs occur in the text. It is recommended that figures/graphs also be submitted as image files (preferably as .jpeg or.gif files) of high resolution. All identifying data of the subject/s or patient/s under study such as name, case numbers, etc., particularly in case reports should be removed.

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EFFICACY OF VIRGIN COCONUT OIL SUPPLEMENTED-MILK FEEDING IN AUGMENTING WEIGHT GAIN AMONG VERY LOW BIRTH WEIGHT PRETERM INFANTS: A META-ANALYSIS

ALISSA D. BARCELONA, MD, MICHAEL M. RESURRECCION, MD

ABSTRACT

BACKGROUND: Nutritional status is crucial in neonatal survival, especially among the Very Low Birthweight (VLBW) preterm infants. They have low nutrient reserves with increased metabolic needs and immature gut system. Several studies have proven the efficacy of medium-chain triglycerides (MCT) as good source of calories among preterm infants. However, such is not commercially available. Virgin coconut oil (VCO) has the most concentrated content of MCTs, hence a possible source of MCT.

OBJECTIVES: This review aims to determine the efficacy of VCO-supplementation to milk feeding in augmenting weight gain among very low birthweight preterm infants.

METHODS: Pubmed (1975- September 2016), Cochrane Central Register of Controlled Trials (The Cochrane Library, September 2016), HERDIN (1966-September 2016), Google Scholar (September 2016), and https://clinicaltrials.gov (last searched September 2016) were thoroughly searched. Manual search in reference and citation lists of the eligible studies, and list of abstracts from the Philippine Pediatric Society was also reviewed. Only randomized controlled trials comparing VCO-supplemented milk versus standard care in weight gain among very low birthweight preterm infants were included. The author reviewed each study's quality and extracted data on weight gain. Weighted mean differences with 95% confidence intervals were reported. Risk of biases among studies were also evaluated.

RESULTS: Three randomized controlled trials involving 290 infants were included. All trials were of good quality with relatively low heterogeneity (39%), and low risk of biases. Overall, infants receiving VCO-supplemented milk feeding had statistically significant weight gain compared to those given non-fortified milk (Mean difference 5.31, 95% CI: 3.83 to 11.93).

CONCLUSIONS: Virgin coconut oil is effective in augmenting weight gain among very low birthweight preterm infants.

RECOMMENDATIONS: Small trials were used in this review, and a single multicenter randomized controlled trial would be ideal to further establish these findings.

KEYWORDS: "virgin coconut oil," "coconut oil," "medium chain triglyceride," "preterm," "very low birthweight," "weight gain"

INTRODUCTION

Nutritional status is a crucial element in neonatal survival, especially among the Very Low Birthweight (VLBW) preterm infants. Due to their prematurity, these infants are at high risk for the development of overwhelming infections and serious medical complications during their stay in the hospital. For this reason, it is of utmost importance that aggressive nutritional management be rendered beginning at birth.

Breastfeeding and human breast milk remains the gold standard of nutrient source for

all infants, including the VLBW preterm. Unfortunately, preterm human milk has been found inadequate for the special demands of the preterm infants, hence, the advent of milk supplements. Milk supplements may be in the form of protein, carbohydrate, fats, or a combination of these. Among these, fats provide the highest energy density, especially when given in the form of medium chain triglycerides. Medium chain triglycerides (MCTs) are notably advantageous among the preterm infants as these are readily digested, absorbed, and utilized in spite of the relative pancreatic insufficiency and gut immaturity of these patients. However, MCTs are not readily available in the Philippines, such that the use of virgin coconut oil as food supplement has gained popularity in its stead. Virgin coconut oil (VCO) is found to be the richest natural source of MCT, comprising of 48% lauric acid. This saturated fatty acid is believed to be responsible for most of its medical uses, including antimicrobial effects. Few studies on the use of VCO in weight augmentation among children had been done in the country, and all showed promising results.

Nutritional buildup among VLBW preterm infants is a primary concern among pediatricians. With the previous studies on MCTs and its alternative, VCO, revealing promising results, proving that it is effective in augmenting weight gain among this specialized subgroup of patients would greatly impact the practice of neonatal care in this country. Moreover, VCO is readily available and affordable in the Philippines. Further evidence on its efficacy could justify its use and applicability in the nutritional management of preterm infants.

Nutrition is a vital aspect in the care and management of neonates, particularly among preterm infants. Infants born premature are characterized with low nutrient reserves in a state of elevated metabolic rates, high evaporative loss, and immature gastrointestinal systems.[1-2] Such characteristics put these infants at high risk for nutritional compromise and its complications, that early and aggressive nutritional intervention is deemed synergistic to their survival.[1]

It is a standard practice in neonatal care to initiate parenteral nutrition in the first days of life among low birthweight and very low birthweight infants. This is to achieve the required caloric intake to prevent protein catabolism, while promoting growth and development comparable with intrauterine growth of a fetus of the same gestational age. Although replication of intrauterine growth is difficult to attain, the American Academy of Pediatrics recommend a weight gain of 15-20g/kg/day, an increase of 1cm/week in length, and 0.5-1cm/week in head circumference as goals for adequacy in nutrition.[1,2,4]

On the other hand, initiation of enteral feeding in the earliest possible time is crucial in the preservation of the structural and functional integrity of the gastrointestinal tract. However, rapid advancement of enteral feeding among very low birthweight preterm infants poses a risk for the development of necrotizing enterocolitis (NEC). Hence, cautious trophic feeding is initially recommended, a technique found to result in better feeding tolerance, improved levels of gut hormones, and in turn facilitating early progression to full enteral feedings.[1]

Despite recent advancements in milk formulation, human breast milk remains the gold

standard source of nutrition among term and preterm infants.[1,4] It provides both nutritional and immunologic benefits to the growing child, which no other milk formula could replicate.[1,2] However, nutrient levels in preterm human milk remain below the recommended levels, with varying composition through time. For these reasons, preterm human milk is usually supplemented with human milk fortifier (HMF), which increases its protein, energy and mineral content. Aside from HMF, other oral supplements may be given with varying caloric densities and inherent benefits and caveats.[1] These include supplemental protein, fat, carbohydrates or a combination of these. Studies have shown that increasing the protein content of the milk would result to greater, if not the greatest, increments in weight and length among VLBW and ELBW infants, even approximating their reference intrauterine anthropometrics after four weeks.[5, 6] However, high protein intake would result to positive nitrogen balance and elevated renal osmotic load, which may have deleterious neurologic and renal seqeuela among preterm infants. Another means of enhancing caloric value of infant feeding is the use of carbohydrate supplements.[1,2] However, due to the low disaccharidase levels in preterm infants, carbohydrate load of more than 50% of the dietary intake would result to gastrointestinal upset such as flatulence, colic, and diarrhea.[1]

Fats have the highest energy density among the three, with low osmolarity and rapid absorption. It comprises 40-50% of calories in human milk or formula. Fats are generally provided as a mixture of long chain triglycerides (LCT) and medium-chain triglycerides (MCT). LCT is a good source of polyunsaturated fatty acids and essential fatty acids, which make up 75-80% of all fatty acids in human milk. However, due to the relative pancreatic insufficiency and decreased bile salt excretion in early life, absorption of LCTs are impaired in this subset of the population. On the other hand, MCTs are readily absorbed even with gut immaturity. This is due to the presence of lingual and gastric lipases which hydrolyze MCTs to free fatty acids, allowing direct absorption, transport and cellular utilization without the need of micelle formation, chylomicrons, and carnitine.[1,2,7] It is for this reason that MCT supplementation in preterm milk holds great promise.

Several studies have been done in the past five decades on the use of MCTs as milk supplement for augmenting weight gain among preterm infants, albeit with conflicting results. Most studies would show incremental weight with MCT, however, not all would reach statistical significance.[5,8-13] A meta-analysis was done in 2008 which compared the effect of high-MCT with low-MCT formula on short-term weight gain among healthy VLBW preterm infants. This included eight randomized controlled trials with an average study duration of one week of full enteral feeds. However, results of this review revealed that there was no significant difference in the short-term growth parameters between high and low MCT formula.[15] On the other hand, a local study done in 1999 at the Philippine General Hospital revealed positive results in weight augmentation, with shortened hospital stay among preterm LBW infants supplemented with MCT.[14] The controversy surrounding the evidence on its efficacy for weight enhancement among preterm infants hinders its niche in standard management of neonatal nutrition. But different institutions consider it as a good option, hence, its continued use. However, MCTs are not commercially available in our country. Nevertheless, an alternative source of MCT in the form of coconut oil is of abundance in the Philippines.

Virgin coconut oil is the most concentrated natural source of medium chain fatty acid, which comprises nearly two-thirds of its saturated fat content. The main fatty acids in

coconut oil are lauric acid (48%), capric acid (7%), and caprylic acid (8%). Its high lauric acid content is said to be responsible for majority of its health benefits.[16-18] In vitro studies revealed conversion of lauric acid to monolaurin in the small intestines, demonstrating antibacterial, antiviral, and antifungal properties.[18] In a study done in India in 1992, results concluded that VCO as source of MCT supplementation in preterm milk was effective in augmenting weight gain among VLBW infants.[7] In the recent years, few researches in the Philippines had been done on the efficacy of VCO-supplementation in improving nutritional status of both VLBW preterm infants, and school-aged children. All studies revealed positive incremental weight in VCO-supplemented group versus the control group, with greater significance found among VLBW preterm infants.[19-26] Moreover, VCO was also found to shorten duration of hospital stay by decreasing the time to reaching the discharge weight, thereby decreasing the chance to develop nosocomial infections.[19,26] However, similar to the international studies on MCT-supplemented milk, results were also inconsistent, hence, this review was conducted.

The general objective of this study was to determine, by meta-analysis, the efficacy of virgin coconut oil supplemented milk feeding in augmenting weight gain among very low birth weight preterm infants.

METHODOLOGY

This meta-analysis only included randomized controlled trials (RCTs) of very low birthweight infants weighing ≤1500 grams assigned to virgin coconut oil (VCO)-supplemented breast milk or formula versus placebo or standard care. The studies included infants born less than 37 weeks with a birth weight of less than or equal to 1,500 grams, who were able to tolerate enteral feeding. Trials which included infants with co-morbid conditions such as congenital anomalies, inborn error of metabolism, and those who underwent surgical procedures, were excluded from this review. The studies included compared virgin coconut oil supplementation in preterm milk formula or breast milk to placebo or to standard care. Trials which made use of other fortifiers together with coconut oil or compared VCO supplemented milk with other weight gain enhancers were excluded. This review only measured the difference in weight gain between those who received VCO-supplemented milk versus those infants who received standard care.

The study made use of thorough literature review via the internet on available publicly accessible scientific journal databases such as PUBMED (1975- September 2016), Cochrane Central Register of Controlled Trials (The Cochrane Library, September 2016), HERDIN (1966-September 2016), Google Scholar (September 2016), and on-going trials in https://clinicaltrials.gov (last searched September 2016). Using the keywords "virgin coconut oil," "coconut oil," "medium chain triglyceride," "preterm," "premature," "very low birthweight," and "weight gain," a thorough literature search was performed. Manual search in the reference and citation lists of the eligible studies, and list of abstracts from the Philippine Pediatric Society was also conducted to look for other relevant unpublished studies.

The review author (ADB) and a research assistant used the titles and abstracts to already exclude trials which clearly did not meet our inclusion criteria. The common reasons encountered for exclusion of the articles from the electronic search were: non-human studies, the non-use of virgin coconut oil; measurement of outcomes which did not include weight gain.

Full articles were retrieved for further assessment if the abstracts indicated that there was a possibility that the study fulfilled the inclusion criteria. The two reviewers then independently selected the trials for inclusion in

the review from the list of potentially eligible trials. Seven potentially eligible papers were identified and reviewed. Four published and three unpublished articles were retrieved.

The author of this review was the one who contacted the trial authors for clarifications hence, was not blinded to their identity.

Two reviewers, (i.e. author and independent researcher) independently extracted the data and assessed trial quality. Missing data were requested from the trial authors.

A meta-analysis tool Review Manager version 5.3 downloaded from the Cochrane website was used in the meta-analysis. Data concerning the details of the trials included in the review using a specially designed data extraction form of "The Cochrane Collaboration" (Cochrane Library, 2009) were extracted. This included the following information:

- **General Information**: published/ unpublished, title, authors, year of publication;
- **Trial characteristics**: method of randomization and allocation concealment, blinding (participants, clinician, outcome assessor, loss of participants to follow up, intention to treat analysis;
- **Intervention**: dose, frequency of VCO supplementation and non supplementation with breast milk/expressed breast milk (EBM) or pre term milk formula
- **Participants characteristics**: preterm, very low birth weight, excluding those with congenital anomalies, inborn error of metabolism, and those who underwent surgical procedures
- **Outcomes**: weight increase (grams/day)
- **Results**: continuous data were expressed as weighted mean differences (WMD) and standard deviation (SD), use of intention to treat analysis.

Difference or conflicts in data extraction was resolved by discussion and consensus of the reviewers.

Using the Review Manager program, tests for heterogeneity and sensitivity were done. Quantification of the effect of heterogeneity were assessed by means of I^2.

Both positive and negative results were reported for all studies to be included. Each study to be included in the review was evaluated based on the following indicators of risk of bias:

- Adequate sequence generation
- Allocation concealment
- Blinding of participants, personnel, and assessors
- Incomplete data
- Selective outcome reporting

RESULTS

The search through PUBMED, Cochrane Library and Google Scholar only yielded two potential studies (Vaidya 1992; Singhania 1989), however, upon further assessment, only one study complied with the inclusion criteria for this review (Vaidya, 1992). The local search through the HERDIN yielded only two published pilot studies on VCO and infant weight gain (Amante 2005; Banzali, 2007). Unfortunately, both were excluded since the former study was subsequently completed and reported by Mantaring 2007, and the latter was an experimental, non-concurrent control study. Manual search in the reference and citation lists of the eligible studies, and list of abstracts from the Philippine Pediatric Society yielded three unpublished studies, two of which were included in this review (Mantaring 2007, Perez 2007).

A total of three studies were included in this review (Mantaring 2007, Perez 2007, Vaidya 1992). There was a total of 290 subjects who were included in this review. One hundred

and fifty-one (151) subjects were allocated the VCO supplemented milk feeding, while 139 subjects served as control, receiving non-fortified milk. The mean study size was 97 participants (range of 48 to 161 subjects). One study was published in 1992 and was conducted in India (Vaidya 1992), while the other two unpublished studies were conducted in the Philippine General Hospital (Mantaring 2007, Perez 2007). It was clarified with the authors that the studies had distinct and non-overlapping subjects.

The mean birthweight and age of gestation for the control and treatment groups in all trials had no significant difference. The mean birthweight of VCO group included in this review was 1304g (range of 1215.1±220.3 to 1399±46.7), while that in the control group was 1324g (range of 1238.8±29.9 to 1437±63.8). The mean age of gestation of the VCO group was 32.03 weeks (range of 31.8±2.2 to 32.21±1.15), while that in the control group was 32.34 weeks (range of 32.12±3.2 to 32.6±2.1).

All three studies included weight gain as either a primary or a secondary outcome, together with other anthropometric parameters. The study of Vaidya in 1992 made use of the brand "Parachute," by the Marico Industries Ltd, manufactured in Bombay, comprising of 43-49% MCT of total fat. Fortification of feeds in this study was done by adding 2 drops of VCO per 5 mL milk feeding. On the other hand, the two studies done locally made use of the brand "Oleum" whose composition had been documented by the Philippine Institute of Pure and Applied Chemistry[27]. The dose for both studies was 0.5 ml per ounce of milk given.

There were four studies that were excluded from this review. The study of Amante 2005 was a pilot study which was eventually completed and reported by Mantaring in 2007, which was the one included in the review. Another study was done in the Philippine Children's Medical Center in 2005 (Banzali 2005) was also excluded since it was an experimental non-concurrent study. The control group used in the trial was a cohort of infants admitted a year prior to the treatment group. Another local study done in The Medical City (Mendoza 2007) was also excluded since the comparator used was karo syrup. An earlier study in 1989 (Singhania) was also excluded as it used a combination of virgin coconut oil and sugar as the intervention, and included infants weighing up to 1750g as its subjects.

Randomization

All three trials were randomized controlled trials which made use of computer generated randomization software or the table of random numbers. However, the study of Vaidya in 1992 failed to elaborate on the exact method of randomization applied. There is an overall low risk of selection bias.

Allocation

The two local studies reported allocation concealment with the use of sealed, opaque brown envelopes. However, in the study done by Vaidya, the risk was unclear as there was no mention of the allocation method applied. Nevertheless, the baseline characteristics of the study subjects in both groups were not statistically significant, hence, it may be prudent to assume that allocation bias is generally low among these trials.

Blinding

The two local studies specified blinding of the physicians and outcome assessors during the study period. However, no blinding method was mentioned in the study done by Vaidya. Regardless of the unclear risk, the author did not consider such to greatly impact the risk for performance or detection bias.

Incomplete outcome data

In the study of Mantaring, 40 subjects who developed sepsis or died were excluded in the analysis of weight gain as the authors considered the presence of sepsis to have a "large influence on growth." The study of Vaidya excluded 5 subjects who died shortly after enrollment to the study, with one infant developing necrotizing enterocolitis (NEC). The reviewers agreed with the exclusion of these subjects from the trials as any comorbidity such as sepsis, NEC, and subsequent death may be a potential source of bias in data analysis.

Selective Reporting

Both significant and non-significant results were reported by the studies.

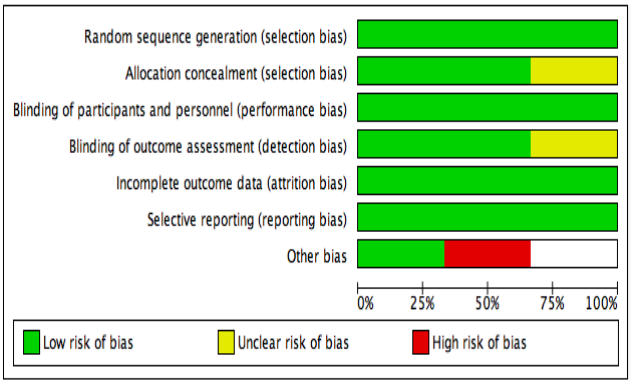

Figure 1. Risk of Bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

Effects of Interventions

The three trials included in the review consistently revealed an increasing trend in the weight of the infants given VCO-supplemented milk feeding. In the study of Mantaring 2007 and Vaidya 1992, mean weight gain between groups were statistically significant, favoring VCO-fortified milk feeding. However, the study by Perez in 2007 did not reach statistical significance, albeit, the trend also favored VCO-supplementation. Combination of the three trial results revealed statistically significant difference (Mean difference 5.31, 95% CI: 3.83 to 11.93) in the positive effect of virgin coconut oil in augmenting weight gain among very low birthweight preterm infants. Heterogeneity of the three trials was at 39% which may not be significant.

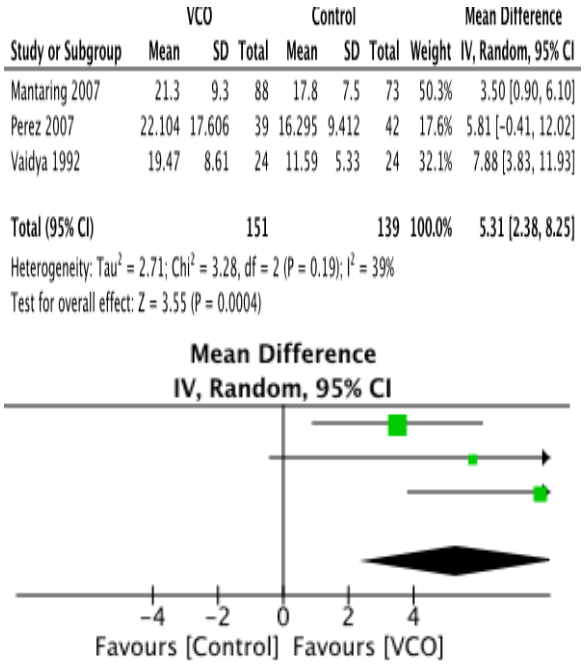

Figure 2. 1 Comparison of weight gain in VCO fortified milk group versus Control group, outcome: 1.1 Weight gain

DISCUSSION

Nutrition is a vital aspect in the care and management of neonates, particularly among preterm infants which comprise 10% of all babies born. Premature infants have low nutrient reserves with elevated metabolic rates, high evaporative loss, and immature gastrointestinal systems.[1-2] These put them at high risk for nutritional compromise and its complications, that early and aggressive nutritional intervention is crucial to their survival.[1]

Human breast milk remains the gold standard source of nutrition.[1,4] It provides both nutritional and immunologic benefits to the growing child, which no other milk formula

could replicate.[1,2] However, nutrient levels in preterm human milk remain below the recommended levels, with varying composition through time. For this reason, preterm milk is usually fortified with supplements to enhance its caloric density. Oral supplements include carbohydrate, protein and fats. Among these, fats have the highest energy density and is provided as a mixture of long chain- and medium-chain triglycerides. However due to the relative pancreatic insufficiency, decreased bile salt excretion and gut immaturity, MCTs are favored over LCTs. This is due to the presence of lingual and gastric lipases which hydrolyze MCTs to free fatty acids, allowing direct absorption, transport and cellular utilization without the need of micelle formation, chylomicrons, and carnitine.[1,2,7] Unfortunately, MCT oil is not available in the market, hence, alternative sources would be beneficial. Virgin coconut oil (VCO) contains two-thirds of its fat as medium chain triglycerides and is therefore, a good alternative source of MCT as milk supplement. Moreover, it is widely available and affordable in the Philippines.

Based on the results of this review, VCO supplementation of breastmilk or preterm milk augmented weight gain among very low birthweight preterm infants. The trials included in this review were of good quality. Although overall bias was relatively low, the trials were relatively small and two of which came from the same center. Therefore, the benefit of VCO in augmenting weight gain documented in this trial may have been spurious. A single, large, multicenter trial is ideal to accurately measure its benefit.

