The PCMC Journal

VOL. 15 NO.2 DECEMBER 2019

Official Publication of the
Philippine Children's Medical Center
Quezon Avenue, Diliman, Quezon City 1100
ISSN:0117-3774 E-ISSN:2704-3665

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EDITORIAL STAFF

Welcome to the second issue of The PCMC Journal for 2019!

As you have noticed, we have now migrated to the digital realm. We hope this will vastly improve access of the wider public to the important research studies being produced by our trainees and staff.

We are now hopefully well on the way to being accredited by Western Pacific Region Index Medicus (WPRIM) and thus being indexed in this important online database of medical literature.

May you have a meaningful holiday season!

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

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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

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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.

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

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1. Generally, the text should be organized consecutively as follows: Introduction, Materials and Methods, Results and Discussion (and Conclusion).
2. All References, tables, figures and illustrations should be cited in the text, in numerical order.
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Contact Information
For comments, questions, and concerns, contact:

Paul Matthew Pasco, MD, MSc

Editor – in – Chief

PCMC Journal

Clinical Research Department

Philippine Children's Medical Center

Quezon Ave., Quezon City

Tel No. (8) 588-9900 local 356

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THE USE OF PREPROCEDURE ULTRASOUND AS AN ADJUNCT TO LUMBAR EPIDURAL ANESTHESIA IN PARTURIENTS: A RANDOMIZED CONTROL TRIAL

JOSE PAULO Z. ALILING, MD, AIDA Z. CRISTOBAL, MD

ABSTRACT

BACKGROUND: Conventional epidural anesthesia technique is a blind procedure, which relies solely on the palpation of the landmarks. Pregnancy makes epidural insertion more difficult because of the exaggeration of the lumbar iordosis, increase in subcutaneous fat, and difficulty in positioning due to the gravid uterus. These changes may make the conventional palpation technique less reliable in placing the epidural catheter during labor. Preprocedure ultrasound may be used as an adjunct in facilitating lumbar epidural insertion.

OBJECTIVES: The objective of the study was to determine the efficacy of preprocedure ultrasound in facilitating lumbar epidural insertion. This was achieved by determining the number of attempts, number of needle redirections, and incidence of adverse events with and without the use of ultrasound.

METHODS: The study was a randomized controlled trial. Forty two (42) subjects were enrolled in the study and were randomized into either the preprocedure ultrasound gorup or the conventional palpation technique group. Efficacy of the technique was measured according to the following variables: number of attempts, number of redirections, incidence of traumatic insertion and incidence of accidental dural puncture.

RESULTS: There was a significant difference in the number of attempts (p value of 0.03) and needle redirections (p value of 0.04) between the two (2) groups. There was no significant difference noted in the proportion of subjects with accidental dural puncture and traumatic insertion between the two (2) groups (p=1.00).

CONCLUSION: The number of attempts and needle redirections were significantly lower in those with ultrasound use compared to those without. No adverse events were noted on both groups.

RECOMMENDATIONS: Future studies may focus on the obese population utilizing larger samples wherein the landmarks needed for epidural placement are extremely difficult to identify. The lenght of time required to successfully insert the epidural with and without the use of preprocedure ultrasound can also be considered.

KEY WORDS: preprocedure ultrasound, attempts, redirections, dural puncture, traumatic insertion

INTRODUCTION

Epidural anesthesia is the mainstay for labor analgesia. During the first stage of labor, pain comes from the distention of the lower uterine segment and cervix. Pain impulses during this stage enter the T10 to L1 spinal segments. However, as labor progresses (second stage of labor), the fetus descends into the pelvis and stretches the perineum which is innervated by the S2 to S4 nerve fibers. In clinical practice, epidural anesthesia is the most effective method of intrapartum pain relief. It is the only form of analgesia which can provide complete analgesia for both stages of labor.[1] It provides superior analgesia compared to intravenous analgesics and is safe for the fetus because of the limited transplacental transfer of drugs given via the epidural space. The existing epidural catheter for labor analgesia is also very flexible because it can be used for either vaginal delivery or cesarean section.

Conventional epidural anesthesia technique is a blind procedure, which relies solely on the palpation of the landmarks. Pregnancy may make epidural insertion even more difficult because of the exaggeration of the lumbar lordosis, increase in subcutaneous fat, and difficulty in positioning due to the gravid uterus.[2] These changes may make the conventional palpation technique less reliable in placing the epidural catheter during labor.

Difficulty in epidural anesthesia may translate into multiple attempts, needle redirections, traumatic insertions, and failed epidurals. This could lead to epidural

hematoma[3,4], postdural puncture headache[5,6], trauma to neural structures[7], and pain during insertion. Because of these potential problems, the use of ultrasound has been advocated to aid in epidural anesthesia insertion. It can help improve the success rate of epidural insertion by allowing the anesthesiologist to view the relevant anatomic structures and vertebral space.[8] The ultrasound machine is readily available at the labor room or delivery complex because it is utilized by the obstetricians and can therefore be utilized by the anesthesiologist as well. It is inexpensive and safe for the fetus because of the lack of radiation.

Although previous studies were done in foreign countries, no local data is available in the Philippines. Doing a study in the local setting is warranted because differences in the demographics may yield different results. In fact, a study done by Sharma et.al. showed the distance from the skin to the lumbar epidural space differed among different ethnic groups at any given body mass index.[9] Also, previous studies were done in ASA physical status I and II patients. Parturients at the Philippines Children's Medical Center are mostly high risk patients. These patients do not tolerate pain very well. Pain leads to an increase in circulating catecholamines, which could manifest as an increase in blood pressure, heart rate, and cardiac workload.[10] These changes could be detrimental to the condition of the patients. It is therefore important to provide epidural anesthesia in a more efficient and less traumatic manner.

The efficacy and safety of regional anesthesia is affected by several factors such as anatomic variation which makes it difficult to identify the landmarks for epidural insertion, body habitus of the patient, and difficulty in positioning a parturient. This study aims to investigate the use of preprocedure ultrasound as an adjunct in facilitating lumbar epidural insertion.

Significance of the Study

Lumbar epidural anesthesia is considered the safest and most effective means of providing analgesia in laboring women. However, it is more difficult to perform epidural anesthesia in laboring women because of weight gain and an increase in subcutaneous tissue, increase in lumbar lordosis, difficulty in positioning and flexing the spine due to the gravid uterus, and anatomic variations.[11] A difficult epidural insertion results in multiple attempts and needle redirection which can potentially lead to hematoma, nerve injury, accidental dural puncture and pain during insertion. A failed lumbar puncture could also lead to general anesthesia. A preprocedure US can aid in the success of epidural placement because it could help in identifying the midline, vertebral interspace, optimal puncture point, angle of needle insertion and relevant anatomic structures.[12,13] Ultrasound is readily available in the delivery suite, easy to perform, relatively cheap and involves no radiation, and safe both for the mother and fetus. The use of US could therefore increase the success rate and safety during the placement of epidural anesthesia.