CONCLUSIONS

Implications for practice

There is statistically significant difference between VCO-supplemented milk feeding among preterm very low birthweight infants compared to those given non-fortified milk formula or breastmilk. Despite the small number of trials reviewed, the trend of positive weight gain was consistent in all trials, although one trial did not reach statistical significance. The results of this review provides supportive evidence in the practice of VCO supplementation among this special population.

Implications for future research

This review only involved three trials of small subject population. Further research ideally involving a single, multicenter randomized controlled trial would be highly recommended to further establish the benefit of VCO-supplementation in augmenting weight gain among preterm infants. Moreover, subgroup analyses based on different weight categories and age of gestation may provide a more comprehensive analysis of the role of VCO in weight augmentation among neonates.

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EFFECT OF PHILHEALTH ENROLMENT IN THE DELAY IN DISCHARGE OF PEDIATRIC PATIENTS WITH ACUTE ILLNESS IN A GOVERNMENT TERTIARY HOSPITAL

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ABSTRACT

BACKGROUND: Philhealth, the national health insurance program, aims to reduce out-of-pocket expenditures by subsidizing hospital admission expenses. A possible determinant of its success is the timeliness of management and prevention of discharge delay.

OBJECTIVES: To determine the effect of Philhealth enrollment on the timeliness of discharge of patients with acute illness in a government tertiary hospital

METHODS: A retrospective cohort study involving 98 patients (49 Philhealth members and 49 non-Philhealth members) was done. Data including age, sex, admitting diagnosis, social service classification, and type of Philhealth membership, were collated from the database of patients from the admitting section. Reasons for delay in discharge and number of days delayed from discharge point were obtained. Comparison of baseline characteristics was analyzed using independent t-test for quantitative variables, and Fisher's exact test for qualitative variables. Association between PhilHealth coverage and hospital delay was analyzed using logistic regression analysis.

RESULTS: Discharge delay is 3 times more likely to occur among non-Philhealth members as compared to the Philhealth group. Other variables were not significantly associated with discharge delay.

CONCLUSIONS: Discharge delay is significantly associated with non-membership to Philhealth. Further investigation through focus group discussions with patients' families may be done to uncover other possible causes for discharge delay.

INTRODUCTION

Hospital length of stay has been used as an indicator of efficiency of hospital resource utilization [4, 14]. Although it is largely affected by disease severity and other non-patient factors, it has reflected how proficiently the hospital processes are carried out from the time of admission to discharge. Needless to say, any delay in such processes ultimately leads to prolonged hospital stay.

Hospital length of stay has been unnecessarily prolonged by delay in discharge. [5]. Such administrative dilemma of many hospitals is translated to bed unavailability, which in turn, leads to longer waiting times for patients at the emergency room or outpatient department to be admitted in the wards, ultimately delaying the delivery of health care to the patients. Hence, proper discharge planning, vis-à-vis, identifying and addressing the impediments to timely discharge should be done in every hospital admission.

Financial barrier is only one of the factors identified to contribute to extension of patients' hospital stay. However, in the Philippine setting, it may be deemed as the major consideration as far as delays in discharge are concerned. The "fear of incurring a significant financial burden for health care or falling into a 'medical poverty trap' can cause ill individuals to either delay or refrain from seeking essential medical services " [11]. The same rationale may explain to some extent, the delays encountered in performing necessary procedures and administering essential medications in the in-patient setting. Moreover, patients who delay consult for any condition are more likely to present with more severe manifestations and complications as compared to those who seek healthcare early into the disease. The size of out-of-pocket payments varied widely, hence beneficiaries are uncertain about how much they will have to pay from their own pockets until they receive the bill [11]. As a result, the patient and/or his family may need more time to procure funds that would cover for expenses incurred above the insurance coverage. This translates to additional time, more often days of hospital stay beyond the point of discharge. Hence, a reliable source of funding expedites both the admission and the discharge process.

The National Health Insurance Program embodied by the Philippine Health Insurance Corporation (Philhealth), is the government's effort to have a universal healthcare coverage for all Filipinos in order to eliminate finances as a stumbling block for health utlization. Since Philhealth is able to cover the expenses for laboratory work-up and medications, utilization of its benefits reduces the financial burden of patients. However, since majority of the health expenditure still comes from out-of-pocket resources, the effect of having Philhealth coverage on the health outcomes is yet to be established. Therefore, this study aims to determine the effect of Philhealth benefit availment in the timeliness of discharge of patients admitted for acute conditions.

This study will highlight the advantage of Philhealth enrolment and availing its benefits during hospital admissions. The results of this study would also help determine whether enrolment of patients to Philhealth contribute to maximization of the hospitals resources, particularly bed turnover. Also, this study may be able to elucidate other bottlenecks in the discharge planning process, which may be discussed and addressed in succeeding studies.

Rather than a mere event, discharge can be viewed as a process which involves clinical, financial, legal and administrative and recordkeeping aspects [6]. A delay in discharge can be a reflection of bottlenecks in the process, which could be improved.

Particular interest has been placed on the length of hospital stay as an indirect measure of discharge delay and a parameter of health resource efficiency. It is the most common measure of how resources are used to produce health care [3]. A number of studies have investigated factors affecting patient's hospital length of stay including patient factors, physician factors, hospital factors and source & type of payment [1, 13]. Each of these factors have been shown to contribute to over- or under-hospitalization of patients, both status have their disadvantages. Nevertheless, the degree to which each factor influences the length of hospital stay is yet to be determined.

Under-hospitalization occurs when the patient is prematurely discharged from the hospital. It has been observed to sometimes result from cost-containment strategies but could lead to unsatisfactory outcome [1]. For instance, patients who are discharged prior ascertainment of recovery could rebound to their ill state due to inadequately treated conditions. In the setting of

infectious diseases, insufficiently given antibiotics could lead to drug resistance which poses a problem during readmission. On the other hand, prolonged hospitalization carries the disadvantage of higher cost and increased risk of nosocomial infections and iatrogenic complications [1]. In this light, a timely discharge has always been the target of an efficient hospital management. Timely discharge may be defined as being sent home from the hospital on the same day that a discharge order is made.

There have been a number of studies done to determine the factors affecting the length of hospital stay and causes of delay in discharges. Nonetheless, such researches are limited to foreign data. To date, no investigation has been made on the causes of delay in discharge of patients admitted in hospitals in the Philippines.

Philhealth is a "single-fund social health insurance that covers families, wherein the primary member and his dependents (declared children below 21 and parents above 65) can avail of the in-patient and outpatient PhilHealth benefits" [8]. In the study by Quimbo et al. in 2008, Philhealth support rates in the study hospitals average only 30% [7]. Data lifted from the Asia Pacific Observatory on Health Systems and Policies published in 2013, showed that majority of the health expenditure still comes from out-of-pocket sources. Although funds from Philhealth increase through time, it is still far from its target of 30% coverage of total national health expenditure [15].

Given this statistic, it is expected that a lesser number of poor, sick Filipinos, particularly children are able to access health care in times of illness, primarily because of financial limitations. This poses a challenge to the health sector given that hospitalized children without insurance or other source of health funding has increased mortality because of higher disease severity [8]. Also, based on the study of the Children's Health Insurance Program (CHIP), it was found that children who receive health insurance from the government were "more likely than uninsured children to receive well-child care, see a specialty doctor, avail of dental care service and be fully immunized" [8]. In the same way, a Philippine study by the Quality Improvement Demonstration Study (QIDS) showed that low-income children that have Philhealth coverage had greater long-term health improvements compared to those without health insurance [8].

Conversely, it was also found that the length of hospital stay influences the decision to avail Philhealth benefits in that, patients are more likely to make use of their Philhealth accounts to pay for hospital expenses if they were admitted for a longer period of time (average of 5 days) [8]. However, the length of confinement in the said study was used as a determinant of disease severity rather than a marker of hospital resource efficiency. Hence, another conclusion made from the same investigation is that, Philhealth benefits are more of use to those with more morbid conditions.

Objectives of the Study

General Objective

To determine the effect of Philhealth enrollment on the timeliness of discharge of patients with acute illness in our institution

Specific Objectives

1) To present the demographic profile of patients who have utilized Philhealth benefits during their admission

2) To demonstrate how many patients stayed more than 1 day after being given a send home order
3) To determine how many patients who have Philhealth accounts overstayed

4) To identify other reasons for delay in discharge of patients with acute illness

METHODOLOGY

A retrospective cohort study was done to determine which among those children who were admitted for acute illness were enrolled and availed of Philhealth benefits and were discharged timely.

The sample population was randomly selected from the database of admitted patients from January 2016 to June 2016. All private patients were excluded. Those patients who have chronic illness as co-morbidities (i.e. all forms of malignancy, cardiac conditions, neurologic conditions) as well as neonates will be excluded. However, those patients who are admitted for acute exacerbations of a chronic illness are included (i.e. bronchial asthma).

Using NCSS-PASS 2013, the minimum sample size requirement is at least 98 based on the percentage of uninsured patients with hospital delay = 32.2% [15] and odds ratio= 4.51 [12] with level of significance= 5% and power= 80%.

The service patients were classified as to having Philhealth membership or not. From the list of patients with Philhealth, 49 were randomly selected. The same number was randomly selected from the list of non-Philhealth patients. All patients who are enrolled at the beginning of the study, except those who expired, were analyzed at the end of the study regardless of outcome (i.e. acute illness which complicated during admission).

The demographic profile (age, sex), the acute condition for which the patient was admitted, the social service classification and the Philhealth membership type were taken from the patient database from the Admitting section. The discharge delay form was duly accomplished based on such data.

A list of discharge clearances during the time period of the study was obtained from the Social Services Unit. From such list, each patient included in the study was cross-referenced to determine delay in discharge. If the patient was not in the list, the patient was considered able to go home on the day the discharge order was made. On the other hand, if the patient's name is on the discharge clearance list, the number of discharge clearances was noted. This was noted in the discharge delay form. The number of discharge clearances was equivalent to the number of days that the patient's discharge was delayed from the time the order for discharge was made. The reason for the delay is also noted in the discharge clearance list provided by the Social Service Unit. Moreover, fund sources (PCSO, DSWD, etc.) for settling the hospital bill of patients who were unable to go home at the discharge point were recorded in the said document.

The protocol underwent approval of the Institutional Review Board (IRB) prior to execution. The primary investigator had no conflict of interest in conducting this study. Permission from the departments from which data were collected (Medical Records, Social Service, Admitting section and Philhealth section) was sought in order to access the charts and other records of the patients. The patients' identity was not disclosed in the publication of the results of this research. To ensure patient confidentiality during data processing, the patients were number codes so as to avoid revealing their identity. The research s carried

out in accordance to the guidelines stated in the Good Clinical Practice as per Global Health Network.

Data analysis was performed in Stata SE version 13. Quantitative variables were summarized as mean and standard deviation, while qualitative variables were tabulated as frequency and percentage. Comparison of baseline characteristics was analyzed using independent t-test for quantitative variables, and Fisher's exact test for qualitative variables. Association between PhilHealth coverage and hospital delay was analyzed using logistic regression analysis. The level of significance was set at 5%.

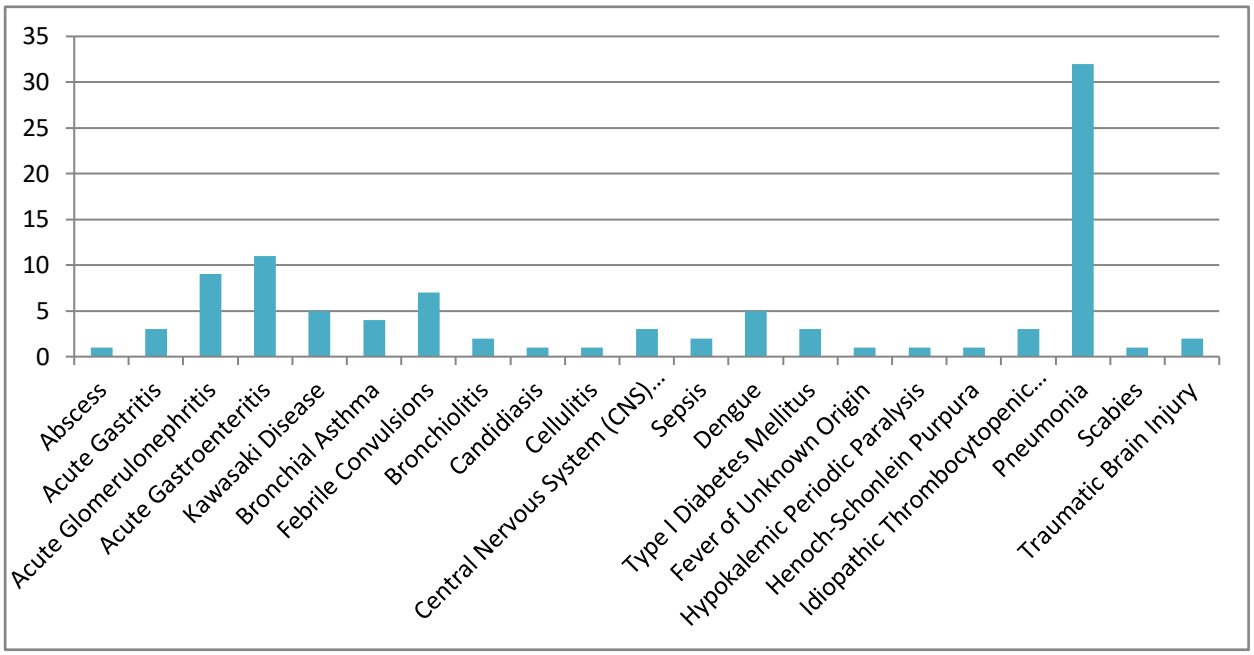
RESULTS

There are 3,302 patients who were admitted at the service wards from January – June 2016. Of these patients, 2,845 or 86% were enrolled to Philhealth, while the remaining 457 or 14% were non-Philhealth members. There were a total of 98 patients included in the study, 49 are enrolled in Philhealth while the remaining are non-Philhealth members. Approximately 45% of the patients belong to the 1 – 4 years old age group. Majority of the patients included in the study are females, comprising 62% (Table 1). The most common conditions of patients included in the study are pneumonia (32%), acute gastroenteritis (11%) and acute glomerulonephritis (9%). This finding is reflective of the hospital-wide data, which also shows these conditions to be the most prevalent diagnoses of admitted patients (Figure 1)

Table 1. Demographic Profile of Subjects with Philhealth and Non-Philhealth

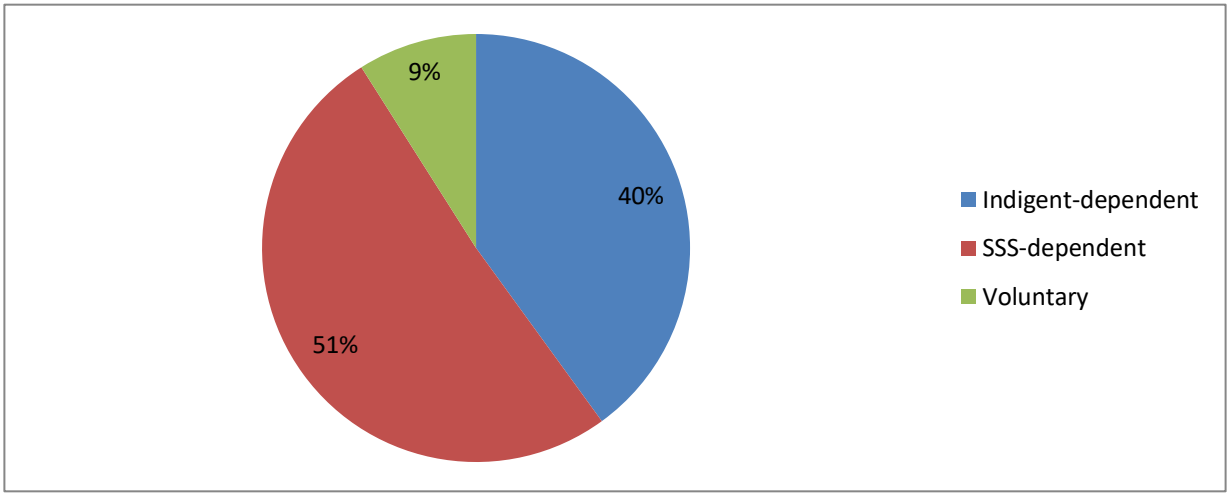
	With Philhealth (n = 49)	**Without Philhealth (n = 49)**	**p-value**
Age			
1 mo – 11 mos	13 (26.53%)	15 (30.61%)	
1 – 4 years old	26 (53.06%)	18 (36.73%)	0.332
5 – 9 years old	4 (8.16%)	10 (20.41%)	
10 – 13 years old	3 (6.12%)	4 (8.16%)	
14 – 18 years old	3 (6.12%)	2 (4.08%)	
Sex			
Male	19 38.78%)	18 (36.73%)	1.00
Female	30 (61.22%)	31 (63.27%)	
Social Service Classification			
C1	0 (0%)	1 (2.04%)	
C2	15 (30.61%)	8 (16.33%)	
C3	34 (69.39%)	40 (81.63%)	0.152

Figure 1. Acute Conditions of Patients in the Study.



Based on the social service classification, most of the patients (75%) are classified as C3, indicating that a considerable number of patients belong to the lower income bracket. However, it is of note that there are more patients in the C3 group who do not have Philhealth. This contrasts with the other social service classification group (C2), which shows that there are more patients who are enrolled to Philhealth than those who are non-members. Further classification of the Philhealth group based on the membership type showed that the most common membership type is the SSS-dependent type comprising 51% of the said group (Figure 2), while indigent-dependent members and those who have voluntary contributions consist 40% and 9%, respectively.

Figure 2. Distribution of Patients with Philhealth based on Membership Type



The characteristics of enrolled patients such as age, sex and acute illness for which they are admitted were analyzed against discharge delay so as to identify other contributory factors. However, none of them demonstrated any significant association. However, analyzing Philhealth enrolment against delay in discharge showed that non-membership to Philhealth is a risk factor for delay in discharge, in that those without Philhealth are 3 - 4 times more likely to experience delay in discharge (OR 3.6, p-value = 0.03) compared to those with Philhealth (Table 2). Comparing the number of days delayed between Philhealth and non-Philhealth groups, there is no significant difference in the number of days delayed (1 vs. 1.33 days). On the average, those who experience delay in discharge stay in the hospital for 1-2 days after being given the discharge order.

Table 2. Discharge Delay among Study Patients.

	With delay (n = 16)	**Without Delay (n = 82)**	**P-value**
Age			
1 mo – 11 mos	3 (18.75%)	25 (30.5%)	
1 – 4 years old	9 (56.3%)	35 (42.7%)	
5 – 9 years old	0 (0%)	14 (17.1%)	0.08
10 – 13 years old	3 (18.75%)	4 (4.88%)	
14 – 18 years old	1 (6.25%)	4 (4.88%)	
Sex			
Male	7 (43.7%)	30 (36.6%)	0.58
Female	9 (56.3%)	52 (63.4%)	
Acute Illness			
Abscess	0 (0%)	1 (1.22%)	
Acute Gastritis	0 (0%)	3 (3.66%)	
Acute Glomerulonephritis	0 (0%)	9 (10.98%)	
Acute Gastroenteritis	2 (12.5%)	9 (10.98%)	
Kawasaki Disease	0 (0%)	5 (6.10%)	
Bronchial Asthma	0 (0%)	4 (4.88%)	
Febrile Convulsions	3 (18.75%)	4 (4.88%)	
Bronchiolitis	0 (0%)	2 (2.44%)	
Candidiasis	0 (0%)	1 (1.22%)	
Cellulitis	0 (0%)	1 (1.22%)	
Central Nervous System (CNS) Infection	0 (0%)	3 (3.66%)	
Sepsis			
Dengue	1 (6.25%)	1 (1.22%)	0.59
Type I Diabetes Mellitus	1 (6.25%)	4 (4.88%)	
Fever of Unknown Origin	1 (6.25%)	2 (2.44%)	
Hypokalemic Periodic Paralysis	0 (0%)	1 (1.22%)	
Henoch-Schonlein Purpura	1 (6.25%)	0 (0%)	
Idiopathic Thrombocytopenic Purpura			
Pneumonia	0 (0%)	1 (1.22%)	
Scabies			
Traumatic Brain Injury	0 (0%)	3 (3.66%)	
	7 (43.75%)	25 (30.49%)	
	0 (0%)	1 (1.22%)	
	0 (0%)	2 (2.44%)	
Philhealth Membership			
With Philhealth	4 (25%)	45 (54.9%)	0.03
Without Philhealth	12 (75%)	37 (45.1%)	

Table 3. Non-Philhealth Sources of Funding Among Patients with Delay

Source of Funding	With Philhealth (n = 4)	Without Philhealth (n = 12)
Out-of-pocket	4 (100%)	10 (83%)
PCSO	0 (0%)	1 (8.3%)
DSWD	0 (0%)	1 (8.3%)

All patients who experienced delay in discharge identified financial constraint as the reason for delay. The patients' discharges were facilitated by securing funds out-of-pocket and from government agencies such as the Philippine Charity Sweepstakes Office (PCSO) and Department of Social Welfare and Development (DSWD). For the Philhealth group, all patients who experienced delay utilized out-of-pocket resources to fund their hospital bill. Similar findings were seen in the non-Philhealth group - 83% of those who had delay in discharge used out-of-pocket resources to pay for their hospital bill. Other sources of funding identified in this study were PCSO and DSWD (Table 3).