OBJECTIVES OF THE STUDY

a. General Objective

To determine the efficacy of preprocedure US in facilitating lumbar epidural insertion

b. Specific Objectives

1. To determine the number of attempts with and without the use of ultrasound
2. To determine the number of needle redirections with and without the use of ultrasound
3. To determine the incidence of adverse events (i.e. traumatic insertion, accidental dural puncture) with and without the use of ultrasound

METHODOLOGY

The study was a randomized controlled trial. Included in the study were parturients ages 15- 45 years old, with a BMI of 18.5- 40, ASA II-IV. Excluded were those with coagulopathy, spinal deformity, hypovolemia, infection at puncture site, increased intracranial pressure, allergy to local anesthetic, and patients who refused to undergo regional anesthesia.

For the sample size computation, the number of samples collected were computed using a 95% level of confidence and 80% power. Twenty one subjects for each group were needed to account for 48% difference in the success rate between the two groups (preprocedure US technique and conventional palpation technique). The study also took into account the possible 20% drop- out rate.

During the prenatal check-up between the second and third trimester, patients were referred to the perinatal anesthesia service for preoperative evaluation. Those who met the inclusion and exclusion criteria were oriented on the study. When these patients arrived at the perinatal center on their delivery date, the study was again discussed.

After signing the informed consent, laboring parturients were randomly assigned to

either group I (ultrasound group) or group II (conventional group), predetermined by the RALLOC software. The investigator emphasized to the patients that they may withdraw from the study anytime.

Group I (Ultrasound Group)

For the ultrasound group, US imaging was performed in a nonsterile manner. Patients were positioned in the left lateral decubitus position. The vertebral interspace was identified by palpation based on the Tuffier's line. Imaging of that area was then be performed using Aloka SSD 1100 Flexus with convex array probe. The image of the spine was captured by positioning the probe perpendicular to the long axis of the lumbar spine, also known as the transverse approach.[12] The spinous process, located at the midline of the spine was identified as a small hyperechoic (bright) signal, found underneath the skin, and continued as a long triangular hypoechoic (dark) acoustic shadow.[12] Using a marker, a line was drawn at the center of the upper horizontal surface of the probe to indicate the midline of the spine. The probe was then be moved in a cephalad or caudad direction to capture a view of the upper or lower intervertebral space, visualized as an acoustic window containing the vertebral body, transverse process, articular process and ligamentum flavum– dura mater unit.[12] Again, another mark was made on the midpoint of the lateral vertical surface of the US probe to indicate the vertebral interspace. The distance from the skin to the ligamentum flavum– dura mater unit was measured to serve as a guide in finding the epidural space when doing the LOR technique. The site of puncture was determined by the intersection of the two marks on the skin on the vertical and horizontal planes.[12] The intersection of the two planes was marked using a syringe cap.

Group II (Conventional Group)

Patients were placed in left lateral decubitus position. The anterior superior iliac spine (ASIS) was palpated and an imaginary line was drawn to the opposite ASIS. This imaginary line was called the Tuffier's line. It was used as reference to the L4 vertebra or L4-L5 interspace. The vertebral interspace above or below this line was palpated where epidural anesthesia was inserted.

Epidural Catheter Insertion

The back was sterilized using iodine. The puncture site was then infiltrated with 3ml of 2% lidocaine to anesthetize the skin. Using a gauge 18 Tuohy epidural needle, the epidural space was identified using the LOR technique. After locating the epidural space, the epidural catheter was threaded 5cm into the epidural space. Aspiration of the catheter was done to confirm the presence or absence of blood and/or cerebrospinal fluid. If no blood or CSF was aspirated then the catheter was secured to the back of the patient and labor analgesia was started.

In both groups, the number of attempts, needle redirections, incidence of traumatic injury, and accidental dural puncture were noted. Since epidural anesthesia is a skill, only one anesthesiologist (principal investigator) performed the epidural insertion to standardize the skill. The principal investigator verbally recited the number of attempts, redirections, traumatic insertions, and accidental dural puncture. The nurse assisting during the procedure recorded the data. There was no blinding in the study.

Outcome/ Assessment, Data collection method, Instruments

Efficacy of the technique was measured according to the following variables:

1. The number of attempts
2. The number of redirections
3. Incidence of traumatic insertion
4. Incidence of accidental dural puncture

The study commenced upon the approval of the Institutional Review Board of Philippine Children's Medical Center. No subject participated in this study without written documentation of informed consent.

Data were encoded and tallied in SPSS version 10 for windows. Descriptive statistics were generated for all variables. Frequencies and percentages were generated for all data since these are expressed categorically. Chi-square test and t-test were used in the analysis of the data.

RESULTS:

A total of 42 subjects were included in the study randomly assigned into two groups. Table 1 shows the comparison of the demographic characteristics between the two groups. There was no significant difference noted in the age, BMI and ASA of patients between the two groups as proven by all p values >0.05.

Table 1. Comparison of the Demographic Characteristics Between the Two Groups

	Groups		*p-value**
	Preprocedural US (n=21)	**Conventional Palpation** (n=21)	
Age (in years)			
15 – 24	7 (33.3%)	11 (52.4%)	
25 – 34	13 (61.9%)	6 (28.6%)	
35 – 45	1 (4.8%)	4 (19.0%)	
Mean ± SD	26.64 ± 5.61	26.17 ± 7.96	0.82 (NS) ‡
BMI			
18.5 – 24.9	13 (61.9%)	6 (28.6%)	
25.0 – 29.9	6 (28.6%)	9 (42.9%)	0.08 (NS) †
30.0 – 34.9	2 (9.5%)	6 (28.6%)	
ASA			
II	5 (23.8%)	12 (57.1%)	
III	15 (71.4%)	9 (42.9%)	0.07 (NS) †
IV	1 (4.8%)	0	

** p>0.05- Not significant; p ≤0.05-Significant*
† Chi-square test; ‡ t-test

Comparing the number of attempts between the two groups, there was a significant difference noted as proven by the p value of 0.03 (Table 2). There were significantly more proportion of subjects in the conventional palpation who had more than one attempts than those in the preprocedural US. There was a lesser chance of having >1 attempt among patients in the preprocedural US than those in the conventional palpation group (OR=0.17; 95% CI: 0.02 – 1.01; p=0.03). Even when the mean number of attempts was compared, there was a significant difference as shown by the p value of 0.03 derived from the t-test. The mean number of attempts of patients in the preprocedural US was significantly lower than those in the conventional palpation group with 1.09 (SD=0.30) and 1.38 (SD=0.50) respectively (Table 2).

Table 2. Comparison of the Number of Attempts Between the Two Groups

	Groups		*p-value**
	Preprocedural US (n=21)	**Conventional Palpation** (n=21)	
Number of Attempts			
1	19 (90.5%)	13 (61.9%)	0.03 (S) †
2	2 (9.5%)	8 (38.1%)	
3	0	0	
>3	0	0	
Number of Attempts			
Mean ± SD	1.09 ± 0.30	1.38 ± 0.50	0.03 (S) ‡

** p>0.05- Not significant; p ≤0.05-Significant*
† Chi-square test; ‡ t-test

Comparing the number of needle redirections between the two groups, there was a significant difference noted as proven by the p value of 0.04 (Table 3). There were significantly more proportion of subjects in the conventional palpation who had more than one needle redirection than those in the preprocedural US. Even when the mean number of needle redirections was compared, there was a significant difference as shown by the p value of 0.01 derived from the t-test. The mean number of needle redirection of patients in the preprocedural US was significantly lower than those in the conventional palpation group with 1.81 (SD=0.87) and 2.43 (SD=0.68) respectively (Table 3).