DISCUSSION

Delay in discharge contributes to the cascade of administrative concerns of hospitals, especially in the setting of resource scarcity. Discharge delays have been shown to increase the cost of treatment and even aggravate the patients' outcome (15). In the study by Gaughan et al., the cost of delay in discharge is identified as both financial and clinical. The hospital tend to unnecessarily spend resources for a patient who is deemed clinically fit for discharge by allotting a bed which could have been occupied by another patient who has a greater need for medical service. Its clinical implication is also note-worthy as patients who experience delay in discharge may acquire hospital-associated infections, leading to a prolonged hospital stay than expected.

Studies have been made in an attempt to elucidate the factors contributing to discharge delays so as to adequately address them. Most researches conclude that majority of discharges are delayed due to medical causes (awaiting laboratory results, managing complications, awaiting consultants' opinion). However, little is known regarding non-medical causes of discharge delay, more so in the Philippine setting.

Financial capacity to access healthcare has been identified in several studies to cause delay in seeking treatment (11, 16). Social health insurance health programs have been developed and encouraged so as to alleviate the financial burden that has been an impediment to healthcare access, especially by the poor. In the study by Fowler et al., being uninsured was identified as a risk factor for discharge delay presumably because these patients arrive in the hospital in a more critical state, needing more intensive management due to delay in initial medical consult. However, the direct effect of health insurance status and its utilization to health outcomes has not been thoroughly looked into, especially in the local setting.

An indicator of a successful national health insurance program is a decreased percentage of out-of-pocket expenditure (16).

Therefore, reinforcing the national health insurance program through Philhealth benefit utilization is one strategy to alleviate the financial concerns of the patients and expedite the diagnosis, management and ultimately the discharge of these patients.

During the study period, 86% of admitted patients are Philhealth members while the remaining are non-Philhealth members. This is comparable to the statistics released by Philhealth where approximately 9 out 10 Filipinos are covered by Philheatlh. By increasing their coverage, Philhealth comes close to achieving its aim to for universal healthcare by easing the financial burden imposed by healthcare costs. Aside from voluntary and compulsory contributions, the government also subsidizes funding of the said program especially for those belonging to the lowest economic quintiles through the Indigent Program (IP). Despite these efforts, there are still a number of Filipinos who remain non-members or become members but do not utilize the benefits of Philhealth to avail healthcare services. In the 2015 Philhealth statistics, only 12% of total eligible Philhealth members utilize its benefits. In this research, however, it is assumed that Philhealth membership is equivalent to utilization of its benefits during the admission. Philhealth members who did not avail of Philhealth benefits were not identified in this paper.

The reasons for non-enrolment to Philhealth are beyond the scope of this study. However, there were endeavors to give light to this phenomenon. In a study by Faraon et al., sex, income and type of Philhealth membership were identified variables to be significantly associated with underutilization of Philhealth. The outcome of this study had a similar result. Based on the patients' social service classification, vis-à-vis their income status, most of non-Philhealth members belong to C3 or the lowest income group. Such finding may be supposed to be also linked to the educational attainment and subsequently, the knowledge and awareness of the families of these patients regarding the Philhealth benefits and how to avail them. In the same study by Faraon et al., other reasons for underutilization of Philhealth are as follows:

- Lack of knowledge on benefits
- Lack of knowledge on filing claims
- Lack of cooperation from doctors in getting required documents
- Cumbersome or unmanageable process
- High transaction costs compared to benefits
- Ineligible claim

In this study, most patients are subscribed to Philhealth by compulsory contributions through the employer, also known as SSS-dependent members, comprising 51% of the sample population. However, latest Philhealth data demonstrates that majority of covered members are indigents, comprising 49%. This discrepancy may be explained by the fact that some patients are initially admitted as non-Philhealth members and are only enrolled to Philhealth during admission, through the assistance of the social service unit. These patients are usually indigents who are granted a no balance billing status (NBBB) during their stay. Such enrolment mechanism is noted in the records of social service and the admitting section. However, none of the patients who are included in this study experienced said mechanism of enrolment to Philhealth. All non-Philhealth members remained unenrolled to Philhealth until discharge.

Those patients who experienced delay in discharge reported financial setback as the reason for the delay. Data from the social service unit showed that majority of these patients still resorted to out-of-pocket resources

to settle their hospital bill, regardless of their Philhealth membership. However, there are 2 patients who sought financial assistance from PCSO and DSWD. This agrees with the finding that household budget for healthcare is still mostly out-of-pocket (16). This reliance on out-of-pocket sources for healthcare has detrimental effects. In the study by Ulep and Dela Cruz, high out-of-pocket expenditure for health needs can:

- redistribute income "in the wrong direction" (i.e., from chronically ill to healthy individuals and, typically, from the relatively poor to the relatively affluent groups [Plumper and Neumayer 2012])
- lead people to make tough choices concerning their health such as not complying with prescribed drug use due to high costs, forgoing necessities, or borrowing money to pay for prescriptions;
- affect women and minorities who may forgo critical prevention screenings and skimp on medications due to high costs; and
- increase the financial burden on those with valid insurance (Aji et al. 2013).

CONCLUSION

In summary, this study demonstrated that Philhealth enrolment and its subsequent utilization affect timeliness of discharge of pediatric patients admitted for acute illnesses. Non-membership to the national health insurance program increases the risk of discharge delay three-fold. Other patient factors such as age, sex, social service classification and the acute illness for which the patients are admitted did not show any significant association with discharge delay.

Further investigations can be made to elucidate on other factors affecting discharge delay. This study is limited to review of patients' records from the admitting section and social service unit. It is recommended that a prospective study be done in order to identify the reasons for delay in discharge as will be reported by patients' families, which may not be solely financial in nature. Focus group discussions among the patients' parents may be done in order to fully understand the reasons for delay. Such method of study can also give light to the reasons for non-Philhealth membership. Recognizing other variable affecting discharge delay may be helpful for the hospital administration and even the national government, to draft policies and systems to improve the health insurance program so as to achieve universal healthcare for all.

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CLINICAL PROFILE AND FACTORS ASSOCIATED WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AMONG OVERWEIGHT AND OBESE CHILDREN: A PROSPECTIVE STUDY

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ABSTRACT

INTRODUCTION: In the past decades, the prevalence of childhood overweight and obesity has increased worldwide. Childhood obesity has been associated with wide range of serious health complications and increased risk of premature adult illnesses. Non-alcoholic Fatty Liver Disease (NAFLD) was of concern because of limited data among children. The study aims to determine the prevalence and demographic/clinical factors associated with NAFLD among overweight and obese children.

METHODOLOGY: The study was a cross sectional study among overweight and obese participants aged 2-18 years old. A total of 96 subjects were included. Frequencies and percentages of clinical characteristics were determined. Chi-square, linear correlation and logistic regression analysis for different factors were performed.

RESULTS: Among the 92 subjects, 26 (28%) were overweight while 66 (72%) were obese. The M:F ratio was 1.8:1 and majority belonged to 6-10 years old (44%). As to socioeconomic class, majority (59%) were from the low-income group. The overall prevalence of NAFLD among the overweight and obese subjects was 29.3%. None of the clinical factors (age, gender, socioeconomic status, BMI, waist circumference, actual caloric intake and dietary fat consumption) were significantly associated with NAFLD. Analysis of biochemical factors revealed that alanine aminotransferase, aspartate aminotransferase, serum triglycerides and total cholesterol were found to be associated with NAFLD. Amongwhich AST and ALT were identified predictors of NAFLD.

CONCLUSION: There was high prevalence of NAFLD among overweight and obese children. Screening among the pediatric population may aid in early identification and prevent its progression. ALT, AST, serum triglycerides and total cholesterol were independently related with NAFLD. AST and ALT were identified predictors of NAFLD.

KEY WORDS: overweight, obese, Non-alcoholic fatty liver disease, clinical factors, liver function tests

INTRODUCTION

In the past decades, the prevalence of childhood overweight and obesity has increased worldwide. The perception that "bigger is better" has changed because of evidence that obesity in childhood is associated with wide range of serious health complications and increased risk of premature illnesses and mortality later in life. The overall worldwide prevalence of children who are overweight and obese increased from 4.2 % in 1990 to 6.7 % in 2010; this was based on the data from 450 nationally representative surveys from 144 countries included in the WHO Global Database on Child Growth and Malnutrition. (1) In 2013, World Health Statistics reported that obesity is on the rise in low and middle-income countries. (2)

Due to the growing concern on prevalence of overweight in developing countries, a cross-sectional study on prevalence of overweight among preschool children was done using the data obtained from national nutritional surveys of World Health Organization. The study estimated that 3.3% or 17.5 million of preschool children in developing countries were overweight. Asia ranked third with 2.9%. However, in absolute numbers, Asia had the highest number of overweight children (10.6 million or 60%). (3) Over the last few decades, the rise in prevalence of overweight and obese children warrants attention because of its association with serious health concerns, one of which is NAFLD. In the Philippines, the sixth National Nutrition Survey conducted in 2003 by the Food and Nutrition Research Institute (FNRI) showed that among children aged 0-5 years, 1.4% were overweight. Among children 6-10 years and 11- 19 years, 1.3% and 3.6% were overweight, respectively. (4) The latest NNS Survey in 2013 reported the prevalence of overweight among 6-10 years old was 9.1% while prevalence of overweight and obese among 11-19 years old was 8.3%. Increasing rate was also evident as the 2013 World Health Statistics revealed that prevalence of overweight among Filipino children <5 years of age is 3.3%. (2) However, the Philippine data on the pediatric prevalence of NAFLD among overweight and obese is still unknown.

In different population-based studies, obesity was identified as the main risk factor for the development of NAFLD. The increasing trend of NAFLD reflects the worldwide annual increment of obese individuals. Data from the National Health Nutrition Examination Surveys showed that 17% of all children in Western countries were overweight, and 70 to 80% of them have NAFLD. It has recently emerged as a leading cause of chronic liver disease in children (7) and rapidly becoming a global health issue. (8) The prevalence among pediatric patients was estimated to be between 3 % and 10 %. (7)

NAFLD refers to a wide spectrum of liver abnormalities ranging from simple steatosis (fat accumulation in the liver) to steatohepatitis, which may be associated with fibrosis and later on progress to cirrhosis then end-stage liver disease. The pathogenesis remains unclear but different factors were identified to contribute to disease development. (9) Among pediatric patients, NAFLD was first described nearly 3 decades ago and since then, it emerged as the most common cause of liver disease in the developed world. (10)

Biopsy of the liver remains to be the gold standard for diagnosis of NAFLD and it can determine severity of liver damage or the presence and extent of fibrosis. However, it is not usually performed as first step because it is an invasive procedure and may be associated with complications, such as bleeding. Thus, research has been undertaken to develop initial non-invasive tools to confirm the diagnosis of NAFLD. (9) Different imaging techniques can be used to detect fatty liver disease. Among them, liver ultrasonography is the most commonly used modality, primarily because it is widely available, inexpensive and user friendly. It can provide a good estimate of the degree, or extent of hepatic steatosis based on a series of ultrasonographic characteristics. (7) In several studies, a strong correlation was demonstrated between ultrasound and liver biopsy findings, concluding that this modality is useful for quantification of steatosis. (10) Ultrasonography has a good sensitivity and specificity (89% and 93%) in detecting steatosis. (11)

In many countries, NAFLD becomes an important health issue. With the different studies done, it is of great interest to note the rising numbers of overweight and obese children. The primary concern would be avoidance of its health consequences including Non-alcoholic

fatty liver disease (NAFLD) and progression to adult complications. Early diagnosis of Non-alcoholic fatty liver disease would be the initial step and a significant factor in the prevention of progressing to an irreversible liver damage.

Health consequences due to increasing trend of overweight and obesity in children continue to be alarming. It poses a major risk for developing obesity-related liver disease and may contribute to a significant number of adult cases later in life.

Our objective is to determine the prevalence and factors associated with NAFLD among overweight and obese Filipino children and factors to help identify those at risk. Of greater concern for us pediatricians are to increase awareness on increasing prevalence of childhood overweight/obesity and its significant impact in development of NAFLD. This remains to be a "silent disease" and an emerging health problem. Early identification will help prevent progression into more serious liver disease.

METHODOLOGY

This study was a cross sectional study that aimed to determine the prevalence and factors associated with NAFLD among overweight and obese children. NAFLD was determined by means of liver ultrasound. Factors associated with NAFLD were also investigated. The study was conducted in a tertiary center in Quezon City, Philippines from October 2015 to June 2016. The Philippine Children's Medical Center is a 200-bed capacity hospital, dedicated in delivering the most responsive service to patients, achieve best health outcome and protect the vulnerable Filipino children. It is a referral center that offers wide array of services among pediatric cases.

In the assumption that rho (ρ) is equal to zero and $\propto$ err = 0.05, a sample size of 96 respondents was obtained using G*Power info software with a confidence level of 95% and power at 85%. To optimize the sample size, the patients were classified into degrees of BMI (overweight and obese) and liver ultrasonography characteristics (normal liver, mild NAFLD, moderate NAFLD or severe NAFLD).

The study was done in accordance to the principles stated in the Declaration of Helsinki. The data collection form, information sheet and informed consent/assent form were reviewed by the Ethics Review Board of the Institution prior to its use and prior to conduct of the study.

NAFLD definition requires that (a) there is evidence of hepatic steatosis by imaging or histology and, (b) there are no causes for secondary fat accumulation. (17) Presence of fatty liver was further classified as to: diffuse hyperechoic texture (bright liver) as mild; increased liver echo texture compared with the kidneys as moderate; and, vascular blurring with deep attenuation as severe. However, with the absence of the following findings, subject was classified as to normal liver. (14)

Statistical analysis was performed using SPSS (version 21; SPSS Inc., Chicago, IL USA) software considering 95% confidence interval in demographic data analyses. The researcher summarized the subjects' characteristics and clinical findings using percentages for dichotomous variables and means with standard deviations for continuous variables. For non-continuous variables, Chi square test was used. Frequencies and means (± standard deviation) were calculated to describe the demographic data. To assess the significant relationship between biochemical tests and classification of NAFLD, a linear correlation and logistic regression analysis were performed.

RESULTS

A total number of 106 subjects were screened to participate in this study. Ten (9%) of the subjects were excluded due to the following reasons: presence of exclusion criteria (intake of valproate), did not give parental consent and refusal of the child to join because of blood extraction. The target number of ninety-six (96) subjects was included. However, four (4) patients dropped out (4%) as they opted to withdraw consent and refuse to proceed in the study.

Among the 92 subjects, 26 (28%) were classified as overweight while 66 (72%) were classified as obese. There were slightly more males (64%, n= 59) than females (36%, n= 33). The male-to-female ratio was 1.8:1. Almost forty four percent (44%) of these children were in the 6 – 10 years age group, followed by 11 – 15 years age group (32%) as seen in Table 1.

Table 1. Frequency Distribution of 2-18 years old overweight and obese subjects according to Age Group and Gender

	Overweight	**Obese**	**TOTAL**
	n = 26	*n = 66*	(%)
Age Group (yrs)			
2-5	0	11	11 (12.0)
6-10	7	33	40 (43.5)
11-15	12	17	29 (31.5)
>16	7	5	12 (13.0)
Gender			
Male	10	49	59 (64.1)
Female	16	17	33 (35.9)

Table 2 shows the frequency distribution according the socioeconomic status and physical activity of the subjects. As to socioeconomic status, 59% of subjects belong to the low socioeconomic class while the rest of the subjects belong to the middle class. After cross tabulation, socioeconomic class revealed significant results (*p*-value = 0.007). Sixty seven percent of subjects were classified under moderate physical activity while ten percent under light physical activity.

Table 2. Comparison of 2-18 years old overweight and obese subjects according to Socioeconomic Class and Physical Activity

	Overweight *n = 26*	**Obese** *n = 66*	**TOTAL** (%)	**Chi square**	***p*-value**
Socioeconomic class					
Low	21	33	54 (58.7)	7.284	0.007*
Middle	5	33	38 (41.3)		
Upper	0	0	0		
Physical activity					
Light	4	6	10 (10.9)	0.894	0.640
Moderate	16	46	62 (67.4)		
Vigorous	6	14	20 (21.7)		

**p-value of <0.005 is considered significant*

Different clinical factors among overweight and obese subjects were tabulated in Table 3. Fifty five percent (55%) of subjects had acanthosis nigricans while hepatomegaly was only noted in about fifteen percent (15%) of participants. The mean waist circumference among subjects was 82.2 cms (±11.8). Sixty-nine subjects (75%) were classified above the 90th percentile and maximum number seen among obese participants. With regards to family history, 37 subjects had at least 1 overweight family member. Among the clinical factors, waist circumference was found to be significantly associated with increased BMI.

Table 3. Comparison of 2-18 years old overweight and obese subjects according to different Clinical Factors

	Overweight *n= 26*	**Obese** *n = 66*	**TOTAL** (%)	**Chi square**	***p-value***
Acanthosis Nigricans					
Present	13	38	51 (55.4)	0.433	0.510
Absent	13	28	41 (44.6)		
Hepatomegaly					
Present	3	11	14 (15.2)	0.380	0.537
Absent	23	55	78 (84.8)		
Waist circumference					
< 90th Percentile	17	6	23 (25.0)	31.524	0.000
≥ 90th Percentile	9	60	69 (75.0)		
Family History					
Overweight	10	27	37 (40.2)	1.375	0.712
Obese	3	11	14 (15.2)		
Both	1	5	6 (6.5)		
None	12	23	35 (38.0)		

**p-value of <0.005 is considered significant*

Ultrasonography was done in the 92 subjects to identify those with NAFLD. The overall prevalence of NAFLD among overweight and obese subjects during the study period was 29.3%. Based on ultrasound findings of 27 subjects with NAFLD, only one patient was graded as moderate while the rest was graded mild.

Table 4 shows that 12 of 27 subjects with NAFLD are in the age group of 6-10 (44%) and has a male predominance (78%). The mean age was 11-year-old. Most of the subjects identified with NAFLD were classified as obese with BMI >+2 SD (85%) while 15% of subjects were classified as overweight with BMI >+1 SD. Majority of subjects with NAFLD (85%) had waist circumference above the 90th percentile. The Actual Caloric Intake (ACI) of sixteen participants with NAFLD (59%) was more than the Recommended Energy Nutrient Intake (RENI) for age. Moreso, eighty five percent (85%) of those with NAFLD has increase dietary fat consumption as seen in table below. Notable increase in dietary fat consumption was also seen in 77% of sujects without NAFLD.

Clinical factors among overweight and obese subjects were determined if they were associated with Non-alcoholic Fatty Liver Disease (NAFLD), including age, gender, socioeconomic class, physical activity, body mass index (BMI), waist circumference, actual caloric intake (ACI) and dietary fat consumption. None of the factors showed statistically significant results but the Body Mass Index (BMI) was close to being statistically significant.

Table 4. *Chi-square* Analysis of Demographic/Clinical Factors among overweight and obese children with Non-alcoholic Fatty Liver Disease

FACTOR	With NAFLD (%)	Without NAFLD (%)	TOTAL (%)	Chi-Square	*p*-value
Age (yrs)					
2-5	1 (3.7)	10 (15.4)	11 (12.0)		
6-10	12 (44.4)	28 (43.1)	40 (43.5)		
11-15	11 (40.7)	18 (27.7)	29 (31.5)	6.72	0.347
>16	3 (11.1)	9 (13.8)	12 (13.0)		
Gender					
Male	21 (77.8)	38 (58.5)	59 (64.1)	3.32	0.190
Female	6 (22.2)	27 (41.5)	33 (35.9)		
Socioeconomic status					
Low	11 (40.7)	43 (66.2)	54 (58.7)	5.79	0.055
Middle	16 (59.3)	22 (33.8)	38 (41.3)		
Upper	0	0	0		
Physical Activity					
Light	4 (14.8)	6 (9.2)	10 (10.9)		
Moderate	19 (70.4)	43 (66.2)	62 (67.4)	1.44	0.487
Vigorous	4 (14.8)	16 (24.6)	20 (21.7)		

Table 4. (Continuation)

FACTOR	With NAFLD (%)	Without NAFLD (%)	TOTAL (%)	Chi-Square	*p*-value
BMI (SD)					
> +1	4 (14.8)	22 (33.8)	26 (28.3)	3.408	0.065**
> +2	23 (85.2)	43 (66.2)	66 (71.7)		
Waist circumference					
< 90th Percentile	4 (14.8)	19 (29.2)	23 (25.0)	2.11	0.146
$\geq$ 90th Percentile	23 (85.2)	46 (70.8)	69 (75.0)		
Actual Caloric Intake					
Above RENI	16 (59.3)	32 (49.2)	48 (52.2)	0.769	0.381
Within RENI	11 (40.7)	33 (50.8)	44 (47.8)		
Dietary Fat Consumption					
Above	23 (85.2)	50 (76.9)	73 (79.3)	0.795	0.373
Normal	4 (14.8)	15 (23.1)	19 (20.7)		

p-value of <0.05 is considered significant
***** almost significant***

Table 5 presents the cross tabulation of biochemical results and ultrasonography findings among overweight and obese children. Elevations were seen in Alanine aminotranferase (ALT) and Serum Triglycerides among subjects with NAFLD. Analysis of the biochemical results among subjects were determined if there was an association with NAFLD – alanine aminotransferase, aspartate aminotransferase, LDL, HDL, serum triglycerides, total cholesterol and fasting blood sugar. The statistical value of ALT is 0.485 with mean of 44.45 ($\pm$SD, 47.87) while AST is 0.504 with mean of 34.99 ($\pm$ 21.52). Generally, significant relationships were evident in the subjects' ALT and AST when cross tabulated with the ultrasound findings of NAFLD.

Analysis revealed that among the biochemical parameters – Alanine Aminotranferase (ALT), Aspartate Aminotransferase (AST), Serum triglycerides and Total cholesterol were found to be associated to NAFLD and all revealed statistically significant results.