Table 3. Comparison of the Number of Needle Redirections Between the Two Groups

	Groups		*p-value**
	Preprocedural US (n=21)	**Conventional Palpation** (n=21)	
Number of Needle Redirections			
1	10 (47.6%)	2 (9.5%)	0.04 (S) †
2	5 (23.8%)	8 (38.1%)	
3	6 (28.6%)	10 (47.6%)	
>3	0	1 (4.8%)	
Number of Needle Redirections			
Mean ± SD	1.81 ± 0.87	2.48 ± 0.75	0.01 (S) ‡

** p>0.05- Not significant; p ≤0.05-Significant*
† Chi-square test

There was no significant difference noted in the proportion of subjects with accidental dural puncture and traumatic insertion between the two groups (p=1.00). None of the patients in each group was noted to have accidental dural puncture and traumatic insertion.

DISCUSSION

The results of this study support the results of previous studies done abroad with regards to the effectiveness of ultrasound use in epidural anesthesia placement. The use of preprocedure ultrasound decreased both the number of attempts and needle redirections needed to insert the epidural catheter. This can be attributed to the identification of the optimal entry point of the needle with the ultrasound using the transverse approach. Both the midline and the intervertebral space were easily identified. The results of this study are consistent with the study done by Abdelhamid and Mansour in 2013. Their study showed that the successful first needle attempt was significantly higher in patients who underwent preprocedure ultrasound compared to patients who underwent the conventional surface landmark palpation. Needle redirection attempts were also significantly lower in the US group. Patient satisfaction was significantly higher in the US group.[8]

A highly skilled anesthesiologist may have no problem inserting epidural anesthesia using the conventional palpation technique. However, even the most skilled anesthesiologist sometimes finds himself/herself faced with a difficult epidural insertion. Ultrasound can be a useful tool in these situations to help or complement the landmark palpation technique, especially in placing epidural anesthesia in pregnant patients because these patients are considered to have difficult backs. Pregnancy makes epidural insertion technically more difficult because of the exaggeration of the lumbar lordosis, increase in subcutaneous fat, and difficulty in positioning due to the gravid uterus.[2] These changes may make the conventional palpation technique less reliable and more challenging in placing the epidural catheter.

Preprocedure ultrasound can also be used to avoid general endotracheal anesthesia. When the anesthesiologist fails to insert an epidural catheter after multiplte attempts, he/she resort to general anesthesia. As much as possible, anesthesiologists try to avoid general anesthesia in pregnancy because it may lead to a lower Apgar score of the fetus. In addition to that, anesthesiologists want to avoid dealing with a potentially difficult airway. Pregnant patients are at risk for airway complications because of airway edema, decreased functional residual capacity, increased oxygen consumption, decreased lower esophageal tone, decreased gastric emptying, and weight gain.[24] By using ultrasound in patients with difficult landmarks, general anesthesia can be prevented along with its potential complications.

The results showed no significant difference in adverse events (dural puncture, traumatic insertion) between the two groups, This is in contrast with the paper done by Shaikh et al. which showed that the use of US decreased the failure rate and incidence of traumatic procedures.[18] The investigator, however, still believes that parturients admitted at the Philippine Children's Medical Center could still benefit from the use of preprocedure ultrasound during epidural anesthesia placement. The PCMC is an institution that caters to high risk pregnant patients with special needs. A good number of parturients admitted at PCMC have heart conditions which require anticoagulation. These patients could potentially benefit from the use of ultrasound because a decrease in attempts and redirections could also decrease the likelihood of hematoma formation.

The study proved the efficacy of preprocedure ultrasound in the placement of lumbar epidural anesthesia. However, there was one limitation to the study. The researcher was also the operator. Although the results were measured objectively, there was a potential bias in the results. This issue can be addressed in future studies by allowing another anesthesiologist to insert the epidural.

CONCLUSION

The results of the study showed that there was a significant difference in the number of attempts and number of needle redirections between those with and without use of ultrasound. The number of attempts and needle redirections were significantly lower in those with ultrasound use compared to those without. No adverse events were noted in both groups.

RECOMMENDATION

The author hereby recommends a follow-up study validating the results of the present study. Future studies may focus on the obese population utilizing larger samples wherein the landmarks needed for epidural placement are extremely difficult to identify. They may also want to compare the length of time required to successfully insert the epidural with and without the use of preprocedure ultrasound. In addition, the author recommends that the operator be different from the researcher to avoid any potential bias in the results.

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UTILITY OF URINE KOH IN DETECTING CANDIDURIA IN INFANTS

MARK JOSEPH S. CASTELLANO, MD, MARY ANTONETTE C. MADRID, MD

ABSTRACT

BACKGROUND: Candida species are common cause of urinary tract infection in infants requiring medical care. Candida fungal elements may be demonstrated in urine using microscopic examination with 10-20% KOH. However, detection of these elements does not always correlate with candiduria.

OBJECTIVES: The main objective of this study was to establish the utility of urine KOH in identifying candiduria in terms of sensitivity, specificity, PPV, and NPV. The study also aims to determine the risk factors, as well as urinalysis and CBC parameters associated with candiduria.

METHODS: This prospective study included admitted infants 1 year and below with urine culture request and with any risk factor for candiduria. Additional urine KOH testing was done using clean catch or catheter method (for those with indwelling catheter).

RESULTS: Among the 90 study participants, 13 had candiduria (14%). The use of indwelling catheter, presence of urinary tract anomalies, leukocyte esterase in urinalysis, and increased monocyte counts in CBC are all associated with development of candiduria. Urine KOH had a sensitivity of (100%; CI 75.2-100%), specificity (59.7%; CI 47.9-70.7%), PPV (29.5%; CI 17.7-45.2%), and NPV (100%; CI 92.2-100%) in detecting candiduria.

CONCLUSIONS: A negative urine KOH has excellent negative predictive value, while a positive result does not always mean true infection.

RECOMMENDATIONS: This study recommends that urine KOH results be interpreted with caution depending on patient's risk factors, clinical status, and other laboratory tests such as urine culture, and that a positive urine KOH result will not always require prompt treatment.

INTRODUCTION

Candida species are one of the causes of urinary tract infection (UTI) in neonates and infants requiring medical care.[1] Candida UTI may present with asymptomatic candiduria, sepsis, or acute renal failure.[2] Symptomatic infants and children with UTI may present with fever, diarrhea, vomiting, abdominal pain, or poor weight gain.[3]

Risk factors for candida UTI include low birth weight, prematurity, use of IV steroids, congenital urinary tract anomalies, broad-spectrum antibiotics, and parenteral nutrition.[1] Other risk factors include ICU admission, with indwelling urinary catheter, those who underwent abdominal surgery, with hematologic malignancies, or those on immunosuppressive drugs (e.g. chemotherapy).[4,5]

Fungal elements (e.g. yeast cells and pseudohyphae) may be seen in *Candida* infected tissue or body fluid specimens such as urine. These fungal elements may be identified by microscopic examination of scrapings using 10-20% potassium hydroxide suspension (KOH).[6] However, detection of fungal elements such as *Candida* in urine does not always correlate with significant candiduria or UTI.

In our clinical setting, urine KOH is frequently requested in the ER, ward, and ICU for sick infants and children. It is becoming a routine diagnostic procedure in the search for focus of infection. In most cases, once urine KOH becomes positive (i.e. yeast cells/fungal elements are present), clinicians often start empiric fluconazole therapy as treatment. However, the role of KOH in urine for detection significant candiduria has not been well studied.

This study will educate and guide clinicians regarding the value of urine KOH in diagnosis of candiduria in infants. If highly sensitive or specific, it may be recommended as a screening tool for candiduria. However, if not sensitive, we will be able to prevent unnecessary urine KOH testing, and thus unnecessary expenses for our patients. And if proven that it is not specific, this will prevent unwarranted exposure of patients to antifungal therapy (i.e. fluconazole).

OBJECTIVES

1. ***General Objective***
   - To establish the utility of urine KOH in identifying candiduria in infants
2. ***Specific Objectives***
   - To determine the sensitivity, specificity, PPV, and NPV of urine KOH in detecting candiduria in infants
   - To identify the risk factors significantly associated with candiduria in infants
   - To detect association of urinalysis and CBC parameters in development of candiduria in infants

METHODOLOGY

This was a prospective study which determined the utility of urine KOH in detecting candiduria in infants.

Inclusion Criteria: Admitted infants 1 year old and below, with urine culture request, and with any of the following risk factors: low birth weight (<2500g), prematurity (<37 weeks AOG), on prolonged steroids (>14 days), with congenital urinary tract anomalies, on broad-spectrum antibiotics (e.g. third and 4th generation cephalosporins, piperacillin tazobactam, vancomycin, carbapenems), on parenteral nutrition, admitted at ICU, on endotracheal intubation, with indwelling urinary catheter or on clean intermittent catheterization, those who underwent recent (≤ 1 month) abdominal, pelvic or urologic surgery, with hematologic malignancies, or those on immunosuppressive drugs (e.g. on chemotherapy).

Exclusion Criteria: infants with urine culture without any risk factor for candiduria, infants with cutaneous candidiasis on the pelvic/perineal area (i.e. satellite pustules with erythematous base, and marginal scaling), and infants with diaper dermatitis.

Using Epi Info Version 7, the minimum sample size requirement is 90 based on the specificity of KOH smear in evaluation of fungal foot infection (62%)[16], with a margin of error 10% and confidence interval of 95%.

Admitted infants (≤12 months old) with urine culture request were identified from the laboratory logbook daily. Once identified, the following risk factors were determined if present in the infant:

- Low birth weight (<2500g)
- Prematurity (<37 weeks AOG)
- On prolonged steroids (≥14 days)
- With congenital urinary tract anomalies
- On broad-spectrum antibiotics (e.g. 3rd and 4th generation cephalosporins, piperacillin tazobactam, vancomycin, carbapenems)
- On parenteral nutrition
- Admitted at Intensive Care Unit (ICU), Neonatal ICU (NICU)
- On endotracheal intubation
- With urinary catheter (indwelling or clean intermittent catheterization)
- With central vascular catheters (central lines)
- Who underwent recent (≤ 1 month) abdominal, pelvic or urologic surgery
- With hematologic malignancies
- On immunosuppressive drugs (e.g. on chemotherapy)

If any one of these risk factors was present, and the infant had no clinical signs of diaper dermatitis or cutaneous candidiasis on the pelvic/perineal area, an informed consent was obtained from the parents/guardian of the infant for inclusion in the study. Thereafter, urine collection for KOH testing was obtained for those infants without prior urine KOH test. Infants with prior KOH test were included in the study but no additional KOH testing was done.

Urine specimen for KOH testing was collected either via clean catch method, or from catheter (in catheterized patients), within 24 hours after urine culture collection.

Results of urine culture and urine KOH were obtained from the laboratory. The main outcome of this study was the urine KOH results of infants with candiduria on urine culture, compared to those with urine culture without candiduria. Other outcomes assessed in the study include urinalysis and CBC parameters of infants with candiduria, compared to those without candiduria.

Data analysis was performed in Stata SE version 13. Qualitative variables were summarized as mean and standard deviation, while quantitative variables were tabulated as frequency and percent. Accuracy of urine KOH in predicting candiduria were computed in terms of its sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV). Factors associated with candiduria was analyzed using logistic regression. The level of significance was set at 5%.

RESULTS

Majority of the participants included in the study were males (69%), and infants more than 1 month old (67%) (Table 1).

Table 1. General Characteristics of the Study Participants

Characteristics	n = 90	%
Age		
< 1 month	30	33%
> 1 month	60	67%
Sex		
Male	62	69%
Female	28	31%

The most common risk factor identified for candiduria in the study participants was the use of broad-spectrum antibiotics in 72 of the 90 cases (80%), followed by admission to an Intensive Care Unit (66%), and having endotracheal intubation (36%) (Table 2).

Table 2. Known Risk factors Identified for Candiduria Present in the Study Participants

Risk factors	n = 90	%
Low birth weight (<2500g)	24	27%
Prematurity (<37 weeks AOG)	18	20%
On prolonged steroids (≥14 days)	1	1%
With congenital urinary tract anomalies	14	16%
On broad-spectrum antibiotics (e.g. 3rd and 4th generation cephalosporins, piperacillin, vancomycin, carbapenems)	72	80%
On parenteral nutrition	5	6%
Admitted at Intensive Care Unit (ICU), Neonatal ICU (NICU)	59	66%
On endotracheal intubation	32	36%
With urinary catheter Indwelling (19) Clean intermittent catheterization (1)	20	22%
With central vascular catheters (central lines)	17	19%
Recent (≤ 1 month) abdominal, pelvic or urologic surgery	11	12%
With hematologic malignancies	3	3%
On immunosuppressive drugs (e.g. on chemotherapy)	1	1%
Others:		
Candidemia	3	3%
Intra-abdominal mass	1	1%
Abdomen congenital malformation	1	1%

The urinalysis and complete blood counts (CBC) of the study participants are shown in Table 3. Of the 90 infants, 7% showed positive nitrite results, and 29% showed positive for leukocyte esterase. The mean values for urine WBC (29/hpf), RBC (105/hpf), and CBC parameters (hemoglobin, hematocrit, WBC, differential counts, and platelet) were also noted.

Table 3. Laboratory Characteristics of the Study Participants

Parameters **n = 90**	**Mean ± SD** **n (%)**
Urinalysis	
Nitrite (+)	6 (7%)
Leukocyte esterase (+)	26 (29%)
WBC (per high power field)	29 ± 77
RBC (per high power field)	105 ± 498
CBC	
Hemoglobin (g/dL)	11.6 ± 2.56
Hematocrit (%)	34.65 ± 7.33
WBCs ($x10^3$/mL)	20.17 ± 22.5
Neutrophils (%)	55.31 ± 22.32
Lymphocytes (%)	35.73 ± 22.2
Eosinophils (%)	2.14 ± 3.10
Monocytes (%)	5.77 ± 4.28
Platelet ($x10^3$)	266.7 ± 187. 8

Majority of the study participants did not have growth in both urine (62%) and blood cultures (70%). Among those participants with positive growth in urine culture, the most common organisms identified were non-albicans *Candida* spp. (47%); *Candida albicans* was identified in 7% of the urine culture isolates (Table 4).