Table 5. Pearson Linear Correlation Analysis of Biochemical Factors among overweight and obese children with Non-alcoholic Fatty Liver Disease

FACTOR	With NAFLD (%)	Without NAFLD (%)	TOTAL (%)	Mean ± SD	*r*-value	p-value
Alanine aminotransferase (ALT)						
Elevated Male >25 U/L Female >22 U/L	16 (59.3)	4 (6.2)	20 (21.7)	44.45 ± 47.87	0.485	0.000*
Normal	11 (40.7)	61 (93.8)	72 (78.3)			
Aspartate aminotransferase (AST)						
>50 U/L	9 (33.3)	0 (0.0)	9 (9.8)	34.99 ±21.52	0.504	0.000*
≤50 U/L	18 (66.7)	65 (100.0)	83 (90.2)			
Low Density Lipoprotein (LDL)						
≥130 mg/dL	2 (7.4)	4 (6.2)	6 (6.5)	95.49 ±22.21	0.077	0.463
<130 mg/dL	25 (92.6)	61 (93.8)	86 (93.5)			
High Density Lipoprotein (HDL)						
≤35 mg/dL	3 (11.1)	17 (26.2)	20 (21.7)	44.22 ±10.57	0.023	0.825
>35 mg/dL	24 (88.9)	48 (73.8)	72 (78.3)			
Serum triglycerides						
≥160 mg/dL	14 (51.9)	14 (21.5)	28 (30.4)	134.38 ±87.24	0.389	0.000*
<160 mg/dL	13 (48.1)	51 (78.5)	64 (69.6)			
Total cholesterol						
≥200 mg/dL	6 (22.2)	5 (7.7)	11 (12.0)	165.60 ±31.42	0.292	0.005*
<200 mg/dL	21 (77.8)	60 (92.3)	81 (88.0)			
Fasting Blood Sugar (FBS)						
>100 mg/dL	4 (14.8)	3 (4.6)	7 (7.6)	91.11 ±5.54	0.038	0.719
≤100mg/dL	23 (85.2)	62 (95.4)	85 (92.4)			

p-value of <0.01 is considered significant

The biochemical factors were further analysed to determine the association with NAFLD. Results revealed that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were significantly associated with NAFLD as seen in table below.

Table 6. Logistic Regression Analysis of Biochemical Factors among overweight and obese children with Non-alcoholic Fatty Liver Disease

FACTOR	B	S.E.	Wald	Exp(B)	p-value
Alanine aminotransferase (ALT)	2.448	0.835	8.583	11.56	0.003*
Aspartate aminotransferase (AST)	2.0218	0.926	7.020	9.70	0.009*
Low Density Lipoprotein (LDL)	-0.866	1.408	0.378	0.421	0.539
High Density Lipoprotein (HDL)	-0.730	0.874	0.697	0.482	0.404
Serum triglycerides	0.725	0.739	0.962	2.065	0.327
Total cholesterol	1,693	1.163	2.117	5.434	0.146
Fasting Blood Sugar (FBS)	1.835	1.008	3.311	6.265	0.069
Constant	-2.194	0.493	19.825	0.112	0.000

p-value of <0.05 is considered significant

DISCUSSION

In the 21st century, increasing trend of childhood overweight and obesity is one of the major global health concerns. The World Health Organization (WHO) reported the alarming increase in the rate of its prevalence, which is estimated to reach over 42 million children in 2013. Among Filipino children less than 5 years of age, the prevalence of overweight as reported in 2013 World Health Statistics is 3.3%. (2) In the latest NNS Survey by the Food and Nutrition Research Institute (FNRI) 2013, prevalence of overweight among 6-10 years of was 9.1% and prevalence of overweight and obese among 11-19 years was 8.3%. When compared with data from 1998 the results were indeed alarming. (4)

The rise in number of overweight and obese in the pediatric population leads to health consequences specifically the Noncommunicable Diseases (NCDs) that may continue into adulthood. One consequence is the effect on the liver, NAFLD, that warrants attention as it can cause more serious health problems among the pediatric population in the future. NAFLD has been recognized as the most common cause of liver disease in paediatrics. (22) The Philippine data on NAFLD prevalence among overweight and obese children remains unknown.

Over the last few decades, increasing trend of obesity was observed in both developed and developing countries. (23) In 2013, a systematic review reported that signicantly higher body composition were seen in urban and higher socioeconomic status. (24) Similarly, a study in the Philippines reported that majority of overweight and obese children were found in the affluent socioeconomic class. (25) However, this present study revealed that it was also seen in the middle- and low-class group which signify that this problem transcends socioeconomic status. This finding requires much attention because the scope of population with health

threats is expanding. The study setting of this research was done in a government hospital, giving us limited number of possible subjects from the upper class. Thus, in order to lessen bias in the selection of subjects and to further strengthen our results, a larger populational study is encouraged.

Traditional pratices of long-distance walking and habitual physical activities have been replaced by motorized transport and other sedentary activities. Lifestyle and environmental factors which could have contributed to the burden of overweight and obesity have changed tremendously. It is evident in the study done by Cruz et al. (26), most overweight and obese subjects engaged in "no to light" forms of physical acitivity. In our research, subjects' physical activity was classified as light, moderate or vigorous. Majority of overweight and obese subjects were involved in moderate physical activity. However, a more precise description of physical activity among children and adolescent should be a focus in the future trials.

Different techniques can be used to detect NAFLD, the most common modality used is liver ultrasonography. It has a good sensitivity and specificity (89% and 93%) in detecting fatty liver comparing with histology. (11) Liver biopsy remains to be the gold standard in diagnosis, but its use has been limited as it is an invasive procedure with known complications. (9) The 2-18 years old overweight and obese participants underwent ultrasonography and classified as: normal findings, mild, moderate or severe NAFLD. The findings of this study demonstrate that the prevalence of NAFLD has risen substantially. The prevalence of NAFLD was determined as 29.3% in this study, which is quite distant from the reports in Japan (12) and SCALE study by Schwimmer. (13) Our results were, however, comparable with other populational studies - the 3rd National and Nutrional Examination Survey (NHANES III) from USA and the Dionysus study from Italy. Based on these studies, the prevalence of NAFLD is between 9% and 34%. Differences in the findings in the different populational studies can be due to the various criteria used in defining NAFLD.

Among subjects of this study, NAFLD was identified in 3.7% of children below 6 years of age and 74% of children 7 to 14 years. This trend is supported by Fusillo et al., (10) obesity or higher body mass index (BMI) is directly proportional with age. In SCALE trial, NAFLD was seen in 5% of children with normal-weight and with higher percentages among overweight and obese children, 16% and 38%, respectively. The data indicate the importance of recognizing occurrence of NAFLD among children with normal weight, although less frequently than in overweight and obese children. (10)

The prevalence of NAFLD in this trial was found to be higher in males than females approximately 64% and 36%, respectively, but the difference between the two sexes did not show statistical significance. According to the study done by Schwimmer (13), the prevalence is higher among males rather than females because the excess body fat is distributed within the intra-abdominal compartment and also due to the influence of sex hormones. In the previously cited literature (7), one hypothesis was estrogens can be liver protective or may indicate that androgens can aggravate the condition.

Waist circumference (WC) has been used to estimate intra-abdominal fat and the importance of intra-abdominal fat in childhood obesity has also been established. Different pediatric studies showed its direct correlation with metabolic syndrome. Thus, it can be a useful tool in clinical assessment of childhood obesity. (28) However, in the Philippines, there has been no Waist Circumference (WC) reference cut-off existing among Filipino

children or its association as risk factor for NAFLD. In 2004 (29), a study was done to describe and provide estimates of the waist circumference distribution according to percentile among African-, European-, and Mexican-American children. Careful attention should be given to children and adolescents with WC values on the 75th and 90th percentile, as it poses increased risk of obesity related comorbidities. Several studies have used different cut-off for waist circumference in relation to abdominal obesity. However, children with waist circumference higher than 90th percentile were more likely to be linked with multiple cardiovascular risk factors. In this present trial, the cut-off used was the consensus defined by the International Diabetes Federation (IDF). (30) As confirmed in the present study, WC was increased in majority of subjects but did not show significant association with both BMI and NAFLD.

Most children nowadays are exposed to unhealthy food choices which have significantly contributed to the rise in overweight and obese among pediatric population. Energy intakes have not increased greatly in the past years but with the advent of technology and modernization, decrease in physical activity or increased inactivity was observed. The Actual Caloric Intake (ACI) of most subjects in this trial was categorized above the RENI for Filipinos for age. Similar outcome was seen in the percentage of the dietary fat, in which fat consumption of subjects were above the recommended. This may reflect the increase consumption of energy dense diets that are high in fat and sugars such as fast foods, ready-mix food or instant food choices. Though some parents/subjects were cautious to give their exact actual caloric intake (ACI) in the dietary recall and this was one limitation identified in this trial.

In this research, associated factors were analysed to identify their association with NAFLD detected with ultrasonography. Results of our study showed that alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum triglycerides were mostly elevated in patients with NAFLD. For total cholesterol, majority of subjects in both categories have normal results. Similar outcome of increased ALT and serum triglycerides were noted in the study in Iran. (14) This is in contrast with the study in Mexico (31), in which elevated total cholesterol was the finding associated with fatty liver. We however did not analyze the cholesterol content of the diet o f our subjects.

In linear correlation analysis, independent factors associated with non-alcoholic fatty liver disease (NAFLD) were alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum triglycerides and total cholesterol. Logistric regression analysis revealed that spartate aminotransferase (AST) and alanine aminotransferase (ALT) were predictors of NAFLD.

SUMMARY AND CONCLUSION

The growing obesity epidemic is believed to be the main root in the increase of pediatric NAFLD. Although the pathogenesis of fatty liver in children and adolescents is not fully understood, the contribution of both genetic and environmental risk factors to some extent is generally recognized. (10) Due to limited studies done locally on NAFLD, this study deemed it appropriate to focus on identification of cases as well as the associated factors among overweight and obese children.

The study revealed that there was a high prevalence of NAFLD among overweight and obese children. Screening for NAFLD among the pediatric population may help in early identification and prevent its progression. Attention should be directed towards programs that address the increasing trend in number of overweight and obese Filipino children. These

may help reduce the risk of development of NAFLD as well as the other consequences of overweight and obesity.

Overall, the researchers concluded that none of the clinical factors (age, gender, socioeconomic class, physical activity, body mass index (BMI), waist circumference, actual caloric intake (ACI) and dietary fat consumption) was found to be associated with NAFLD. While among the biochemical factors such as ALT, AST, serum triglycrides and total cholesterol were independently related with NAFLD. Among which, aspartate aminotransferase and alanine aminotransferase were the predictors of NAFLD.

It is recommended to emphasize routine weight monitoring to identify overweight and obese children at risk for development of NAFLD. Screening should be done to facilitate early detection of cases and to prevent further progression to a more severe liver damage. Emphasis is warranted to increase awareness of parents regarding health consequences of being overweight and obese. Strengthening the drive to promote wellness among our youth should always be part of our advocacy.

At present there are no reference values for waist circumference that may indicate abdominal obesity for children and adolescents. It is recommended that a study be done to establish waist circumference cut-off or percentiles that can be used as a guide among Filipino children.

With regards to actual caloric intake of the subjects, it was one limitation identified in this study. The parents/subjects were cautious in giving information regarding the exact amount of dietary intake due to awareness that this study focuses on the subject as being overweight or obese. Future trial that will concentrate on the different macronutrients that may be associated with NAFLD is also recommended.

Further studies should focus on "modern" health issues on NCDs such as NAFLD which is an emerging disease with health challenges among pediatric population. Inclusion of subjects with normal BMI is recommended to further assess the extent of the disease. More so, one priority of health care systems should concentrate in exploring further this disease and identification of treatment specific for children and adolescents.

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REFERENCE VALUES FOR NERVE CONDUCTION STUDIES IN HEALTHY NEWBORNS, INFANTS AND CHILDREN IN PHILIPPINE CHILDREN'S MEDICAL CENTER

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ABSTRACT

BACKGROUND: Nerve conduction studies play a diagnostic role in the clinical evaluation of neuromuscular disorders in children. Reference ranges define the expected parameter values in disease-free children.

OBJECTIVES: To propose reference values for sensory and motor nerve conduction and late responses in upper and lower limb peripheral nerves in Filipino children 5 years and below.

METHODS: Sensory nerve conduction studies on median, ulnar, radial, superficial peroneal, and sural nerves and motor nerve conduction and late response studies on median, ulnar, peroneal and posterior tibial nerves were done using standardized techniques among 100 healthy Filipino children.

RESULTS: Subjects were stratified according to age groups. Reference values for the following parameters: (1) sensory conduction velocity and amplitude; (2) motor conduction velocity, amplitude and latency at distal sites; (3) F-wave latency; and (4) H-reflex latency were summarized. These were expressed as mean ± standard deviation or median (range) for values that follow Gaussian and non-Gaussian distributions. The 5^{th} and 95^{th} percentile values were likewise reported. Age had direct correlation with various nerve conduction parameters. Height was directly correlated with F-wave parameters of median, ulnar and peroneal nerves but not posterior tibial nerve.

CONCLUSIONS: Reference standards for nerve conduction studies of commonly tested nerves of Filipino children are presented. Values are comparable to reference ranges elsewhere except for the H-reflex latency which is higher in this study.

KEYWORDS: nerve conduction study; late response; reference values

INTRODUCTION

Reference values for nerve function assessment are used to define the limits of normal function, such that test values outside the range suggest peripheral nerve dysfunction or damage. Although different nerve conduction studies have yielded respective reference values, the results vary considerably from population to population, region to region and laboratory to laboratory. Hence, it is important that the institution's neurodiagnostic Laboratory Clinical Electromyography Unit obtain separate standardized reference values by conducting nerve conduction studies among healthy Filipino pediatric patients with age ranging from of one

day to 5 years to determine the normal motor and sensory nerve conduction velocity, nerve action potential and amplitudes, H-reflex, F wave and latencies of the median, radial, ulnar, peroneal, posterior tibial and sural nerves.

To date, our Neurodiagnostic Laboratory Clinical Electromyography Unit has not established its own set of normal values for the various nerve conduction studies and since its establishment, we have been using normal values from published studies[2]. This study therefore intends to obtain a reference value database from healthy Filipino children and compare it with published data.

NORMATIVE DATA IN CHILDREN AND MATURATIONAL CHANGES

Conduction velocity. The relationship between conduction velocity of motor nerve fibers and age, specifically for children under six has been studied by many authors. Historically, Thomas and Lambert first described the maturation of motor conduction velocity of the ulnar nerve during the first years of life in 1960. Although there are many different sources of information, the motor conduction velocities of newborns were roughly half of those in adults. They all showed rapid increase in motor conduction velocity during the first two years of life and less increase later, reaching adult value by 3-5 years. Locally, in 1997 Amante had reported normal nerve conduction velocity among 1 to 60 month old children seen at the University of the Philippines-Philippine General Hospital. The conduction velocity of the upper limbs was 65-70% of adult values at a younger age of below 6 months and it reached adult values at 3 years of age. While the conduction velocity of the tibial nerve and peroneal nerve is 70% and 75% of adult values at 6 months. Like in the upper limbs, it reached adult values at age 3 years [10]. Tables showing the motor nerve conduction velocity of both the upper and lower limbs of the different age groups can be found in the Appendix.

Motor and sensory action potentials. Compound muscle action potential (CMAP) amplitudes also differ by age. In the neonatal group, CMAP are one-half adult values for tibial nerve and one-third adult values for peroneal, median and ulnar nerve in the study of Garcia et al. Tibial CMAP (from abductor hallucis) is the first to reach adult values around 2 and 3 years of age according to Garcia et al and Cai and Zhang studies, respectively. CMAP amplitudes of median, ulnar and peroneal nerves get doubled around 4 years of age and reach adult values between 4-6 years age in the study of Miller and Kuntz and Cruz Martinez et al.

In contrast, Amante found that the amplitudes of the motor action potentials of the median, tibial and peroneal nerves were 50-60% of adult values at 6 months of age while the ulnar nerve was 80%. All the nerves had amplitudes similar to adult values earlier at 2-3 years except for the tibial nerve which had reached adult values at 1 year of age. Maturational changes for sensory nerve action potential (SNAP) amplitudes are different to that of motor fibers. At birth, SNAP amplitudes are only 25-30% of adult values in the study of Cai and Zhang. In the neonatal period, SNAP amplitudes are about half of those of adult values. It reaches adult values already by the age of 2 years according to the study of Gamstorp and Shelburne, Garcia et al and Cruz Martinez et al. but in the study of Gucchait et al, it is reached later by 3-4 years of age similar to CMAP amplitudes.

Distal motor latency. Available normative values of distal motor latency (DML) in the study of Cruz Martinez, Miller and Kuntz, Parano et al, Hamdan, Cai and Zhang are described according to the different distance in every age group. Recently, the group of Garcia reported corrected DML for standard distances for children by applying the formula: Corrected DML = measured DML – [L-X/MCV], where L = actual distance between stimulating cathode to the active recording electrode, and X = standard distance (4

cm for nerves of upper limbs and 5 cm for nerves of the lower limbs. This approach avoided the influence of extremity growth on the DML measurement.

F-wave latency. There are only a few age-related studies of F-wave parameters in pediatric population: (1)Shahani and Young in 1981; (2) Kwast and Kozlowski in 1985; (3) Miller and Kuntz in 1986; (4) Misra et al in 1989; (5) Parano et al in 1993; (6) Cai and Zhang in 1997; (7) Garcia et al. in 2000; and (8) Nadeem et al. in 2002 [2,3,6,7,12]. In general, the minimum F-latency of median or ulnar nerve stimulation at the wrist in children younger than 6 years of age is less than 20 msec, while in the lower extremities recorded from intrinsic foot muscles with peroneal or tibial nerve stimulation at the ankle is less than 30 msec. Evolution of F-wave latencies in children may remain stable (Cai and Zhang, 1997), show a linear increase (Parano et al, 1993) or exhibit differential evolution according to age: diminution during the first year of life, stabilization and increasing afterwards (Garcia et al, 2000; Nadeem et al, 2002).

H-reflex. In young infants, the H-reflex is present in both the upper extremities (median and ulnar) and lower extremities (with tibial stimulation). It is evoked easily even in normal prematures and newborns because of increased alpha motor neuron excitability due to the imbalance between facilitory and inhibitory effects on the spinal motor neuron as a result of the immaturity of the central nervous system (CNS). Thereafter, H-reflex responses become suppressed in the upper extremity in most children after first year, while the tibial H-reflex persists in adulthood [2]. Mayer and Mosser in 1969, Tiwari et al in 1996 and Cai and Zhang studied H-reflex latency in the gastrocnemius-soleus muscle in infants and children [2,3,6,13]. Mayer and Mosser concluded that H-reflex latency greater than 17 msec is abnormal for newborns and infants, while in children, H-reflex latency greater that 20 msec is abnormal.

They showed that the minimum latencies of H-reflexes remained relatively constant during the first 3 years of life like the F-wave latencies.

For this study we wished to establish an institution-based normal values for the motor nerve conduction velocity, motor and sensory nerve action potential, F-wave and H-reflex values in healthy newborn, infants, and children by performing nerve conduction studies at the Neurodiagnostic Laboratory Clinical Electromyography Unit of the Philippine Children's Medical Center

METHODOLOGY

This was a prospective cross-sectional study. One hundred healthy children with age ranging from one day to 5 years were divided into 5 groups. The infant and children group is further subdivided according to different maturational changes observed in the development of various nerves among full term newborn, infants and children. The highest age limit is set at 5 years, because by the age 4 or 5 years, both MNCV and SNCV have attained adult range. Subjects were recruited from the outpatient and inpatient departments of PCMC and neighboring barangays from October 2015 to April 2016

The sample size was computed using the formula for estimation of one group mean: $n = (z^2 \times s^2)/d^2$ where $z = 1.96$ for 95% confidence level, s = sample standard deviation, d = accuracy of estimate or min difference from true mean. Sample standard deviation was based from the highest standard deviation of baseline mean conduction velocity among the nerves under each age group obtained by the UP-PGH study. The sample size of each age group was selected based on the largest sample size calculated and feasibility of recruiting the number of subjects.

The data was collected by a single experienced technician. The procedure was done using a VIASYS NicoletOne Viking Quest 4-

channel NCS/Electromyography/EP system machine serial number OL091835, with Viking quest NCS Software Bundle version 8.1 installed. A standard size 10 mm disc electrode was used for all ages except for neonates in which 6 mm surface electrode was used to the hands or feet as a reference recording electrode. Ring electrodes were used for sensory conduction studies of the fingers. A current stimulator probe model Nicolet S403 with an interelectrode distance of 2.0 cm was used to evaluate neonates, infants and children. Supramaximal square pulses of 0.1 ms duration were used. All testing was conducted in an air conditioned room and the room temperature was thermostatically controlled between 25-28 degrees Celsius. Skin temperature (measured by a thermometer at the axilla) was kept at ranges between 36.0 to 36.9 degrees Celsius, with a mean of 36.3 degrees Celsius.

Nerve conduction studies were done on either side of the extremity per examinee as there was no significant difference in the motor nerve conduction study on either side of the limbs as demonstrated in several studies[6]. The choice of the laterality of the extremity was based on convenience for the procedure. Unilateral examination of the limb simplified the procedure, allowing quick execution of the test and better compliance of the test subjects.

The presence of a parent was encouraged during the procedure because it could reduce fear and elicits child's cooperation. They could participate by holding the child's hand, having the child sit on the parent's lap or restraining the extremity to be tested. Stimulus artifacts were avoided through the following: (1) grounding of the machine; (2) instructions to avoid application of any medicinal or cosmetic products to the skin were given; (3) skin preparation using rubbing alcohol; (4) Reduce the electrical interference of the testing environment by disconnecting or switching off any irrelevant electrical appliances. Meticulous drug history was obtained prior to the procedure. Presence of any devices implanted in the body of the patient was asked to safeguard the patient.

A. MEASUREMENT OF SENSORY NERVE CONDUCTION VELOCITY

In the upper and lower limb, sensory nerve action potentials were recorded using antidromic technique. Conventional methods for sensory NCS of the different nerves were employed (Table 3) [15,24]. The reference electrode was placed about 2 and 3 cm distal to the active electrode for young infant and bigger children. For sensory nerve conduction, the machine was set as follows: sensitivity of 20 uV, sweep speed of 1 ms per division and filters low cut 20 Hz and high cut 3 KHz.

B. MEASUREMENT OF MOTOR NERVE CONDUCTION VELOCITY

For motor nerve conduction, the low cut filter was 2 Hz and the high cut was 10 KHz. Sweep speed was 2 ms/division. Sensitivity was 5 mV.

Measurements of motor nerve conduction followed conventional methods (Table 4).

C. MEASUREMENT OF F-WAVE LATENCY

For F-wave recording, the machine was calibrated at sweep speed 5 ms per division for the median and ulnar nerves and 10 ms per division for posterior tibial and peroneal nerves. Sensitivity was 200 uV per division for posterior tibial and peroneal nerves while 500 uV for ulnar and median nerve. Filter was between 2 Hz - 3 KHz for ulnar, posterior tibial and peroneal nerves, while in the median nerve 2 Hz – 10 KHz. The placement of the recording and stimulating electrodes was similar to the CMAP recording, with the only difference of placing the cathode of the stimulating electrode proximal to the anode. Stimulation of nerve was done at anatomical

landmarks, particularly wrist crease for median and ulnar nerves and ankle for peroneal and posterior tibial nerves. The ground electrode was placed between stimulation and recording surface electrode. F-wave studies were performed after motor studies of the same nerves. Minimum of 10 stimuli free of artifacts were passed as satisfactory recording of the F-waves and the minimum F-wave latency (shortest) and the maximal F-wave (longest) latencies were noted[12].

D. MEASUREMENT OF H-REFLEX LATENCY

The posterior tibial nerve was stimulated with a rectangular electrical pulse of 0.1 ms duration applied once every five seconds. The electromyographic setting was: low frequency filter of 2 Hz and high frequency filter of 3 KHz, sensitivity of 2 mV and sweep speed of 5 ms/division. Method for the measurement of H-reflex latency was similar to the method demonstrated in literature [15,24].

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. The correlation between the NCS parameters and age as well as the height and F-wave latencies was assessed using Spearman's correlation coefficient. All valid data was included in the analysis.

RESULTS

Out of 120 subjects screened, 100 were eligible and 20 failed screening mostly due to abnormal anthropometrics and poor compliance of the subject with the procedure. The distribution by age and sex are shown in Table 1. There were more males than females in all age groups. Effect of sex was not considered as there is no significant difference in latency or velocity between males and females [6].

Table 1. Demographic profile of 100 healthy Filipino children who underwent nerve conduction studies

	<30 days (n=17)	**1-6 months (n=17)**	**7-12 months (n=25)**	**1-3 years (n=26)**	**4-5 years (n=15)**
	Frequency (%); Mean ± SD				
Sex					
Male	9 (52.94)	9 (52.94)	16 (64.00)	16 (61.54)	11 (73.33)
Female	8 (47.06)	8 (47.06)	9 (36.00)	10 (38.46)	4 (26.67)
Age (Months)	0.43 ± 0.28	3.59 ± 1.50	9.36 ± 1.68	31.12 ± 9.77	52.6 ± 3.02

Tables 2 and 3 present summary statistics for sensory nerve conduction velocity and amplitude, for proximal motor nerve conduction velocity and amplitude and for distal motor nerve conduction latency and amplitude. All the CMAP morphologies were similar and biphasic except for one in the ulnar nerve, in which a double negative peak was found. The values for F-wave recordings of median, ulnar, posterior tibial and peroneal nerves as well as H-reflex

latency of the posterior tibial nerve were listed. Of the 100 participants, we were able to perform F-wave recordings of the peroneal nerves for 83 children. We were unable to complete the test for the 17 children because of technical difficulty obtaining adequate number of reliable measurements, which happens infrequently particularly in the peroneal nerve. Sometimes, no elicitable F-wave for the peroneal nerve is determined and is considered a normal variant[25]. The mean and standard deviation for the commonly tested peripheral nerves were reported if the parameter follows Gaussian distribution. Parameters that remained non-normal despite attempts of transformations to normal distribution were expressed as median and range.

Table 2. Average sensory nerve conduction parameters in 100 healthy Filipino children, according to age group

	<30 days (n=17)	**1-6 months (n=17)**	**7-12 months (n=25)**	**1-3 years (n=26)**	**4-5 years (n=15)**
	Frequency (%); Mean ± SD; Median (Range)				
Median Nerve					
SNAPA (uV)	20.35 ± 6.89	22.82 ± 7.38	29.08 ± 8.51	38.54 ± 1.37	40.6 ± 9.39
SNCV (m/s)	32.18 ± 3.80	43 (32 to 47)	45.92 ± 4.44	52.15 ± 3.50	54.0 ± 2.54
Ulnar Nerve					
SNAPA (uV)	20.65 ± 7.76	20.88 ± 5.97	27.2 ± 8.08	33.08 ± 9.62	29.87 ± 6.21
SNCV (m/s)	32.0 ± 3.72	41.35 ± 3.89	45.68 ± 4.57	51.5 (42 to 57)	53.27 ± 2.99
Radial Nerve					
SNAPA (uV)	14.82 ± 5.54	16.06 ± 4.94	20.28 ± 6.34	27.77 ± 5.67	27.2 ± 5.51
SNCV (m/s)	31.35 ± 3.33	42 (33 to 47)	43 (38 to 53)	51 (42 to 58)	54.13 ± 2.03
Sural Nerve					
SNAPA (uV)	15.29 ± 5.03	16.12 ± 5.12	20.0 ± 4.97	26.58 ± 7.67	29.0 ± 9.30
SNCV (m/s)	32.47 ± 3.79	41.71 ± 4.48	47.16 ± 4.90	53.5 (40 to 58)	53.33 ± 2.87
Superficial peroneal Nerve					
SNAPA (uV)	11 (8 to 26)	12.29 ± 3.02	15.84 ± 4.88	25.73 ± 7.20	25.87 ± 5.49
SNCV (m/s)	31 (23 to 35)	41.47 ± 4.57	46.64 ± 4.14	52.23 ± 3.89	53.33 ±2.72

Note: Median (Range) is used to Non normally distributed data

Table 3. Average motor nerve conduction parameters in 100 healthy Filipino children, according to age group

	<30 days (n=17)	1-6 months (n=17)	7-12 months (n=25)	1-3 years (n=26)	4-5 years (n=15)
	Mean ± SD; Median (Range)				
Median Nerve					
MNCV (m/s)	31.47 ± 3.61	41.88 ± 4.57	46.6 ± 5.81	51.65 ± 4.10	55 ± 4.64
DML (ms)	2.28 ± 0.26	2.08 ± 0.25	2.13 ± 0.29	2.20 ± 0.28	2.43 ± 0.28
CMAPA wrist (mv)	4.15 ± 0.70	4.75 ± 0.75	5.91 ± 0.98	6 (5 to 9.3)	6.67 ± 0.92
CMAPA elbow (mv)	3.72 ± 0.74	4.51 ± 0.79	5.65 ± 0.91	6.07 ± 1.21	6.46 ± 0.86
F-wave min (ms)	17.16 ± 1.71	17.26 ± 1.53	16.83 ± 1.27	19.06 ± 1.60	19.81 ± 1.06
F-wave max (ms)	19.06 ± 1.23	18.65 ± 1.74	18.91 ± 1.47	20.59 ± 1.42	21.55 ± 0.92
F-wave disp (ms)	1.91 ± 0.85	1.3 (0.8 to 2.8)	2.08 ± 0.92	1.53 ± 0.46	1.74 ± 0.78
Ulnar Nerve					
MNCV forearm (m/s)	33 (26 to 36)	42 ± 4.85	45 (41 to 63)	53.62 ± 5.76	57.47 ± 3.38
MNCV across elbow (m/s)	34 (25 to 36)	41.65 ± 4.77	45 (41 to 60)	53.15 ± 5.49	57 ± 3.84
DML (ms)	2.02 ± 0.32	1.74 ± 0.20	1.56 ± 0.25	1.63 ± 0.24	1.67 ± 0.25
CMAPA wrist (mv)	4.23 ± 0.89	5.49 ± 1.04	5.6 (4.2 to 8.7)	6.1 (4.5 to 10.6)	7.25 ± 1.15
CMAPA elbow (mv)	3.95 ± 1.02	5.37 ± 1.08	5.5 (4 to 8.7)	6.05 (4.5 to 10.6)	7.21 ± 1.11
CMAPA above elbow (mv)	3.86 ± 1.00	5.25 ± 1.14	5.4 (4 to 8)	5.75 (4.5 to 10.1)	7 ± 1.19
F-wave min (ms)	18.27 ± 1.56	18.22 ± 1.53	17.92 ± 1.67	19.31 ± 1.19	19.61 ± 0.98
F-wave max (ms)	20.18 ± 1.62	19.71 ± 1.74	19.7 (16.2 to 21.8)	20.78 ± 1.10	21.03 ± 0.69
F-wave disp (ms)	1.91 ± 0.84	1.49 ± 0.73	1.56 ± 0.62	1.48 ± 0.59	1.42 ± 0.65

Table 3. (Continuation)

Peroneal Nerve					
MNCV leg (m/s)	29.59 ± 3.10	42 (33 to 44)	45.64 ± 3.74	50 (41 to 53)	50.86 ± 3.62
MNCV across knee (m/s)	30 ± 3.10	42 (31 to 44)	44 (40 to 50)	50 (42 to 52)	50 (44 to 58)
DML (ms)	2.2 (1.7 to 3.5)	1.79 ± 0.32	1.78 ± 0.38	1.92 ± 0.42	2.5 (1.8 to 4.2)
CMAPA ankle (mv)	1.81 ± 0.59	2.24 ± 0.81	2.42 ± 0.66	3.25 (1.6 to 4)	3.37 ± 0.98
CMAPA knee (mv)	1.76 ± 0.55	2.11 ± 0.77	2.41 ± 0.63	3.11 ± 0.52	3.32 ± 0.97
CMAPA above knee (mv)	1.73 ± 0.57	2.02 ± 0.71	2.33 ± 0.62	3.08 ± 0.49	3.27 ± 0.98
F-wave min (ms) (n=83)	18.86 ± 1.37	18.35 (17.4 to 28.9)	18.73 ± 0.73	20.28 ± 1.00	20.89 ± 1.04
F-wave max (ms) (n=83)	21.18 ± 2.01	21.2 (19 to 29.9)	20.9 ± 0.71	21.73 ± 1.02	22.13 ± 1.15
F-wave disp (ms) (n=83)	2.1 (0.7 to 6.2)	2.08 ± 0.78	2.18 ± 0.85	1.2 (0.6 to 4.2)	1.1 (0.6 to 2.6)
Posterior Tibial Nerve					
MNCV (m/s)	31 (24 to 34)	42 (32 to 45)	45 (41 to 52)	51 (43 to 55)	51 (44 to 55)
DML (ms)	2.21 ± 0.32	2.08 ± 0.27	1.9 ± 0.41	2.25 ± 0.40	2.45 ± 0.45
CMAPA ankle (mv)	5.12 ± 1.30	6.73 ± 1.74	7.95 ± 2.38	8.95 (5.4 to 15.6)	8.71 ± 1.57
CMAPA knee (mv)	3.87 ± 1.32	6.28 ± 1.87	7.33 ± 2.20	8.8 (4 to 13)	7.77 ± 1.60
F-wave min (ms)	20.27 ± 2.55	19.65 ± 1.59	19.06 ± 1.39	20.4 (18.8 to 26.3)	20.65 ± 1.34
F-wave max (ms)	22.1 (16.8 to 28.9)	21.65 ± 1.42	21.03 ± 1.09	22.14 ± 1.77	21.79 ± 1.44
F-wave disp (ms)	2.28 ± 1.04	2 ± 0.88	1.97 ± 0.83	1.42 ± 0.78	1.13 ± 0.31
H-reflex (ms)	18.8 ± 2.41	19.13 ± 2.37	19.66 ± 2.97	20.93 ± 2.35	20.65 ± 1.58

Note: Median (Range) is used to Non normally distributed data

We obtained the values for the 5th and 95th percentiles for each age group, as recommended by the AANEM as a more effective way of reporting normal values, thus reported in Table 4-5. Reference values based on estimates of the 95th percentiles for sensory and for motor nerve conduction latency while 5th percentiles for amplitude and velocity were assumed as cut-off or thresholds as the highest and lowest normal value, respectively.

Table 4. Values of the 5th and 95th percentile of select parameters of different types of sensory nerves, by age group

	<30 days (n=17)	**1-6 months (n=17)**	**7-12 months (n=25)**	**1-3 years (n=26)**	**4-5 years (n=15)**
	5th, 95th				
Median Nerve					
SNAPA (uV)	12, 36	13, 39	20, 47	24, 57	25, 62
SNCV (m/s)	26, 38	32, 47	41, 53	44, 58	50, 59
Ulnar Nerve					
SNAPA (uV)	10, 37	14, 37	17, 42	19, 51	20, 44
SNCV (m/s)	26, 38	32, 47	41, 52	45, 56	49, 59
Radial Nerve					
SNAPA (uV)	6, 25	10, 30	12, 29	17, 36	14, 36
SNCV (m/s)	25, 28	33, 47	41, 52	43, 56	51, 58
Sural Nerve					
SNAPA (uV)	8, 27	8, 28	13, 28	17, 39	15, 51
SNCV (m/s)	24, 38	32, 50	41, 55	46, 58	50, 59
Superficial peroneal Nerve					
SNAPA (uV)	8, 26	8, 19	10, 24	16, 41	14, 34
SNCV (m/s)	33, 35	33, 50	41, 53	45, 57	50, 59

Table 5. Values of the 5th and 95th percentile of select parameters of different types of motor nerves, by age group.

	<30 days (n=17)	1-6 months (n=17)	7-12 months (n=25)	1-3 years (n=26)	4-5 years (n=15)
			5th, 95th		
Median Nerve					
MNCV (m/s)	25, 37	32, 50	40, 56	45, 58	46, 62
DML (ms)	1.8, 2.8	1.4, 2.4	1.6, 2.5	1.8, 2.6	2.1, 3.1
CMAPA wrist (mv)	3.2, 5.6	3.4, 5.9	4.7, 7.5	5, 8.7	5.1, 8.6
CMAPA elbow (mv)	2.5, 5.4	3.1, 5.5	4.1, 7.4	5, 8.7	5, 8
F-wave min (ms)	14, 20.2	15, 19.9	15.1, 18.6	16.6, 21.3	18.4, 21.6
F-wave max (ms)	16.7, 21.3	15.9, 21.5	16.4, 20.9	18.5, 22.7	19.6, 22.5
F-wave disp (ms)	0.7, 3.5	0.8, 2.8	1, 3.4	0.8, 2.1	0.8, 3.4
Ulnar Nerve					
MNCV forearm (m/s)	26, 36	34, 53	42, 60	45, 64	52, 63
MNCV across elbow (m/s)	25, 36	33, 51	41, 59	44, 63	50, 64
DML (ms)	1.2, 2.5	1.3, 2	1.1, 1.9	1.3, 2.1	1.1, 2.3
CMAPA wrist (mv)	2.4, 5.4	3.7, 7.3	4.5, 8.3	5, 7.4	5.8, 9.8
CMAPA elbow (mv)	1.9, 5.3	3.7, 7.3	4.1, 8.4	5, 7.8	5.8, 9.8
CMAPA above elbow (mv)	1.9, 5.3	3.2, 7.3	4, 8	5, 7.8	5.4, 9.7
F-wave min (ms)	15.8, 21	15.6, 20.7	15.2, 20.1	17.1, 21	18.2, 21.6
F-wave max (ms)	17.4, 22.8	17.2, 22.2	16.2, 21.5	18.4, 22.4	19.9, 22.4
F-wave disp (ms)	0.7, 3.8	0.6, 2.8	0.6, 2.8	0.6, 2.4	0.6, 3.2
Peroneal Nerve					
MNCV leg (m/s)	23, 33	33, 44	41, 52	43, 53	43, 57
MNCV across knee (m/s)	24, 33	31, 44	42, 50	42, 51	44, 58
DML (ms)	1.7, 3.5	1.3, 2.6	1.2, 2.3	1.3, 2.7	1.8, 4.2
CMAPA ankle (mv)	1.1, 2.8	1, 3.6	1.5, 3.9	2.1, 3.8	2, 5.7
CMAPA knee (mv)	1.1, 2.8	1, 3.6	1.5, 3.8	2.2, 3.8	2, 5.7
CMAPA above knee (mv)	1, 2.8	1, 3.3	1.5, 3.8	2.3, 3.8	2, 5.6
F-wave min (ms) (n=83)	16.5, 22.1	17.4, 28.9	17.4, 19.7	18.55, 21.8	19.1, 22.4
F-wave max (ms) (n=83)	17.7, 25.3	19, 29.9	19.5, 21.95	19.95, 23.25	20, 24.8
F-wave disp (ms) (n=83)	0.7, 6.2	1, 3.2	1.1, 3.9	0.6, 3.6	0.6, 2.6

Table 5. (Continuation)

Posterior Tibial Nerve					
MNCV (m/s)	24, 34	32, 45	42, 50	43, 54	44, 55
DML (ms)	1.7, 2.7	1.5, 2.6	1.4, 2.7	1.7, 2.9	1.9, 3.3
CMAPA ankle (mv)	3.1, 7.3	3, 9.7	5, 11.5	5.7, 14.6	6.4, 11.4
CMAPA knee (mv)	2.2, 6.8	3, 9.7	4.5, 10	4.9, 12.8	5, 10.8
F-wave min (ms)	14.8, 26.1	16.9, 22.5	17.1, 21.3	18.9, 24.1	19, 23.4
F-wave max (ms)	16.8, 28.9	19.1, 23.9	19.2, 23.1	19.6, 25.2	20.1, 25.2
F-wave diff (ms)	0.8, 4.4	1.1, 3.6	0.7, 3.4	0.6, 2.8	0.7, 1.8
H-reflex (ms)	16.1, 23.6	15, 23.8	16.1, 24	17.4, 24	17.6, 23.5

The correlation with age of all sensory and most of motor nerve conduction parameters is evident in the high values of correlation coefficient presented in Table 6-7. Distal motor latency has poor correlation in all motor nerves. Age and height exhibit a direct correlation with F-wave minimum and maximum latency of median, ulnar, and peroneal nerves (Table 8).

Table 6. Correlation between age and sensory nerve conduction parameters

	Correlation Coefficient	**Interpretation**	**P-value**
Median Nerve			
SNAPA (uV)	0.673	Direct, strong	**0.000**
SNCV (m/s)	0.870	Direct, very strong	**0.000**
Ulnar Nerve			
SNAPA (uV)	0.502	Direct, moderate	**0.000**
SNCV (m/s)	0.846	Direct, very strong	**0.000**
Radial Nerve			
SNAPA (uV)	0.641	Direct, strong	**0.000**
SNCV (m/s)	0.904	Direct, very strong	**0.000**
Sural Nerve			
SNAPA (uV)	0.649	Direct, strong Direct, very strong	**0.000**
SNCV (m/s)	0.826		**0.000**
Superficial Peroneal Nerve			
SNAPA (uV)	0.719	Direct, strong	**0.000**
SNCV (m/s)	0.861	Direct, very strong	**0.000**

Statistical test: Spearman's correlation coefficient

Table 7. Correlation between age and motor nerve conduction parameters

	Correlation Coefficient	Interpretation	P-value
Median Nerve			
MNCV (m/s)	0.850	Direct, very strong	**0.000**
DML (ms)	0.156	Direct, very weak	0.121
CMAPA wrist (mv)	0.694	Direct, strong	**0.000**
CMAPA elbow (mv)	0.693	Direct, strong	**0.000**
F-wave min (ms)	0.538	Direct, moderate	**0.000**
F-wave max (ms)	0.559	Direct, moderate	**0.000**
F-wave disp (ms)	-0.037	Indirect, very weak	0.714
Ulnar Nerve			
MNCV forearm (m/s)	0.875	Direct, very strong	**0.000**
MNCV across elbow (m/s)	0.877	Direct, very strong	**0.000**
DML (ms)	-0.326	Indirect, weak	**0.001**
CMAPA wrist (mv)	0.637	Direct, strong	**0.000**
CMAPA elbow (mv)	0.644	Direct, strong	**0.000**
CMAPA above elbow (mv)	0.627	Direct, strong	**0.000**
F-wave min (ms)	0.319	Direct, weak	**0.001**
F-wave max (ms)	0.231	Direct, weak	**0.021**
F-wave disp (ms)	-0.146	Indirect, weak	0.148
Peroneal Nerve			
MNCV leg (m/s)	0.816	Direct, very strong	**0.000**
MNCV across knee (m/s)	0.839	Direct, very strong	**0.000**
DML (ms)	0.094	Direct, very weak	0.398
CMAPA ankle (mv)	0.586	Direct, moderate	**0.000**
CMAPA knee (mv)	0.594	Direct, moderate	**0.000**
CMAPA above knee (mv)	0.610	Direct, strong	**0.000**
F-wave min (ms) (n=83)	0.546	Direct, moderate	**0.000**
F-wave max (ms) (n=83)	0.302	Direct, weak	**0.006**
F-wave disp (ms) (n=83)	-0.442	Indirect, moderate	**0.000**
Posterior Tibial Nerve			
MNCV (m/s)	0.875	Direct, very strong	**0.000**
DML (ms)	0.181	Direct, very weak	0.072
CMAPA ankle (mv)	0.563	Direct, moderate	**0.000**
CMAPA knee (mv)	0.551	Direct, moderate	**0.000**
F-wave min (ms)	0.143	Direct, very weak	0.155
F-wave max (ms)	-0.071	Indirect, very weak	0.481
F-wave disp (ms)	-0.443	Indirect, moderate	**0.000**
H-reflex (ms)	0.333	Direct, weak	**0.001**

Statistical test: Spearman's correlation coefficient

Table 8. Correlation between the height and F-wave minimum and maximum latency (ms)

	Correlation Coefficient estimate	Interpretation	Number of samples	P-value
Median Nerve				
F-wave min (ms)	0.5252	Direct, moderate	100	**0.0000**
F-wave max (ms)	0.5472	Direct, moderate	100	**0.0000**
Ulnar Nerve				
F-wave min (ms)	0.3176	Direct, weak	100	**0.0013**
F-wave max (ms)	0.2212	Direct, weak	100	**0.0270**
Peroneal Nerve				
F-wave min (ms)	0.5482	Direct, moderate	83	**0.0000**
F-wave max (ms)	0.3056	Direct, weak	83	**0.0050**
Posterior Tibial Nerve				
F-wave min (ms)	0.1474	Direct, very weak	100	0.1432
F-wave max (ms)	-0.0860	Indirect, very weak	100	0.3951

Statistical test: Spearman's correlation coefficient

DISCUSSION

The MNCV and SNCV obtained showed an increase as the chronological age increased. The rate of increment of MNCV and SNCV was more rapid between the first two groups. In subsequent groups, the change in nerve conduction velocity showed generally small increase. This trend can be explained by the positive correlation of velocity and increasing diameter of the axon and degree of myelination of fibers in growing children. It parallels the most rapid increase in numbers of myelinated fibers in the 1st year of life, consequently resulting to an increase in the axonal diameter. The association of nerve conduction velocity with age is further reinforced in Table 6-7, which showed strong statistical significance. This finding collaborated with the finding of other researchers in the influence of age on nerve conduction velocities[2-9]. However, no increase was seen in the last two groups for the MNCV of the peroneal and posterior tibial nerve and the SNCV of the sural nerve.