Among the 27 study participants with positive growth in blood culture, Coagulase Negative *Staphylococcus aureus* (CONS) was identified in 44% of cases. *Candida spp.* and *Candida albicans* were isolated from blood in 11% and 7% of participants respectively

Table 4. Culture Characteristics of the Study Participants

Organisms **n = 90**	**n (%)**
Urine culture	
NO growth	***56 (62%)***
WITH growth	***34 (38%)***
Candida spp.	16 (47%)
Candida albicans	6 (18%)
Klebsiella pneumoniae	5 (15%)
Pseudomonas aeruginosa	2 (6%)
Escherichia coli	2 (6%)
Proteus mirabilis	1 (3%)
Serratia marcescens	1 (3%)
CONS	1 (3%)
Blood culture	
NO growth	***63 (70%)***
WITH growth	***27 (30%)***
Candida spp.	3 (11%)
Candida albicans	2 (7%)
Klebsiella pneumoniae	4 (15%)
Pseudomonas aeruginosa	1 (3%)
Escherichia coli	1 (3%)
Serratia marcescens	1 (3%)
Burkholderia cepacia	3 (11%)
CONS	12 (44%)

Of the 90 study participants, 13 had candiduria (14%); majority were males (62%), and infants more than 1 month old (62%) (Table 5).

Table 5. Characteristics of Patients with Candiduria

Characteristics	n = 13
Age	
< 1 month	5 (38%)
> 1 month	8 (62%)
Sex	
Male	8 (62%)
Female	5 (38%)

In participants with candiduria, the most common identified predisposing factor for candiduria was the use of broad-spectrum antibiotics (100%), followed by admission to an Intensive Care Unit (69%), and having a urinary catheter (61%) (Table 6).

Table 6. Risk factors Identified in patients with Candiduria

Risk factors	n = 13	%
Low birth weight (<2500g)	0	0%
Prematurity (<37 weeks AOG)	0	0%
On prolonged steroids (≥14 days)	1	8%
With congenital urinary tract anomalies	5	38%
On broad-spectrum antibiotics (e.g. 3rd and 4th generation cephalosporins, piperacillin, vancomycin, carbapenems)	13	100%
On parenteral nutrition	0	0%
Admitted at Intensive Care Unit (ICU), Neonatal ICU (NICU)	9	69%
On endotracheal intubation	6	46%
With urinary catheter Indwelling (8) Clean intermittent catheterization (0)	8	61%
With central vascular catheters (central lines)	2	15%
Who underwent recent (≤ 1 month) abdominal, pelvic or urologic surgery	1	8%
With hematologic malignancies	0	0%
On immunosuppressive drugs (e.g. on chemotherapy)	0	0%

The urinalysis and complete blood counts (CBC) of participants with candiduria are shown in Table 7. Of the 13 infants, one (8%) showed positive nitrite results, and 9 (69%) showed positive for leukocyte esterase. The mean values for urine WBC (63/hpf) and RBC (62/hpf), as well as CBC (hemoglobin, hematocrit, WBC, differential counts, and platelet) were also noted.

Table 7. Laboratory Characteristics of Patients with Candiduria

Parameters **n = 13**	**Mean ± SD** **n (%)**
Urinalysis	
Nitrite (+)	1 (8%)
Leukocyte esterase (+)	9 (69%)
WBC (per high power field)	63 ± 122
RBC (per high power field)	62 ± 158
CBC	
Hemoglobin (g/dL)	11.7 ± 2.0
Hematocrit (%)	35.3 ± 5.9
WBCs ($x10^3$/mL)	14.9 ± 7.0
Neutrophils (%)	55.6 ± 21.3
Lymphocytes (%)	30.3 ± 17.9
Eosinophils (%)	3.3 ± 5.0
Monocytes (%)	9.2 ± 4.2
Platelet ($x10^3$)	398.0 ± 259.7

Among the 13 participants with candiduria, the most common organisms identified were non-albicans *Candida* spp. 10 (77%); *Candida albicans* was identified in 3 (23%) of the urine culture isolates (Table 8).

Of the 11 study participants with candiduria who had blood culture, 9 (82%) had no growth. Two participants had positive blood culture which were not Candida; one with CONS, and the other with *Serratia marcescens* (Table 8).

Table 8. Culture Characteristics of Patients with Candiduria

Organisms	**n (%)**
Urine culture (n = 13)	
Candida spp.	10 (77%)
Candida albicans	3 (23%)
Blood culture (n = 11)	
NO growth	***9 (82%)***
WITH growth	***2 (18%)***
Serratia marcescens	1 (9%)
CONS	1 (9%)

The presence of congenital urinary tract anomalies or patients with urinary catheter are the significant risk factors identified for candiduria in this study. The odds of developing candiduria increases by 4.72 if a patient has congenital urinary tract anomaly (OR 4.72; 95%; CI 1.27-17.6), and increases by 8.67 if a patient has urinary catheter (OR 8.67; 95%; CI 2.42-31.04). Other risk factors such as low birth weight, prematurity, on broad spectrum antibiotics, prolonged steroids, parenteral nutrition, with hematologic malignancies, and on immunosuppression cannot be analyzed due to limitations in data (i.e. patients who developed candiduria did not have these risk factors, or in the case of use of broad spectrum antibiotics, all patients had this risk factor).

Table 9. Association of Patients' Characteristics and Risk factors with Candiduria

Characteristics Risk factors	***With*** candiduria n = 13	***Without*** candiduria n = 77	**Odds ratio**	**P value**	**C.I**
Sex (male)	8 (62%)	54 (70%)	0.68	0.538	0.20 – 2.30
Low birth weight	0	24 (31%)	-	-	-
Prematurity	0	18 (23%)	-	-	-
On prolonged steroids	1 (8%)	0	-	-	-
With congenital urinary tract anomalies	5 (38%)	9 (12%)	4.72	0.021	1.27 – 17.60
On broad-spectrum antibiotics	13 (100%)	59 (77%)	-	-	-
On parenteral nutrition	0	5 (6%)	-	-	-
Admitted at ICU/NICU	9 (69%)	50 (65%)	1.2	0.763	034 – 4.31
On endotracheal intubation	6 (46%)	26 (34%)	1.68	0.391	0.51 – 5.51
With urinary catheter	8 (62%)	12 (16%)	8.67	0.001	2.41 – 31.04
With central vascular catheters (central lines)	2 (15%)	15 (19%)	0.75	0.728	0.15 – 3.75
Recent (≤ 1 mo) abdomen, urologic/pelvic surgery	1 (8%)	10 (13%)	0.56	0.594	0.06 – 4.77
With hematologic malignancies	0	3 (4%)	-	-	-
On immunosuppressive drugs	0	1 (1%)	-	-	-

From the results of the study, the significant laboratory parameters associated with candiduria are presence of leukocyte esterase on urinalysis and monocyte count on CBC. The presence of leukocyte esterase in urinalysis increases the odds of having candiduria (OR 7.94; 95%; CI 1.54-4.44), and among the CBC differential counts, increase in monocytes also increases the likelihood of having candiduria (OR 1.27; 95%; CI 1.08-1.49). (Table 10).

Table 10. Association of Patients' Laboratory Parameters with Candiduria

Laboratory Parameters	***With*** candiduria Mean ± SD n = 13	***Without*** candiduria Mean ± SD n = 77	**Odds ratio**	**P value**	**C.I**
Urinalysis					
Nitrite (+)	1 (8%)	5 (6%)	1.20	0.873	0.12 – 11.18
Leukocyte esterase (+)	9 (69%)	17 (22%)	7.94	0.002	2.17 – 28.99
WBC	62.9 ± 122.0	23.3 ± 67.0	1.00	0.122	0.99 – 1.01
RBC	62.1 ± 158.0	112.4 ± 534.9	1.00	0.740	0.99 – 1.00
CBC					
Hgb	11.7 ± 2.0	11.6 ± 2.6	1.02	0.697	0.81 – 1.28
Hct	35.3 ± 5.9	34.5 ± 7.5	1.02	0.939	0.93 – 1.09
WBC	14.9 ± 7.0	21.0 ± 24.1	0.97	0.366	0.91 – 1.03
Neutrophil	55.6 ± 21.3	55.2 ± 22.6	1.00	0.957	0.97 – 1.02
Lymphocyte	30.3 ± 17.9	36.6 ± 22.9	0.98	0.350	0.95 – 1.01
Eosinophil	3.3 ± 5.01	1.9 ± 2.6	1.12	0.159	0.95 – 1.30
Monocyte	9.2 ± 4.2	5.1 ± 4.0	1.27	0.004	1.08 – 1.49
Platelet ($x10^3$)	398.0 ± 259.7	244.5 ± 164.9	1.00	0.010	1.00 – 1.00

The sensitivity of urine KOH in detecting candiduria (as well as in urine bag and catheter method) is 100%. This implies that a negative urine KOH has the ability to detect the absence of candiduria in 100% of the time.

The specificity of urine KOH in detecting candiduria is 59.74%. This implies that a positive urine KOH has the ability to detect presence of candiduria in 59.74% of the time.

The positive predictive value (PPV) of urine KOH (i.e. the ability to detect candiduria among those who tested positive for urine KOH) is 29.55%, while the negative predictive value (NPV) of urine KOH (i.e. the ability to detect the absence candiduria among those who tested negative for urine KOH) is 100% (Table 11).

Table 11. Accuracy of Urine KOH in Detecting Candiduria

	Overall % (C.I)	**Urine Bag % (C.I)**	**Urine Catheter % (C.I)**
Sensitivity	100% (75.2-100%)	100% (39.7-100%)	100% (66.3-100%)
Specificity	59.7% (47.9-70.7%)	65.8% (49.4-79.9%)	52.7% (35.4-69.5%)
PPV	29.5% (16.7-45.2%)	22.2% (6.4-47.6%)	34.6% (17.2-55.6%)
NPV	100% (92.2-100%)	100% (87.23-100%)	100% (82.3-100%)

DISCUSSION

Candida spp. are commensal organisms commonly found in the gastrointestinal and genitourinary tracts of healthy individuals.[17] *Candida* is the most important cause of fungal infection in health care settings, including those of the urinary tract. In the majority of asymptomatic persons, the presence of yeast in the urine indicates contamination or colonization. However, in symptomatic patients or those with risk factors for candiduria, the presence of yeast may indicate true infection. Both innate and adaptive arms of the immune system play key roles in the immune response to Candida.[17] Infants who have relatively lower immune responses have greater predilection for developing invasive candidiasis including candiduria.

In the present study, 13 of the 90 infants (14%) who participated had candiduria, and majority of these infants are males 8 (62%). The study of Seifi et. al. involving 402 children with ages 0-14 years old have shown candiduria in 21 (5.2%), as well as male predominance in 15 (71.4%).[5] In another study by Gholamipour et. al. regarding candiduria in children, of the 4813 urine cultures noted, 209 (4.1%) *Candida* spp. isolates were found. Sixty-five percent of candiduria was seen in patients less than one year old, and candida infection was also noted to be more frequent in boys 143 (68%).[14] Malhotra et al. also investigated the prevalence of candiduria in infants (<1 year old) from a tertiary care hospital. Three hundred thirty three (333) urine samples were received from admitted infants, for which 72 (21.62%) showed *Candida* growth, with predominance in male population at 56.8%.[13]

In the study of Gholamipour et al, the highest frequency of candiduria was seen in patients who had received more than 2 or 3 antibiotics during their hospitalization (37% and 24%, respectively).[14] Other risk factors identified in their study include admission in ICU (24.5%) and NICU (12%), those with cardiovascular disorder (18%), with urinary catheter (12%), respiratory diseases (10%), anomaly of the urinary tract (10%), gastrointestinal and liver diseases (9%) and neurologic disorders (8.5%). In relation to this, the present study has identified the use of broad spectrum antibiotics in all (100%) patients who developed candiduria. Furthermore, other common risk factors for candiduria that were identified this study include the following: admission to intensive care unit (69%), use of indwelling urinary catheter (61%), on endotracheal intubation (46%), and presence of congenital urinary tract anomaly (38%).

In the study of Paul et al, prior antimicrobial use was documented in 92% with candiduria (OR 9.1; 95%; CI 2.1-31.9) [21], while in the present study, prior antimicrobial use was documented in 100% of patients with candiduria. The results of this study is also congruent with the findings of Passos et al. wherein, in the 68 ICU patients who developed candiduria, the most common predisposing factors were antibiotic therapy (100%) and

indwelling urinary catheter (92.6%).[22] Furthermore, Alfouzan et al. reported that aside from long term urinary catheterization, prior antibiotic use is the next most significant risk factor for candiduria.[20] In this study, the most frequently used antibiotic in patients with candiduria are cephalosporins (3rd and 4th generations).

The use of broad spectrum antibiotics leads to alteration of the normal bacterial flora, which results to a more conducive environment for the growth of yeasts. The higher number of candiduria cases noted in ICU patients are probably secondary to others factors such as underlying diseases, relative immunodeficiency status, multiple manipulations by health care team and altered bacterial flora secondary to use of broad spectrum antibiotics.[18]

Among the identified risk factors for candiduria in the present study, there was significant association of candiduria with existence of urinary tract anomalies (OR 4.72; 95%; CI 1.27-17.6), and presence of indwelling urinary catheter (OR 8.67; 95%; CI 2.42-31.04). The odds of developing candiduria increases in the presence of urinary tract anomaly, or use of indwelling urinary catheter. Urinary tract anomalies noted in patients with candiduria in this study include horseshoe kidneys, cloacal exstrophy, prune belly syndrome, and bladder exstrophy. The study conducted by Platt et al. showed that 26.5% of urinary tract infections related to indwelling catheter were caused by fungi.[19] Alfouzan et al. also reported that long-term urinary catheterization is considered to be the most significant risk factor for candiduria.[20]

Other risk factors such as low birth weight, prematurity, on broad spectrum antibiotics, prolonged steroids, parenteral nutrition, with hematologic malignancies, and on immunosuppression cannot be analyzed due to limitations in data (i.e. patients who developed candiduria did not have these risk factors, or in the case of use of broad spectrum antibiotics, all patients had this risk factor) (Table 9).