Some of our findings on nerve conduction velocity in older children were observed to be in congruent to those reported by Kimura[15] and Kaeser [3] about normal variations in nerves and segments. The motor conduction velocities were slower in the legs than in the arms as in the present study. This is because of the inverse relationship between height and nerve conduction velocity, so nerves conduct slower in longer nerves than in shorter nerves.[15] On the other hand, we observe minimal to no difference in the ulnar and peroneal nerve motor conduction at proximal than distal sites, contrary to the findings that conduction velocity is always faster in the proximal than in the distal segment

along the same nerve. The distal slowing of nerve conduction velocity can be explained by two factors: (1) temperature difference of approximately 1°C between the proximal and distal parts of the nerve along the extremity, and (2) a decrease in the average fiber diameter of the fastest conducting fibers because of branching and tapering in distal parts of the nerve.[3] The absence of difference in the present study can be because the events in the outgrowth and maturation of the peripheral nerves are probably not yet taking place completely in the included age group. No conclusion about statistical difference between nerves of the arms and legs can be made because this was not included in the study.

In this study, we calculated the percentage of the mean values of conduction velocity and amplitudes of that age to reach the normal adult values. For the actual percentage value, you may refer to the Appendix. Nerve conduction velocities reach adult range at age 3-5 years in the literature. However in this study, the pace of maturation in conduction velocity is faster. The adult values were already reached in group IV (1-3 years) in the nerves of upper limbs namely median, ulnar and radial nerves, while group II (1-6 months) in the nerves of the lower limbs in the peroneal, sural and posterior tibial nerves. All the neonatal conduction velocities were 62-67% of the normal adult values in the nerves of upper limb, 74-78% in the lower limb, which is in contrast with previous reports of 50% of adult values in foreign literature.

Compound muscle action potential (CMAP) amplitudes of the posterior tibial nerve are also the first to reach adult value in group II, which is earlier than observed by Amante (reached at 1 year) and Cai and Zhang and Gucchait (reached at 2 years) While the CMAP amplitudes of ulnar and peroneal nerves reach adult values between 1-3 years age similar to Amante (reached at 2-3 years). The peroneal CMAP is still below the adult range by 5 years like the findings of Cai and Zhang. There was no progressive evolution of SNAP amplitudes noted in this study.

The differences we found in the pattern of maturation as compared with previous report was because estimation of percentage was done using adult normal values obtained before in a different institution. A more accurate relationship between the normal children and adult values can be determined if adult values were simultaneously obtained and compared with the present study. The higher amplitude we noted was influenced by differences in the distance from the skin to the nerve. This is especially true during sensory NCS in which the nearer the G1 recording electrode is from the action potential generator, the higher the amplitude of the response, and vice versa[26]. We hypothesized that our subjects have shorter distances between the skin and the nerve, or thinner subcutaneous tissue.

Comparison to several reference ranges found in the literature is carried out in this study, however normal limits for reference ranges having the same age group of radial and superficial peroneal nerves is not specified in any published data so no comparison was made. The MNCV values of the median, ulnar, peroneal and posterior tibial nerves showed good similarity with local data but rather higher than that of foreign data. The CMAPA values of the ulnar, peroneal and posterior tibial were less than the reported values in the data of Parano and Cai and Zhang while they were in close proximity with the local data. In contrast, the CMAPA of the median nerve was close to the values of Amante and Cai and Zhang. The motor latencies of all nerves, especially the median nerve were similar to others.

The data of median and ulnar SNCV and SNAPA were higher to the results of Miller and

Kuntz, Cruz Martinez. Both median and ulnar SNCV and SNAPA were either higher or lower to data reported by Amante. On the other hand, sural SNCV and sural SNAPA were higher than the local and foreign results.

The values for most of the nerve conduction parameters showed differences between the results of the present study with the data published in literature and could be attributed to variety of causes. The age distribution of the subjects from previous studies did not correspond well with the present study. In the best conditions, increasing the number of examined subjects will smooth data and reduce bias in the statistics. The diversity of the environment and techniques could have resulted for the differences. The difference in NCS values obtained between westerners and Asian populations could also explain the varied results. Based in the experience of Pitt and Kang in the central London hospital, the Caucasian population has the slowest conduction velocity of any ethnic group. They also observe a wide range of amplitudes encountered between ethnic groups. For example, median sensory amplitude reaching as high as 160 uV in certain ethnic groups or as low as 30-35 uV in other ethnic groups without evidence of peripheral nerve damage[27].

The trend of F-wave minimum latency with age in all nerves showed decrease in the first 6-12 months, then a rapid increase after 1 year then remained constant at 3 years as observed in the study of Garcia et al. This evolution is because of two simultaneous processes occurring: 1) a rapid increase of the conduction velocity, and 2) a parallel increase of length of extremity. The period of the most rapid increase in conduction velocity is responsible for the constant value of F-minimal latency or lag time during the first six months of life. In the next six months (6 months to 1 year), the increase in conduction velocity of the fastest fibers would parallel skeletal growth, reducing the F-minimal latency during this period. However, after the first year, the increase in arm length predominates and becomes responsible for the observed increase of F-minimal latency[12].

Age is directly interrelated in children for F-wave min and F-wave max in the median, ulnar and peroneal nerves except the posterior tibial nerve (Table 11). F-wave chronodispersion was not related with age in children in previous study [22] but in the present study it showed good correlation in the peroneal and posterior tibial nerves.

Our observation of F-wave minimum latency in the present study is longer in the median, ulnar, and posterior tibial nerve but shorter in the peroneal nerve as compared to observation made in other studies (Table 18). Such differences can be explained by the effect of limb length discrepancy. Lower mean F-wave latency is seen if the subjects have lower height and hence shorter limbs. For example, from the study of Nadeem et al, they observed that the F-wave minimal latency for the ulnar nerve have lower mean values in Iraqi children than in Western children due to height differences[12].

The F wave maximum latency values also followed the same changes as F-wave minimum latency, reduced in first year of life then increased with age afterwards. In comparison, maximal latency values reflect conduction in the slowest conducting fibers participating in the formation of the F-wave. It showed a nearly constant value during the first year of life, and it increased linearly as the upper limb length increased with age.

Height has positive association with minimum F-wave latency in all motor nerves such that as subject's height increases, latency of conduction increases. The height correlated well with F-wave min and max in median nerve and F-wave min of peroneal nerve (Table 12), which

was also shown in the scatter plots similar to the study of Puksa.

The mean latency of the H-reflex progressively increases with age but the changes are little and then remain constant when it reaches 4-5 years (Table 7). This coincides at the same time the length of the reflex markedly increases as child grows and the body height increases[28]. We did not observe diminishing of latency during the first year of life, which is also the time of maximal increase in conduction velocity due to growth in thickness of the fiber than lengthening develop. This trend was not observed because height and limb length was not factored in the computation of sample size.

The result of the latency of H-reflex in the present study was higher than those reported by studies listed in Table 19. H-reflex latency was found to increase with hip flexion angles (from 0.1 to 3.4 ms with hips flexed at 30^o and from 0.6-4.3 ms with hips flexed at 40^o in normal subjects). Thus, the ideal posture for research studies of H-reflex must be kept, in particular the children may be placed either in a reclining position, with the lower limb supported by a restraining table made in the laboratory, or in a prone position, with the foot resting on a fixed bar. This position keeps the flexion of the knee joint at 120^o and flexion of the ankle at 90^o as recommended by Hugon[28], which takes stretch off the bi-articular gastrocnemius muscles. Unfortunately, the appropriate posture and restraint was not done in the present study because of difficulty with keeping the position of our subjects.

CONCLUSION AND RECOMMENDATIONS

In conclusion, we have constructed a complete and clinically useful reference standard of conduction parameters of the peripheral nerves in the upper and lower limbs. Overall, the nerve conduction parameters of the commonly tested nerves compared favorably with the existing literature data. Some values deviated minimally with previously published results but still fall within the accepted norms, mandating the use of country specific normal values. However, the H-reflex latency showed departure with other researches. Age showed a statistically significant association in all analyses of sensory assessment relating to amplitude and velocity (all $p<0.001$ or higher levels of significance). Statistically significant age effects were also found in all analyses of motor assessments relating to velocity and amplitude for median, ulnar, peroneal and posterior tibial nerves, except motor latency for all nerves. Age and height had major role in the determination of F-wave minimum and maximum latencies. Both of these covariates should be considered in clinical evaluations of peripheral nerve function.

The reference values presented here can be applied to identify impairments among patients with peripheral nerve disorders in our laboratory as well as start researches on neuromuscular disorders in a cohort of children. Nerve conduction parameters are known to vary with demographic profile such as sex and anthropometric measurements such as height, limb length and body mass index. Diagnostic conclusions from nerve conduction data without making corrections or adjustments to factors that influence the data may be invalid. The effect of these variables was not included in the present study and this can be future areas of research. A study with larger sample size that separates subjects into cohorts based on demographic information is also recommended to increase power and precision. It can be done through multicenter collaborative effort to better clarify the generalizability of the results. At the same time, it can validate our results especially the H-reflex. The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) had recommended a set of methodologically sound criteria to establish

high-quality reference values for nerve conductions studies for adult populations and these can guide similar normative studies in children, especially newborns which we have no local data yet[23].

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A COMPARISON OF LEVOBUPIVACAINE AND BUPIVACAINE IN CAUDAL ANESTHESIA IN CHILDREN UNDERGOING SUB-UMBILICAL OPERATIONS

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ABSTRACT

BACKGROUND: Caudal epidural anesthesia is commonly performed in conjunction with general anesthesia. Bupivacaine and Levobupivacaine are used in epidural blockade that provide anesthesia and analgesia intraoperative and post-operatively.

OBJECTIVES: To compare the intraoperative and postoperative efficacy and safety of Bupivacaine and Levobupivacaine in children undergoing elective sub-umbilical operations under general and caudal anesthesia.

METHODS: Randomized control trial done in Philippine Children's Medical Center. Sixty-one subjects aged 6 months - 8 years old, ASA I-II, undergoing subumbilical operations were randomly grouped to receive Bupivacaine and Levobupivacaine during anesthesia induction. Hemodynamic parameters, Bromage, and CHIPPS were recorded.

RESULTS: Results suggest both drugs have a significant effect in lowering heart rate and MAP. Bromage scores for patients from both groups are constant at 0. The number of patients with a CHIPPS classification of 4-10, is significantly higher for bupivacaine group than levobupivacaine group.

CONCLUSION: Both Bupivacaine and Levobupivacaine provide adequate analgesia intraoperatively with no reports of intraoperative movement, increased inhalational agent concentration and additional intravenous analgesics. Post-operatively, no adverse effects and motor block was noted however Levobupivacaine has a longer efficacy as it required lesser rescue doses post-operatively compared to Bupivacaine.

KEYWORDS: Caudal Anesthesia, Bupivacaine, Levobupivacaine

INTRODUCTION

Epidural blockade in children continues to grow in popularity with increasing applications in the operating room. In infants and children, epidural analgesia, particularly via the caudal route, is most commonly performed in conjunction with general anesthesia as a means of providing analgesia or as a combined general-regional anesthetic technique to limit the requirements for general anesthetic agents. When performed preemptively prior to surgical incision, caudal blockade may ablate the surgical stress response, decrease post-operative analgesia requirements, and improve post-operative course.[1]

Bupivacaine is a local anesthetic drug belonging to the amino amide group. It is one of the most common drugs administered caudally and serves as the standard drug in pediatric anesthetic practice. It is an effective analgesic; however it is associated with prolonged motor block and some degree of cardiotoxicity as depicted in some studies.[2,3,4]

Levobupivacaine is also a local anesthetic drug belonging to the amino amide group. It is the S-enantiomer of Bupivacaine. Many studies have demonstrated that although racemic bupivacaine is the most commonly used local anesthetic drug for caudal anesthesia in children, levobupivacaine provides similar analgesic effects as bupivacaine with a wide safety margin when used in the pediatric population however at a higher cost. Levobupivacaine is a generally well-tolerated anesthetic and analgesic with a wide range of clinical effectiveness and can be used as an alternative to bupivacaine.[2,5,6]

Systemic side effects of local anesthetics involve cardiovascular, neurologic, and allergic effects mainly due to inadvertent intravascular injection. Cardiovascular effects include myocardial depression and dysrhythmias with signs and symptoms such as chest pain, shortness of breath, palpitations, lightheadedness, diaphoresis, hypotension, and syncope. Neurologic effects include lightheadedness, dizziness, visual and auditory disturbances, disorientation, drowsiness, muscle twitching, convulsions, unconsciousness, coma, respiratory depression and arrest, cardiovascular depression and collapse. Allergic manifestations of local anesthetics include urticaria and rashes.[7]

Previous studies have been done adult subjects comparing directly Bupivacaine and Levobupivacaine, however no studies have been done in the pediatric population both locally and internationally. This is the first study directly comparing the two study drugs in the local setting. This study uses anesthetic concentrations that are optimal based on previous studies. The aim of this prospective randomized control trial is to determine the efficacy of Levobupivacaine which has less reported adverse effects than the standard drug Bupivacaine.

There are several studies in the adult population regarding the use of Bupivacaine and Levobupivacaine. In 1998, Bardsely et. al. concluded that following intravenous administration of levobupivacaine produces significantly less effects on cardiovascular function than does *rac* bupivacaine. The negative inotropic effect for levobupivacaine was less than that for *rac* bupivacaine as indicated by changes in stroke index, acceleration index and ejection fraction.[8]

In 2011, Davies et. al. compared the use of plain Levobupivacaine and additives such as Ketamine and Clonidine along with Levobupivacaine and have concluded that there are no significant differences among the study groups in terms of analgesic efficacy and that additives increased post-operative sedation.[9]

There are likewise related studies regarding the 2 anesthetic drugs in children. In 2012, Tarkase et. al. compared different concentrations of Levobupivacaine at 0.125%, 0.2%, and 0.25% in children undergoing surgery below the umbilicus. It was concluded in their observations that 0.2% might represent the best clinical option in using Levobupivacaine in the said setting.[6]

In 2013, Bilgen et. al. compared different concentrations of Bupivacaine in children undergoing circumcision surgery and concluded that lower concentration and higher volume provided better analgesia.[10]

In 2003, Ivani et. al. compared three concentrations of Levobupivacaine for caudal blockade in patients undergoing subumbilical surgery. It was concluded that 0.125% was associated with less early motor blockade but resulted in lesser duration of anesthesia. The use of 0.20% Levobupivacaine might represent the

best option to be used in caudal blockade for children.[11]

In 2004, Locatelli et. al. compared Bupivacaine 0.25%, Levobupivacaine 0.25%, and Ropivacaine 0.25% in children undergoing sub-umbilical procedures under caudal anesthesia. It was concluded that the three drugs have comparable analgesic efficacy and that Bupivacaine was associated with higher incidence of residual motor block and longer duration of analgesia as compared to Levobupivacaine and Ropivacaine.[12]

In 2009, Ingelmo et. al. did a study to compare the relative analgesic potencies of Levobupivacaine and Ropivacaine for caudal analgesia in children. It was concluded that there were no significant differences in the ED50 for caudal levobupivacaine and ropivacaine indicating that they have similar potency.[13]

This research aims to compare the intraoperative and postoperative efficacy and safety of Bupivacaine and Levobupivacaine in children undergoing elective sub-umbilical operations under general and caudal anesthesia. Specifically, we aimed:

1. To compare the analgesic efficacy of the study drugs in terms of pain scale using the Children and Infant Postoperative Pain Scale (CHIPPS).

2. To determine and compare the safety between Bupivacaine and Levobupivacaine in terms of the absence of residual blockade, that being the intensity of motor block postoperatively using the Bromage Scale and the absence of adverse events.

3. To determine and compare between Bupivacaine and Levobupivacaine the hemodynamic effects in terms of intraoperative changes in mean arterial pressure and heart rate.

METHODOLOGY

The research design used was a double-blind experimental design/randomized control trial. The target population of this study are patients, American Society of Anesthesiologists (ASA) Physical Status Classification I-II (I – no organic, physiologic, biochemical, or psychiatric disturbance; II – mild to moderate systemic disturbance that may not be related to the reason for surgery; III – severe systemic disturbance that may or may not be related to the reason for surgery; IV – severe systemic disturbance that is life threatening with or without surgery; V-moribund patient who has little chance of survival but is submitted to surgery as a last resort) who underwent sub-umbilical operations such as herniotomy, circumcision, pelvic exploration, and lower extremity operations. The exclusion criteria are any contraindication to caudal anesthesia or to the use of Bupivacaine or Levobupivacaine such as hypersensitivity reactions, infection at the puncture site, and patient or parental refusal.

Sample size computation was based on the results of a similar study conducted by Locatelli et.al. (2004) in which the proportion of children who were recorded to experience no motor block at wake-up (motor block scale = 0) are 0.1212 and 0.4848 for Bupivacaine and Levobupivacaine, respectively. The power of the test used is 0.80 with a significance level of 0.05. Using these specifications, a sample size of 60 with 30 observations each for Bupivacaine and Levobupivacaine group were obtained.

This is a double-blind randomized controlled trial conducted from January 2016 to April 2016 at the Philippine Children's Medical Center (PCMC). The study commenced upon approval from both the Office of Research Development (ORD) and the Institutional Research Board-Ethics Committee of (IRB-EC) of PCMC.

Preoperative visits were conducted at least 1 day prior to the procedure. Medical history was obtained, and physical examination was performed on the patient. Standard preoperative laboratory tests such as complete blood count, chest x-ray, and ECG was obtained. No patients in the study were excluded due to existing cardiac problems.

Informed written consent was obtained from the parent or guardian of each eligible patient as well as assent for patients 7 years old and above. Demographics and patient characteristics were obtained.

All patients received standardized anesthetic care. Patients were placed on nothing per orem (NPO) according to the ASA Fasting Guidelines. Venoclysis was started once on NPO using large-bore IV catheter appropriate for age and Dextrose-containing Lactated Ringer's Solution.

At the operating room, standard monitoring was applied using pulse oxymeter, non-invasive blood pressure, electrocardiogram and temperature probe. General anesthesia was induced using Midazolam 0.2mg/kg, Atropine at 20 mcg/kg, Propofol 2 mg/kg, Sevoflurane 6%, and Rocuronium 0.6 mg/kg or Atracurium 0.5 mg/kg for patients requiring intubation. Anesthesia was maintained using oxygen inhalation and Sevoflurane 1-2%. After general anesthesia induction, patient was placed in lateral decubitus position. Skin was disinfected using 10 % Povidone Iodine solution. Sacral puncture was done at the level of S2-S4 using 23-gauge hypodermic needle. Confirmation of placement at epidural space was done by injecting 1 cc Plain Normal Saline Solution (NSS). In this study, the following team members were assigned; Anesthesiologist A (AA) and Anesthesiologist B (AB) in the pre-induction room, Anesthesiologist C (AC) in the operating room, and Anesthesiologist D (AD) in the Post-Anesthesia Care Unit (PACU). The assigned individual anesthesiologist may have a different role per case, however no overlapping of scheduled cases occured. Prior to anesthetic induction, the patients were randomly distributed by AA into two groups by computerized block randomization. The first group received Bupivacaine 0.2% 1 ml/kg (Group B), while the second group received Levobupivacaine 0.2% 1 ml/kg (Group L), one dose during anesthetic induction. The anesthetic solutions were prepared by AB. There was double blinding on the part of the patient and the attending anesthesiologist AC. After injection of anesthetic solution by AC, patient was placed in supine position and the operation allowed to start.