The presence of pyuria, hematuria, or leukocyte esterase in urinalysis maybe useful in distinguishing infection from contamination or colonization.[17] In this study, urinalysis and CBC parameters were compared between those with candiduria and those without candiduria. Significantly, the presence of positive leukocyte esterase in urine specimen increased the odds of having candiduria by 7.94 (OR 7.94; 95%; CI 1.54-4.44). Monocytes, along with neutrophils and macrophages are important antifungal effector cells. Residing phagocytes in infected organs are involved in the killing of invading Candida, whereas neutrophils and monocytes are recruited to the site of infection.[17] The mean percentage of monocyte in infants is 5%.[28] In this study, increase in monocyte counts was noted to be associated with increased odds of having candiduria (OR 1.27; 95%; CI 1.08-1.49). Candidemia and low platelet counts has been demonstrated and associated by several studies, especially in the neonates.[23,24] However, in this study, platelet count has no significant association with presence or development of candiduria (OR 1; 95%l CI 1-1).

Among the 13 *Candida* species isolated in urine in the present study, 10 were *Candida albicans* (77%), and 3 were non-albicans *Candida* spp. (23%). In the study conducted by Gholamipour et al, of the 209 *Candida* spp. isolates they identified, 150 were *Candida albicans* (72%), and 57 were non-albicans *Candida* spp. (28%).[14] In the study of Malhotra et al, *C. albicans* were isolated in 37 of 333 cases (11.1%) and non-albicans *Candida* spp. were noted in 35 patients (10.5%).[13]

In the present study, no candidemia was noted in those patients who developed candiduria. The frequency of candidemia noted in the study of Gholamipour et al. was noted at 2%, while the study conducted by Philips et al. yielded 52%.[14,8] The findings of this study confirms the reports of Gholamipour et al, and Binelli et al. that the major source of candidemia in patients is not from the urinary tract (candiduria).[25] In relation to this, Drogari-Apiranthitou et al. also stated that in hospitalized patients with candidemia, concomitant candiduria is rare and usually an independent event.[26]

The accuracy of urine KOH in its ability to detect significant candiduria has not been well studied. There is scarcity in data regarding the use of urine KOH in predicting candiduria when compared to urine culture as the gold standard. In this study, the sensitivity of urine KOH was noted at 100%, implying that a negative urine KOH has the ability to confirm the absence candiduria (i.e. if urine KOH is negative, we can say with certainty that the patient has no candiduria). However, the specificity of urine KOH is only 59.74%, which means that a positive urine KOH has the ability to detect significant candiduria in approximately 6 out of 10 cases (i.e. a positive urine KOH result does not always imply substantial candiduria). The importance of these findings has significant impact on how we approach and manage patients with positive urine KOH results.

Not all patients with positive urine KOH should be treated. Based on the findings of this study that approximately only 6 out of 10 patients with positive urine KOH will have

candiduria, it is prudent to not immediately treat these patients with antifungals such as fluconazole, unless correlated with necessary cultures and clinical status of the patient. Exposure of patients to unnecessary drugs or antimicrobials (antifungals included), has its drawbacks and disadvantages.

First, unnecessary exposure of patients to antifungals may lead to emergence of resistant strains of *Candida* species such as *C. glabarata* and *C. krusei*. In the study of Prasad et al, they identified that patients older than 2 years, those with recent surgical procedure, and prior fluconazole use were independent risk factors for infection with *C. glabrata* and *C. krusei* in children.[27] Second, the general recommendation for treatment of candidemia is the use of Amphotericin B, which is usually nephrotoxic and may cause electrolyte imbalances (e.g. hypercalciuria, hypokalemia, hypomagnesemia), renal tubular acidosis, renal failure, acute hepatic failure, and hypotension.[28] In relation to this, patients who are not on prior azole use (e.g. fluconozaole) and not critically ill may use fluconazole for treatment of candidemia with susceptible isolates.[29] In the instance that a patient was previously treated with fluconazole because of other conditions (e.g. positive urine KOH), then we can no longer use fluconazole (a relatively safer agent compared to amphotericin B) to treat candidemia; amphotericin B will be given and continued for at least 14 days, thereby increasing the risk for possible detrimental side effects of this antifungal as previously mentioned.

Lastly, unnecessary use of antifungals such as fluconazole provides additional economic burden to patient's family. Locally, IV fluconazole approximately costs 1500 pesos per vial of 2mg/ml (100ml), while oral fluconazole capsule costs 400 pesos per 200mg tablet, and the recommended duration of treatment for candida UTI is 14 days. Thus, it is prudent to verify first the diagnosis of candiduria by doing a urine culture and correlate the findings to the risk factors and signs and symptoms that the patient has prior to starting antifungal treatment.

Fluconazole is highly water soluble and is mainly excreted in the urine as an active drug (urinary concentrations are more than 10-fold compared to those in serum). With this, fluconazole is considered the drug of choice for both candida cystitis and pyelonephritis.[30] For asymptomatic candiduria, elimination of predisposing factors such as indwelling urinary catheters catheter is strongly recommended. Antifungal treatment is not recommended unless patients has high risk of candidemia (blood stream infection), such as neutropenia, very low birth weight, and patients who will undergo urologic manipulation.[29] In patients with indwelling catheter, removal of the device maybe adequate to resolve the candiduria without antifungal therapy.[17] It is recommended that asymptomatic catheter-associated bacteuria or candiduria should not be treated while the catheter remains in place since this may lead to evolution of resistant flora.[31]

In the review of Lundstrom et al., management of candiduria depends on the clinical manifestations of patients. For those with asymptomatic candiduria, modification of risk factors such as catheter removal, or rational use of broad spectrum antibiotics, is sufficient to address the condition. For those who are symptomatic with cystitis (dysuria, hematuria, frequency, urgency, and suprapubic tenderness), treatment with fluconazole is given, and for patients with pyelonephritis (fever, leukocytosis, costovertebral angle tenderness), treatment with fluconazole is also given (with possible surgical drainage in cases of abscesses or fungal balls).[32] Thomas et al., support this management concept for candiduria and indicated that antifungal therapy is only required in symptomatic or high-risk cases, because spontaneous resolution is common in patients with asymptomatic colonization.[33]

Based from the results of this study and recommendations from other literature, the present study recommends the following alternative approaches which may be done in patients with positive urine KOH. For patients *without* risk factor for candiduria, who are *asymptomatic*, and with positive urine KOH, no treatment is necessary and observation or monitoring for clinical signs and symptoms suggestive of urinary tract infection maybe done. On the other hand, for patients *with* risk factor for candiduria, who remain to be *asymptomatic*, and with positive urine KOH, a urine culture maybe done to verify presence of candiduria; treatment is then directed once urine culture and sensitivities are available. Lastly, for patients *with* risk factors for candiduria, who are *symptomatic* (e.g. febrile, frequency, dysuria) or critically ill (e.g. admitted at ICU, intubated, with shock), and with positive urine KOH, antifungal therapy with fluconazole maybe empirically started with urine collection for culture. Treatment is then continued, stopped, or directed once urine culture result and sensitivities are available, with correlation on the clinical status of the patient.