Systolic and diastolic blood arterial pressure, mean arterial pressure (MAP), and heart rate were recorded every five minutes until awakening. An intraoperative successful blockade is defined as hemodynamic reaction or drop in MAP or heart rate<20% compared with baseline reading before injection of the study drug in response to surgical incision (i.e. subumbilical midline incision, Pfanensteil incision, suprapubic incision). These patients were included in the study. For patients who did not obtain a successful block (i.e. heart rate and blood pressure increase >20% from baseline, movement of patient upon incision, increasing level of Sevoflurane >2% volume concentration), intraoperative Fentanyl 2 mcg/kg was given intravenously and were then excluded from the study. The need for rescue analgesia

intraoperatively was determined by AC based on the above-mentioned criteria for unsuccessful blockade. Adverse events were monitored via direct observation and electronic monitoring by AC in the operating room and post-anesthesia care unit from the time the local anesthetic solution was injected up to the time patient was transferred out of the post anesthesia care unit.

After emergence from anesthesia, patients were transferred to the Post-Anesthesia Care Unit under the care of AD. All patients received four to five liters per minute of oxygen by face mask. Motor block was assessed using the Bromage Scale (0-no motor block, 1-can flex knee, 2-can move foot only, 3-cannot move feet or knees) every 20 minutes. The heart rate, blood pressure, respiratory rate, and pain score were assessed for two hours. Postoperative analgesia was evaluated using the CHIPPS. Each variable (crying, facial expression, posture of the trunk, posture of the legs, and motor restlessness) is given a score of 0-2 with a total score of >/ 4 identifying the need for supplemental analgesia. Nalbuphine 0.2 mg/kg was given as rescue analgesia in patients assessed as needing pain relief. Adverse effects such as nausea, vomiting, and dizziness were also noted.

Subjects whose procedures lasted more than 4 hours or with massive blood loss defined as the volume of blood loss equivalent to the blood volume of the subject, was withdrawn from the study. In this study, there were no patients whose procedure lasted more than 4 hours nor had blood loss equal to blood volume, hence no subjects were withdrawn from the study.

Data analysis of the study utilized mean, standard deviation, frequency distribution and percentages. Homogeneity of patient characteristics was determined using t-test for quantitative data and chi-square for qualitative data. Comparison of outcome parameters in quantitative form was carried out using t-test and chi-square for qualitative variable. A p-value of less than or equal to 0.050 was considered significant.

Ethical Considerations

The investigator of the study observed good clinical practice, full confidentiality of information and likewise complied with the recommendations provided for by the IRB-EC of PCMC.

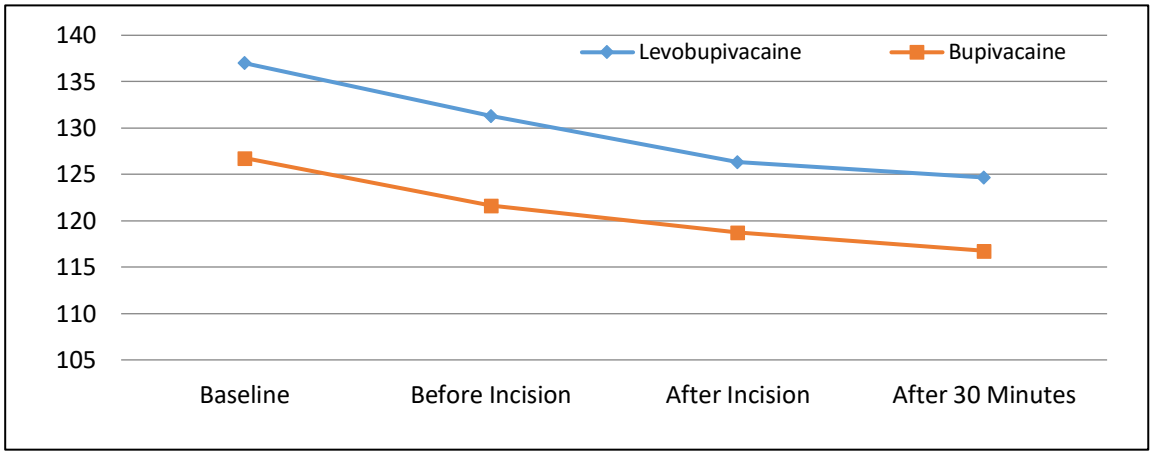
RESULTS AND DISCUSSION

Table 1 summarizes the demographic characteristics (mean and standard deviation, and counts for sex) of the patients in each study group. The results of the statistical tests suggest that the population is generally homogenous, except for baseline heart rate *(p-value=0.015)*.

Table 1. Demographic Characteristics and Vital Signs

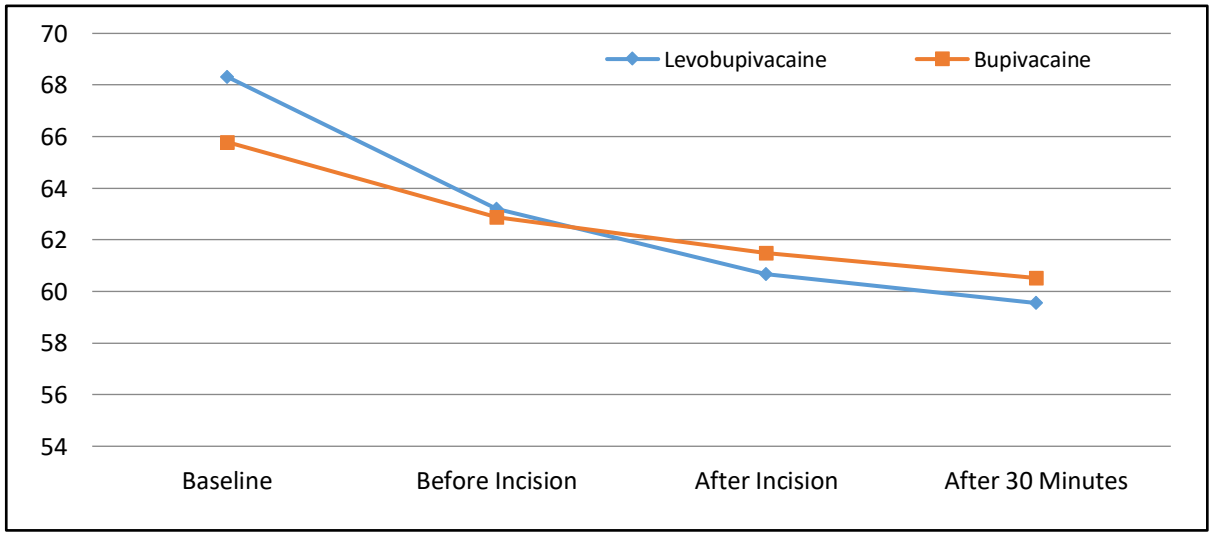
Demographic Characteristics		**Levobupivacaine**	**Bupivacaine**	**p-value**
Age (in years)		4.03 (2.19)	3.74 (2.07)	0.595
Weight (in kg)		15.07 (5.04)	14.80 (5.86)	0.846
Duration of procedure (in mins)		87.33 (54.22)	82.35 (54.91)	0.723
Vital signs				
Heart Rate	Baseline before injection	137.00 (15.57)	126.77 (16.20)	0.015
	Before Incision	131.33 (14.32)	121.61 (15.08)	0.012
	After Incision	126.33 (12.73)	118.71 (15.00)	0.036
	After 30 Minutes	124.67 (13.06)	116.77 (13.51)	0.024
MAP	Baseline before injection (mmHg)	68.32 (9.00)	65.79 (6.50)	0.215
	Before Incision (mmHg)	63.21 (6.09)	62.88 (5.62)	0.829
	After Incision (mmHg)	60.66 (4.05)	61.48 (5.00)	0.482
	After 30 Minutes (mmHg)	59.55 (4.17)	60.52 (5.31)	0.430

Figure 1. Average heart rate



As shown in Figure 1, patients under the levobupivacaine group were observed to have significantly higher baseline heart rates than those under the bupivacaine group. Using paired sample t-test, the average heart rate of patients across different measurement periods in the study are shown to be significantly different between the two groups. Like the noted trend for baseline measures, the heart rate for levobupivacaine is higher than that of bupivacaine before, immediately after, and 30 minutes after incision. Due to the random allocation in the study, there is a non-zero probability that the allocation may be skewed. The significant differences will only have an impact if the analysis was performed on the actual measures. Therefore, the comparison of score changes or improvement per time interval was performed. This virtually normalized the data so that comparison between groups is feasible.

Figure 2. Average MAP measurement



In terms of MAP, the two groups are shown to be homogenous across time periods. This relationship is best depicted in Figure 2 wherein no significant differences are observed between the two groups. Moreover, it can be observed that patients under the levobupivacaine group experienced a steeper decline in MAP measurements than that of the bupivacaine. This provides an indication that levobupivacaine is more effective than bupivacaine in managing MAP.

Table 2. Comparison of MAP and heart rate across measurement periods

Vital signs		**Levobupivacaine**	**p-value**	**Bupivacaine**	**p-value**
Heart rate	Before Incision - Baseline	-5.67 (8.17)	*0.001*	-5.16 (8.11)	*0.001*
	After Incision - Before Incision	-5.00 (6.82)	*0.000*	-2.90 (6.93)	*0.026*
	After 30 Minutes - After Incision	-1.67 (3.79)	*0.023*	-1.94 (4.02)	*0.012*
MAP (mmHg)	Before Incision – Baseline	-5.11 (8.01)	*0.001*	-2.91 (5.23)	*0.004*
	After Incision - Before Incision	-2.55 (4.26)	*0.003*	-1.40 (3.31)	*0.025*
	After 30 Minutes - After Incision	-1.11 (2.81)	*0.039*	-0.96 (2.61)	*0.048*

The differences in heart rate and MAP were also compared across measurement periods as shown in Table 2. The concept of shifting or sliding baseline, wherein the comparison is made with respect to the previous reference point available, is used. This method was used to reflect that the previous measurement period is the current natural state of the patients.

Paired T-Test results suggest both drugs have a significant effect in lowering heart rate and MAP. Further examination shows that the decline in measurements is continuously observed from baseline until 30 minutes after incision.

Repeated Measures ANOVA result suggests that both drugs have effectively lowered MAP and heart rate from Baseline until 30 minutes after the operation. Changes in MAP scores across time are different for each group *(p-values=0.04)*, specifically, Levobupivacaine exhibited a higher marginal decrease in MAP compared to Bupivacaine. However, the improvement of Heart Rate is not significantly different. This result is consistent with the observation noted in Figures 1 & 2. Using chi-square test, the two groups were compared with respect to the distribution of patients in terms of the intensity of the recorded motor block and the need for intervention. These were evaluated based on the obtained Bromage and CHIPPS between the two study groups.

Table 3. Repeated Measures ANOVA (Within-Subject Contrast)

Source	Vital signs	Type III Sum of Squares	Mean Square	F	Sig.
Time	MAP	1619.516	1619.516	69.097	*.000*
	Heart_Rate	4276.851	4276.851	61.757	*.000*
Time * Group	MAP	103.415	103.415	4.412	*.040*
	Heart_Rate	63.081	63.081	.911	.344
Error(Time)	MAP	1382.864	23.438		
	Heart_Rate	4085.935	69.253		

Table 4. Distribution of patients based on the intensity of motor block

Bromage	Levobupivacaine	Bupivacaine	p-value
No motor block (0)	30	31	*NA*
Can flex knees (1)	-	-	
Can move feet only (2)	-	-	
Cannot move feet or knees (3)	-	-	

Table 4 shows that the recorded Bromage scores for patients from both groups are constant at 0, suggesting that all patients regardless of study group experienced no motor block. This constant distribution renders the analysis not applicable as there are no underlying differences that may be used to compare the two study groups.

Table 5. Distribution of patients according to CHIPPS Classification

CHIPPS Classification	Levobupivacaine	Bupivacaine	p-value
Pain free (0-3)	29	24	*0.026*
Intervention required (4-10)	1	7	

On the other hand, Table 5 shows the distribution of patients according to CHIPPS classification, as depicted by the recorded CHIPPS of 0-10. The number of patients requiring intervention, or those with a CHIPPS classification of 4-10, is significantly higher for the bupivacaine group than that of the levobupivacaine *(p-value=0.026)*. This suggests that levobupivacaine is more effective than bupivacaine in terms of pain alleviation.

Table 6. Distribution of patients requiring intervention

CHIPPS Classification	Levobupivacaine	Bupivacaine
4	29	2
5	-	4
6	-	1

Further analyzing the breakdown of those requiring intervention in Table 6, it is shown that the bupivacaine group has patients which registered CHIPPS of greater than 4, whereas the levobupivacaine patient requiring intervention only registered a CHIPPS of 4. This provides a supplementary indication that bupivacaine is less effective in rendering a pain-free situation. Table 7 shows that no side effects such as nausea, vomiting, or dizziness were noted among the subjects post-operatively.

Table 7. Distribution of patients based on side effects

Side Effects	Levobupivacaine	Bupivacaine
Nausea and/or Vomiting	0	0
Dizziness	0	0

DISCUSSION

Caudal epidural anesthesia using the agents Bupivacaine and Levobupivacaine have been successfully used in facilitating surgery in pediatric patients. With the two agents utilized in this study, it was noted that both are effective adjuncts in intraoperative anesthesia as both were able to provide adequate pain control as depicted by the stable vital signs during maintenance of anesthesia during the surgery with the concentration of 0.2% used for both agents as recommended by Ivani et. al. in 2003 and Tarkase et. al. in 2012. Also, a lower concentration and higher volume when computed provided adequate analgesia as recommended by previous study of Bilgen et. al. in 2013.

Post-operatively, the agents used proved to be safe as no adverse events such as nausea, vomiting and dizziness. No motor block was noted as all patients were able to move their lower extremities after the operative procedure. This result showed a better outcome from the study of Locatelli et. al. in 2004 in which Bupivacaine 0.25% and Levobupivacaine 0.25% was associated with a higher incidence of motor block ($p<0.01$) that was not seen in this present study as compared to the 0.2% concentration used in this study as recommended by Ivani et. al. in 2003 and Tarkase et. al. in 2012. Both agents provided adequate analgesia as well however the difference lies such that there were more patients that required rescue analgesia in the Bupivacaine Group as compared to the Levobupivacaine group as depicted in the statistical analysis possibly indicating that Levobupivacaine has a longer duration of action compared to Bupivacaine.

The limitation of the study is that the cost of the study medications were not compared. It is important to note that several factors such as the training of the anesthesia provider, cost and availability of medications and equipment, and socio-economic status play a factor in choosing the appropriate anesthesia for surgical patients. In the field of pediatric anesthesia, the utilization of a well-planned balanced anesthetic technique in which the combination of general and regional anesthesia brings about favorable outcomes when performed with coordinated skills and proper dosaging and concentrations.

CONCLUSION

Both Bupivacaine and Levobupivacaine provide adequate analgesia along with general anesthesia intraoperatively as depicted by the stable trend of hemodynamic parameters with no reports of intraoperative movement, increased inhalational agent concentration and additional intravenous analgesics. Post-operatively, no adverse effects and motor block were noted for both study drugs, however levobupivacaine has a longer efficacy as it required lesser rescue medications post-operatively compared to Bupivacaine.

RECOMMENDATION

The investigator recommends further expansion of the study using a wider age range of children to provide more basis to recommend the use of Levobupivacaine in the pediatric age group. It is likewise recommended to conduct cost-effectiveness studies using both drugs.

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LIDOCAINE AS A DILUENT FOR BENZATHINE PENICILLIN G FOR INJECTION PAIN IN CHILDREN WITH RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE: A RANDOMIZED DOUBLE-BLIND CROSSOVER STUDY

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ABSTRACT

BACKGROUND: Rheumatic fever (RF) and Rheumatic heart disease (RHD) patients necessitate secondary prophylaxis with benzathine penicillin G (BPG) injection every 3 weeks to prevent recurrences and complications. Patients with rheumatic fever on regular benzathine penicillin G injection usually experience moderate to severe pain resulting to poor compliance to treatment.

OBJECTIVES: This study aims to compare the effect of BPG diluted in lidocaine hydrochloride 1% versus diluted water in reducing injection pain in patients with RF and RHD.

METHODS: This is a randomized double blind crossover study conducted at the PCMC OPD. Thirty-three patients diagnosed with RF and RHD were divided into 2 groups; the first group received BPG diluted in sterile water followed by BPG diluted in lidocaine hydrochloride 1% after 21 days, the second group received the same medications in reverse order. Pain scale was measured using Universal pain assessment tool immediately after injection. Paired T test was used to compare the pain score results of the two groups.

RESULTS: Pain score was significantly less in patients who received BPG diluted in lidocaine hydrochloride 1%; from an average pain score of 4.88 to 0.63 ($p<0.0001$), among those who received BPG diluted in sterile water. No adverse effects were seen in all patients.

CONCLUSION: This study concluded that BPG diluted in lidocaine hydrochloride 1% significantly and safely reduced post injection pain. In all patients diagnosed with RF and RHD, BPG injection should be diluted in lidocaine hydrochloride 1% to decrease injection pain and improve patient's compliance.

KEYWORDS: Rheumatic fever, Rheumatic heart disease, Penicillin, Lidocaine, pain

INTRODUCTION

Rheumatic fever (RF) and Rheumatic heart disease (RHD) are the most serious complications of Group A Beta Hemolytic Streptococcus (GABHS) infection. The prevention of both initial and recurrent episodes of acute rheumatic fever depends on controlling GABHS infections of the upper respiratory tract. Therefore, these patients should receive continuous antibiotic prophylaxis to prevent recurrences. Worldwide, rheumatic heart disease remains the most common form of acquired heart disease in all age groups, accounting for as much as 50% of all cardiovascular disease and as much as 50% of all cardiac admissions in

many developing countries.[1] Based on review of Zühlke, there is an overall global burden of 471,000 cases of RF annually, with a peak incidence of RF in children ages 5 to 15 years, ranging from 10 cases per 100,000 in industrialized countries to 374 cases per 100,000 in the Pacific region.[2] In the Philippines, incidence of rheumatic fever and rheumatic heart disease based on the Philippine Pediatric Society registry is 2553 cases since 2006.[3] Antibiotic prophylaxis for secondary prevention of rheumatic fever and rheumatic heart disease use benzathine penicillin G (BPG) 600,000 IU for children weighing less than 60 pounds and 1.2 million IU for those weighing more than 60 pounds.[1] In 2001 WHO Technical report on RF and RHD stated that intramuscular (IM) injection of benzathine penicillin every 3 weeks is the most effective strategy for prevention of recurrent attacks of RF.[4]

Compliance to treatment in secondary prevention of rheumatic fever is an important aspect in preventing recurrences. In the pediatric age group, pain associated with intramuscular injection of benzathine penicillin G is one of the factors affecting compliance. Many centers have tried different techniques to reduce injection pain with benzathine penicillin G. This study was conducted to answer the question: How effective Is lidocaine hydrochloride 1% as diluent for benzathine penicillin G injection in reducing injection pain in patients 10-18 years old with rheumatic fever and rheumatic heart disease as compared with sterile water?

Antibiotic prophylaxis for secondary prevention of rheumatic fever and rheumatic heart disease uses intramuscular benzathine penicillin G every 3 weeks and compliance to treatment is an important part of successful management. In patients receiving prophylactic benzathine penicillin G injection, one of the reasons that affected poor compliance was injection pain and decreasing injection pain may improve compliance of patients to regular injection and prevent further progression and complication of the disease. This study can help increase the awareness of pediatricians and provide options of using lidocaine hydrochloride 1% as an alternative to sterile water as diluent of BPG. This study can guide health policy makers in the Philippines in making future recommendations and clinical practice guidelines on RF and RHD treatment.

In patients diagnosed with RF and RHD, secondary prophylaxis is important to prevent recurrences and further complications. Secondary prophylaxis in these patients is given every 3 weeks for a minimum of 5 years. Thus, compliance to treatment for this long period of time is a challenge to our patients. There are many factors affecting compliance such as lack of funds for medication, lack of knowledge on the importance of prophylaxis and pain associated with injection every 3 weeks. Patients with rheumatic fever on regular benzathine penicillin G injection usually has pain scale of 8-10.[5] Some centers employ techniques to reduce the pain in IM injections, such as use of smaller gauge needles, direct pressure, slow injections and distractions. [6]

There were only two published studies which used lidocaine as diluent for BPG; a study done in 1998 and a study in 2012. Morsy et al did a a randomized, double blind crossover study among 100 patients with rheumatic fever in Egypt in 2012. BPG was diluted in lidocaine or sterile water and patients received both preparation, 21 days apart. Pain score was measured immediately after injection using revised faces pain scale. There was significant decrease in pain level immediately after injection; pain decreased from an average of 6.7 (range of 4 to10) in patients who received BPG

in sterile water to 5.2 (range 4 to 8) among those in which lidocaine was used as diluent. Serum penicillin levels were also measured in this study and there was no significant change in serum penicillin levels in patients given BPG diluted in sterile water compared to those who received lidocaine as diluent.[5] They concluded that lidocaine as diluent does not affect the efficacy of BPG and at the same time will effectively reduce injection pain.

In 1998, Amir et al did a randomized double blind crossover trial among 18 patients with rheumatic fever. In this study, BPG was diluted in lidocaine and sterile water. Pain was measured immediately after every injection. This study also showed significant reduction in injection pain, without altering the serum and urine penicillin levels.

The two studies included adolescent patients aged 10-19 years old to have more accurate assessment of pain with less variability. The two studies did not report any adverse effect or toxic effect to lidocaine when used as diluent.

Lidocaine is one of the most commonly used local anaesthetics. Lidocaine blocks activated and inactivated sodium channels with rapid kinetics. It stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby effecting local anesthetic action.[7] It is a clear colorless, sterile non-pyrogenic aqueous solution. Its most common adverse effect, like those of other local anesthetics include locally at site of infection: mild bruising, redness, itching, or swelling where the medication was injected. Unlikely but serious side effects of Lidocaine, when given intravenously include drowsiness, mental/mood changes, ringing in the ears, dizziness, vision changes, tremors, numbness, headache, or backache.[8]

Lidocaine has been studied and used as a diluent in other medications given intramuscularly to reduce pain. Schichor et al (1994), did a randomized prospective study among adolescents who were culture positive for Gonorrhea, They were given IM Ceftriaxone diluted in either lidocaine hydrochloride or sterile water. Pain score was measured using a visual analog scale. This study showed that lidocaine reduced the injection pain of intramuscular ceftriaxone when compared with sterile water as a diluent.[9]

When using lidocaine as a local anesthetic, the maximum allowable dose is 4.5 mg/kg/dose up to 300mg. [10] In both studies by Morsy et al and Amir et al, lidocaine as a diluent for benzathine penicillin G was given at 3.2 mL, equivalent to 32 mg for every kg of the patient.

In the out patient department of a tertiary government hospital in Quezon City, there were an average of 70 patients diagnosed with rheumatic fever and/or rheumatic heart disease who have BPG injection every month. There were only 37 patients who have regular BPG injection every 21 days in 2015.

A study by Respicio et al in 2015 on the clinical profile and factors related to compliance with Benzathine Penicillin G Prophylaxis among RF/RHD patients at the Tarlac Provincial Hospital, Philippines. It was identified that the compliance rate of patients to treatment is at 46.6%. [11]

At the Philippine Children's Medical Center (PCMC) Out Patient Department (OPD), the current practice is diluting BPG in 4 ml of sterile water, which is the recommended volume of dilution of BPG based on the drug insert. If 4 ml of lidocaine will be used as diluent for BPG, it will be equivalent to 40mg for each patient, still within the maximum allowable dose.

Using lidocaine as diluent in IM medications is not yet a common practice in the Philippines. There are only 2 published studies that used lidocaine as a diluent for benzathine penicillin G, and no study was done yet in Southeast Asia including the Philippines.

In this study we aimed to evaluate the effectiveness of lidocaine hydrochloride 1% as compared to sterile water as diluent for benzathine penicillin G in reducing injection pain in patients 10-18 years old with rheumatic fever and rheumatic heart disease.

METHODOLOGY

This is a randomized double-blind crossover study conducted in Philippine Children's Medical Center Out Patient Department, a tertiary pediatric hospital in Quezon Avenue, Quezon City. Patients enrolled in the study were from the section of Pediatric Cardiology Out patient Department. The patients included in the study were diagnosed with rheumatic fever and rheumatic heart disease, 10 to 18 years of age, receiving benzathine penicillin G injection every 21 days, and with good compliance to injection for the last 6 months. Excluded in the study are RHD patients with severe valvar regurgitation/stenosis, with known sensitivity to lidocaine, and those non-compliant to penicillin injection. The sample size was computed based on the study by Morsy, et al, with the mean pain score for sterile water as diluent of 6.7, versus the mean score of 5.2 using lidocaine. Standard deviations were estimated using the following formula: $S = \frac{1}{12}\left(\frac{(a-2m+b)^2}{4} + (b-a)^2\right)$. STATA 11 was used to compute the sample size. To get a true difference at 0.05 level of significance and 80% power, a minimum sample size of 32 is needed, 16 participants in each group.

Patients were recruited in the study as they come for their BPG injection in the OPD. The primary investigator obtained informed consent (Appendix 1) from all parents or guardians and assent forms (Appendix 2) from patients. The patients were randomly allocated into 2 groups using a computer generated randomization list with Microsoft Excel which assigned patients to either group A or B (Appendix 3).

The duration of the study is for 3 weeks per patient; a total of 9 weeks for the whole study period. Patients were asked to participate in this study during their scheduled injection every 21 days for 2 consecutive follow-ups. Patients in group A received BPG diluted in sterile water in the first visit and diluted in 4 ml of 1% lidocaine hydrochloride in the second visit, 21 days apart. Group B received BPG diluted in 4 ml of 1% lidocaine hydrochloride in the first visit and BPG diluted in sterile water in the second visit. The BPG doses used was 600,000 IU for children weighing less than 60 pounds and 1.2 million IU for those weighing more than 60 pounds.[1]

The pharmacist prepared 2 sets of diluents for the nurse. Lidocaine hydrochloride 2%(Eurocaine by Euromed) was diluted in equal amount of sterile water to make lidocaine hydrochloride 1%. The diluent are both

colorless, clear solutions placed in identical vials. The sterile water and lidocaine hydrochloride 1% were labeled with either red or blue label by the pharmacist.

The nurse was blinded in giving either BPG diluted lidocaine hydrochloride 1% or BPG diluted in sterile water. The nurse in charge washed hands and prepared the materials. The upper outer quadrant of gluteus muscle, which is the injection site was uncovered and disinfected with alcohol circularly from inward to outward then air-dried. A gauge 21 needle was inserted swiftly at an angle of 90 degrees, and then aspirated briefly, if blood appears, needle was withdrawn and another site was selected. If no blood was aspirated, benzathine penicillin G diluted in either lidocaine or sterile water was injected slowly intramuscularly. The needle was withdrawn and a dry sterile cotton was placed in the post-injection site and secured with adhesive tape.[14] A single brand of penicillin (Zalpen by Cathay) was used in the entire study period and one nurse administered the medication to the patients.

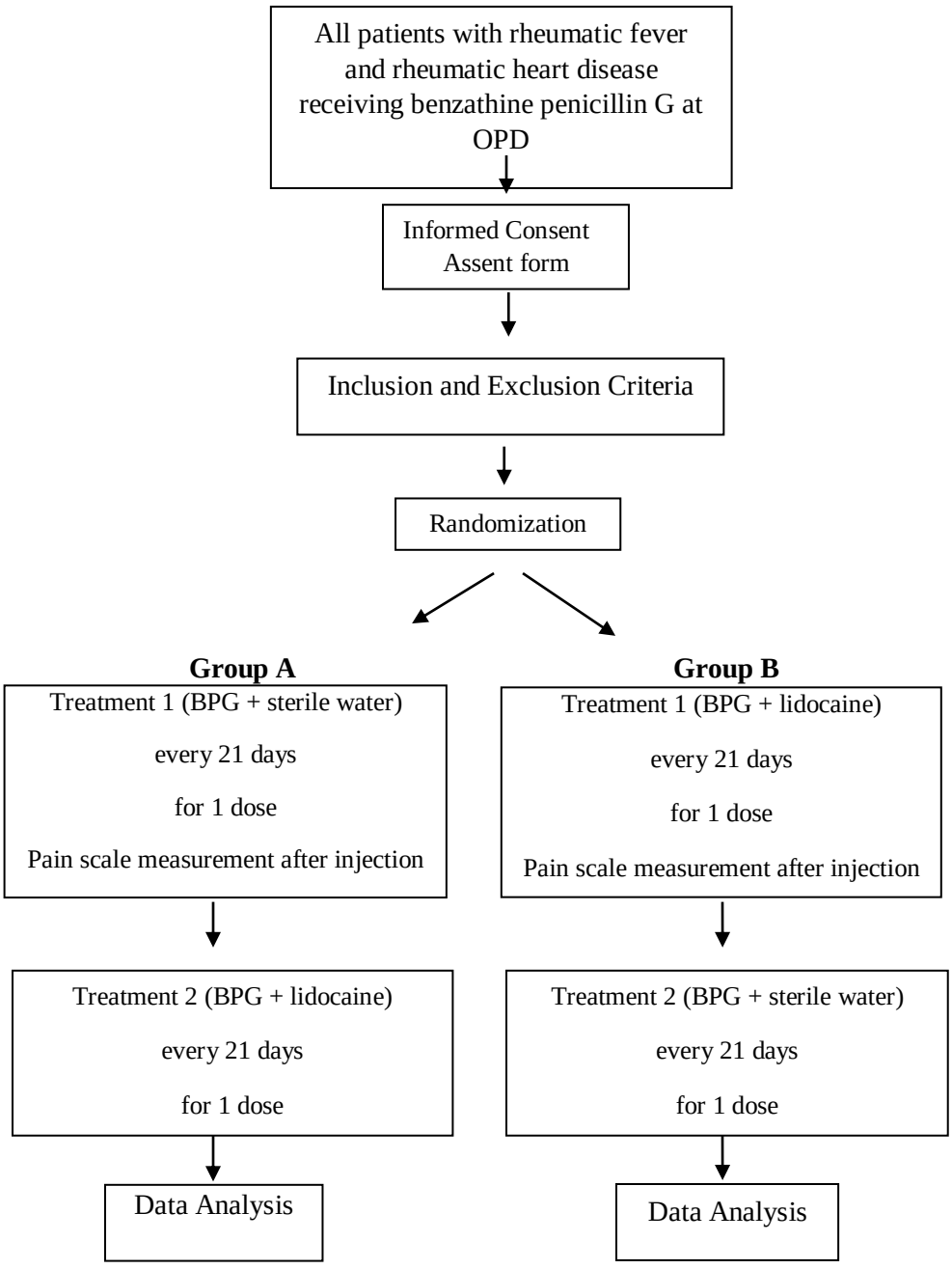
The physician, the patient and the nurse giving the medication were blinded on the patient randomization to either lidocaine or sterile water diluents. The pharmacist who prepared the medication is the only research member aware of the randomization.

Pain was measured using the universal pain assessment tool. Pain assessment was recorded immediately after injection by the primary investigator or the nurse-in-charge by asking the patient to identify the pain scale. The universal pain assessment tool (Appendix IV), was used in this study. It has a scale of 0 to 10 together with facial grimace scale, showing 6 faces from no pain to severe pain. The face and number scale was shown to the patient, but the number equivalent was recorded for data analysis. Pain scores were interpreted as follows: pain score 0: no pain, 1-2 pain score: mild pain, 3-6 pain score: moderate pain, 7-9 pain score: severe pain and pain score of 10 as most severe pain. Patients were observed at the out patient department within 1 hour from the time of injection for any adverse reactions such as generalized pruritus, wheals, flushing or any signs of anaphylaxis.

The baseline characteristics that were recorded in patient data form included the patient age, sex, diagnosis of rheumatic fever or rheumatic heart disease and duration of BPG treatment. In patients diagnosed with rheumatic heart disease, the specific valvular lesion was also documented.

Shown in Figure 1 is the outline of the study procedure.

Figure 1: Flowchart of Study Procedure



Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables and mean and SD for interval/ratio variables. Statistical analysis was computed using Microsoft excel. Paired t test was used to compare the results between the two groups and P value was set at ≤ 0.05.

This research was submitted, reviewed and approved by the IRB-EC prior to its implementation. Participants were recruited at the outpatient department of a tertiary

government hospital by the primary investigator. The subjects were oriented as to the purpose, nature and objective of the study. A written informed consent from parents and guardians and assent forms from patients are necessary prior to inclusion in the study.

All data gathered in this study was kept confidential. The primary investigator is not affiliated with any pharmaceutical company and did not receive any compensation for medications used in this study.

RESULTS

Sixty-five patients came for BPG injection during the study period. Forty-two patients were eligible for the study. There were 9 patients who did not consent to participate in the study. The 33 patients who participated in the study were randomized to group A, 17 patients and group B, 16 patients. All patients were able to follow-up on their scheduled date. There were more females than males in the study (2:1), with a mean age of 14.2 years old, range of 10-18 years old. Five patients were diagnosed with rheumatic fever and 28 patients diagnosed with RHD. Mild mitral regurgitation was the most common valvular involvement, comprising 17.9% of all RHD patients. All patients had regular BPG injection every 3 weeks before enrollment. These patients had an average of 43.6 months of BPG injection prior to enrollment in this study. Table 1 outlines the demographic characteristics of patient enrolled In the study.

Table I: Demographic Data of Rheumatic Fever and Rheumatic Heart Disease Patients (n=33)

	Mean ± SD
Age	14.27 ± 5.66
Sex	**Frequency (%)**
Male	11 (33.3)
Female	22 (66.7)
Diagnosis	**Frequency (%)**
Rheumatic fever	5 (12.2)
Rheumatic heart disease	28 (84.8)
Valvular Lesion:	**Frequency (%)**
RHD MR mild, AR mild, TR mild	1 (3.6)
RHD MR mild TR mild	4 (14.3)
RHD AR mild TR moderate	1 (3.6)
RHD AR moderate MR mild TR mild PR mild	1 (3.6)
RHD MR moderate, AI moderate	3 (10.7)
RHD MR mild	5 (17.9)
RHD MR mild AR mild	1 (3.6)
RHD MR mild TR mild PR trivial	1 (3.6)
RHD MR moderate	2 (7.1)
RHD MR moderate AI mild	1 (3.6)
RHD MR moderate AI moderate	3 (10.7)
RHD MR moderate AR moderate PR moderate	1 (3.6)
RHD MR moderate, AR moderate TR mild	1 (3.6)
RHD MR moderate, TR mild	1 (3.6)
RHD MS moderate MR moderate AR moderate TR mild PR mild	1 (3.6)
RHD TR moderate, MR moderate	1 (3.6)
	Mean ± SD
Duration of BPG treatment (months)	43.6 ± 11.31

As shown in figure 2, group A patients received BPG diluted in sterile water in first injection with an average pain score of 5.5, which means moderate pain. The pain score range from 0 to 10 ± 2.67. In comparison, in the second injection, BPG was diluted in lidocaine and the average pain score was 0.47, which means no pain. The pain score range from 0 to 2 ± 0.47. Comparing group A to group B patients, group B patients received BPG diluted in lidocaine first, with an average pain score of 0.81, no pain. The pain score range from 0 to 4 ± 1.16. In their second injection with BPG diluted in sterile water, the average pain score was higher at 4.12, moderate pain, with pain score range from 2 to 6 ± 1.36. Overall, the pain score was significantly decreased in all patients who received BPG diluted in lidocaine hydrochloride 1%; with an average pain score of 0.63, no pain, range from 0 to 4; ± 1.03 versus 4.88, moderate pain, range from 0 to 10; ± 2.23 in patients whose BPG was diluted in sterile water. The difference between the pain scores of patients who received BPG diluted in sterile water and who received BPG diluted in lidocaine hydrochloride 1% were compared, with mean difference of 4.24 (± 2.12), p value <0.0001, which is statistically significant.

Figure 2: Pain Score of Group A and Group B After Injection of BPG Diluted in Lidocaine and Sterile Water

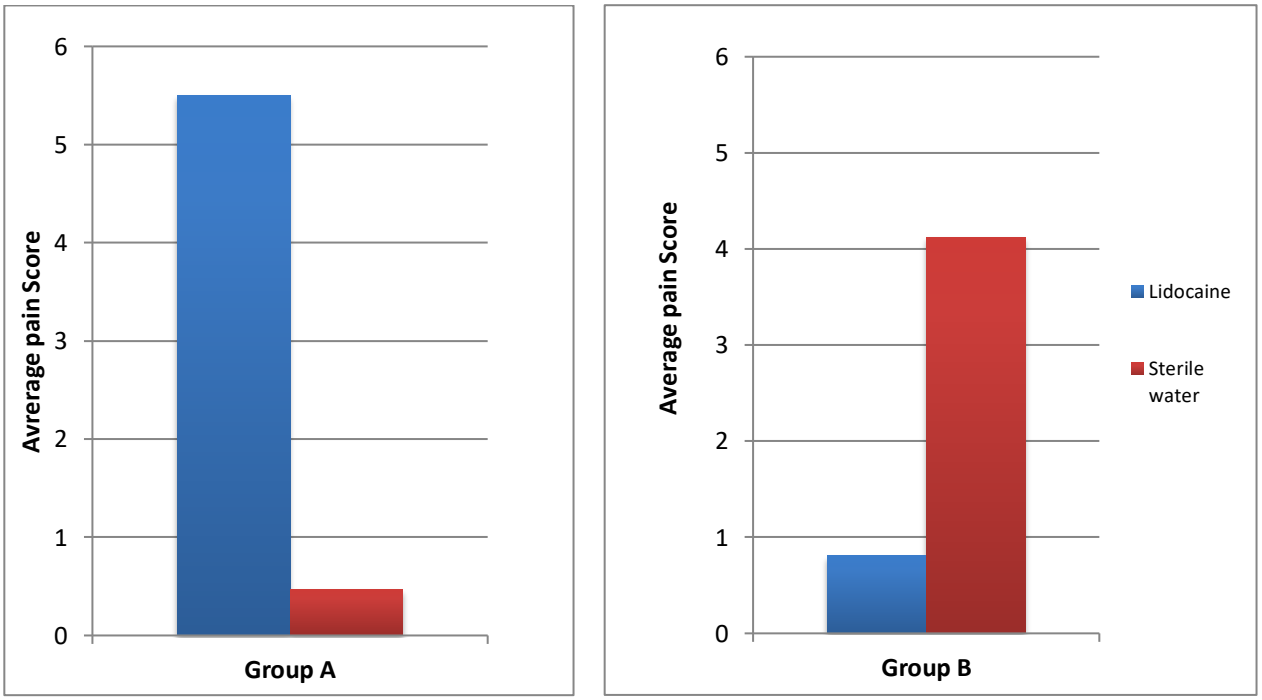
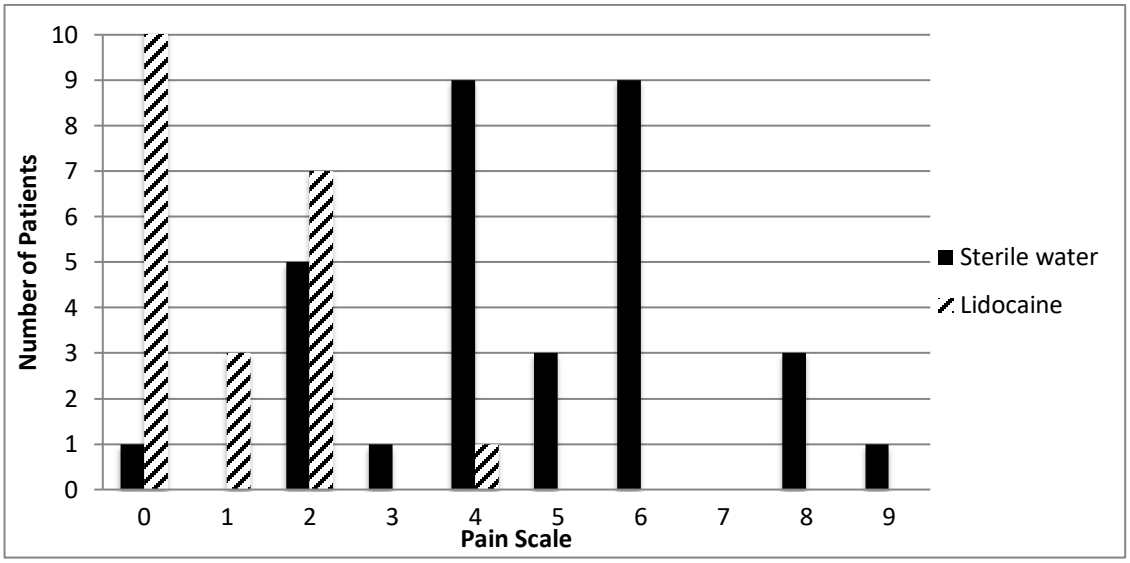


Figure 3 shows that after injection, 97% of patients who received BPG diluted in lidocaine hydrochloride 1% had pain score mainly in the value of 0 to 2. On the other hand, 55% of patients who received BPG diluted in sterile water experienced pain with score of 4 to 6. There was no adverse reaction noted in all patients who participated in this study.

Figure 3: Stratification of Patients According to Pain Score



DISCUSSION

Rheumatic heart disease remains the most common form of acquired heart disease in all age groups, accounting for as much as 50% of all cardiovascular disease and as much as 50% of all cardiac admissions in many developing countries.[1]. Among adolescents in the Philippines, chronic RHD is the 4th leading cause of mortality, with a mortality rate of 2.9 per 100,000.[15] Early diagnosis, treatment, and secondary prevention with benzathine penicillin G is important to ease the burden of RF and RHD in our country. Compliance to treatment in secondary prevention of RF and RHD is an important aspect in preventing recurrences and complications. Pain and tenderness at site of injection is one of the factors affecting compliance because of the need for repeated injection every 3 weeks. Many centers employ techniques to reduce the pain in IM injections, such as use of smaller gauge needles, direct pressure, slow injections and distractions. [6]

This study compared the pain score after using lidocaine hydrochloride 1% versus sterile water as diluent of BPG, and it demonstrated that BPG injection using lidocaine hydrochloride 1% significantly decreased injection pain; from an average pain score of 4.88, it was significantly decreased to 0.63 ($p<0.0001$).

The result of this study was consistent with the two previous studies done by Amir et al and Morsy et al showing significantly decreased pain score among patients who received BPG diluted in lidocaine hydrochloride 1%.

Lidocaine is one of the most commonly used local anaesthetics. It works by blocking activated and inactivated sodium channels with rapid kinetics. As a local anesthetic, it has an onset of action of 10 minutes, and elimination half-life of 1.6 hours.[7] Four ml of lidocaine hydrochloride 1% was used in this study . In the previous 2 studies, 3.2 mL of lidocaine hydrochloride 1% was used for each patient. Both of these volumes are within the maximum allowable dose of 4.5 mg/kg/dose up to 300mg. [10]

A limitation of this study is that only one injection for BPG diluted in lidocaine hydrochloride 1% and one injection for BPG diluted in sterile water was given to each patient due to time limitation. Multiple injections may give more accurate pain assessment scores post-injection since it will be averaging different injection pain scores at different times.

CONCLUSION AND RECOMMENDATIONS

This study demonstrates that the use of lidocaine hydrochloride 1% as diluent for BPG significantly and safely reduced the injection pain among RF and RHD patients ($p < 0.0001$). No adverse effect was noted among patients in the study. In all patients diagnosed with RF and RHD, BPG injection should be diluted in lidocaine hydrochloride 1%. Implementation of a clinical practice guideline by the Philippine Pediatric Society and Philippine Society of Pediatric Cardiology that will standardize the method of diluting BPG using lidocaine hydrochloride 1% and a study on the improved compliance rate of RF and RHD patients receiving BPG diluted in lidocaine can also be done.

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