CONCLUSION AND RECOMMENDATIONS

Candiduria is one of the common infections of the urinary tract in admitted patients especially in infants with predisposing

factors. The most common risk factors seen with candiduria are prior use of broad-spectrum antibiotics (100%), admission to intensive care units (69%), and use of indwelling urinary catheter (61%). The use of indwelling catheter (OR 8.67; 95%; CI 2.42-31.04), the existence of urinary tract anomalies (OR 4.72; 95%; CI 1.27-17.6), the presence of leukocyte esterase in urinalysis (OR 7.94; 95%; CI 1.54-4.44), and increased in monocyte counts (OR 1.27; 95%; CI 1.08-1.49) are all associated with increased odds of developing candiduria. The organisms responsible for candiduria are mostly non-albicans Candida *spp*. (77%), followed by *Candida albicans* (23%). The accuracy of urine KOH in detecting candiduria is expressed in terms of sensitivity (100%; CI 75.2-100%), specificity (59.7%; CI 47.9-70.7%), PPV (29.5%; CI 17.7-45.2%), and NPV (100%; CI 92.2-100%), when compared to urine culture. A negative urine KOH has excellent negative predictive value, while a positive result will warrant further investigation with urine culture and correlation with patient's clinical status prior to initiation of empiric antifungal therapy.

This study recommends that urine KOH results be approached individually with caution depending on patient's risk factors and clinical status, so as to prevent emergence of resistant candida strains, maintain rational use of antifungals, and avoid additional economic burden to the family with the use of unnecessary antifungals. A positive urine KOH will not always require prompt treatment.

The study also recommends to extend the scope of population to older children (beyond infancy > 1 year old) in future studies so as to determine use of urine KOH in candiduria in this age group.

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SURVIVAL OF FILIPINO CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA DIAGNOSED IN A TERTIARY REFERRAL CENTER FOR CHILDHOOD CANCER: A RETROSPECTIVE COHORT STUDY

TRIXY G. CHU, MD, ARDEN MAE S. SHIU, MD, MA. BEATRIZ P. GEPTE, MD, MA. CECILIA LEONGSON-CRUZ, MD

ABSTRACT

BACKGROUND: Acute lymphoblastic leukemia (ALL) represents the largest group of pediatric malignancies. The high cure rate of childhood ALL represents one of the most remarkable success stories in the war against cancer. In a lower middle income country (LMIC) like the Philippines, we reviewed the 5-year survival in a tertiary referral center.

OBJECTIVES: This study aims to determine the 5-year survival of childhood ALL at a tertiary referral center for childhood cancer.

METHODOLOGY: Medical charts of newly diagnosed ALL ages 1 to 18 years old from January 2012 to December 2016 were reviewed.

OUTCOME: A total of 435 subjects were included in the study. The 5-year overall survival (OS) and event free survival (EFS) were 65.3% and 62.8%, respectively. The 5-year OS for standard risk ALL was 68.8% and for high risk ALL was 50%. The 5-year OS for the remission group was 83.7% and for the relapse was 21.1%. Univariate and multivariate analysis showed that WBC count at diagnosis, risk classification, immunophenotyping, and relapse showed significant prognostic impact for mortality.

CONCLUSION: The 5-year OS and EFS were lower compared to developed countries but are comparable with other LMICs. The prognostic factors for relapse and mortality were compatible with the literature. Overall, the adopted treatment protocols for childhood ALL in this institution showed acceptable results.

KEY WORDS: Childhood *Acute Lymphoblastic Leukemia, Filipino, Overall survival, Event Free Survival*

INTRODUCTION

The 5-year event-free survival for childhood cancer is 75% to 79% in high-income countries (HIC). However, 80% of the world's children live in middle- and low-income countries (MIC and LIC), where poverty, lack of public health infrastructure, high mortality rates, and low childhood cancer cure rates are pervasive.[1] Various phenomena accounts for this survival gap, including treatment toxicity, higher rates of relapse and abandonment of therapy in LIC.[2]

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, accounting for a quarter of all childhood malignancies. This potentially catastrophic disease was once fatal in four-fifths of patients, but the clinical outcome has improved remarkably over the past 50 years.[3] ALL is characterized by the clonal proliferation and accumulation of malignant blast cells in the bone marrow and peripheral blood.[4] These abnormal cells are arrested in the lymphoblast stage of the normal maturation pathway. Aberrations in proliferation and differentiation of these cells are common and normal hematopoiesis is suppressed. Symptoms result from varying degrees of anemia, neutropenia, and thrombocytopenia or from infiltration of the blast cells into tissues.[5]

Data from the Philippine Cancer Society–Manila Cancer Registry (PCS–MCR) and the Department of Health–Rizal Cancer Registry (DOH–RCR) from 2001-2005 showed an overall absolute survival of 32.3% for childhood ALL.[6] In 2003 to 2007, local data from a tertiary referral pediatric center, the Philippine Children's Medical Center showed the overall survival (OS) is 82%.[7] Currently, with the use of intensive chemotherapy and with increase in the support therapies such as blood transfusions and antibiotic therapy, around 70 to 75% of affected children can be cured with present treatment protocols.[8]

The high cure rate of children with ALL represents one of the most remarkable success stories in the war on cancer. Many factors have led to this high cure rate, including: (1) the use of combination chemotherapy, (2) presymptomatic treatment of the central nervous system, a sanctuary site, and, more recently, (3) the use of intensified therapeutic regimens. These major advances have been derived empirically through carefully controlled, randomized multi-institutional clinical trials.[9] One of the most well-known protocols for childhood ALL internationally was developed by the German Berlin-Frankfurt-Münster (BFM) group.[10] The primary objective of the treatment is to induce complete remission. The German-Swiss-Austrian study group responsible for BFM 90, published that disease free survival for six years 6 years (±SE) was 78±1% among the 2,178 patients studied.[11] Local Study done from 2005 to 2009 by Dujua et.al. at the University of Santo Tomas Hospital using the Modified Berlin-Frankfurt-Münster/Hong Kong Acute Lymphoblastic Leukemia (BFM95-HKALL97) protocol in 78 patients showed five-year OS and event free survival (EFS) rates were 86.94 % and 86.2%, respectively.[12] In a study at the Philippine Children's Medical Center from 2003 to 2007 in 111 patients by Galano et.al. showed OS of 82% at five years, for standard risk ALL given the modified BFM protocol OS showed 84.4% at five years, and for high risk ALL given CCG 1961 protocol OS was at 77.8% at five years.[7]

Although most children with acute lymphoblastic leukemia (ALL) are cured, certain subsets have a high risk of relapse.[13] Identification of groups at variable risk of relapse is done primarily to be able to inform modifications of therapy to limit short-term and long-term toxicities to those with more easily treatable disease and to intensify therapy for those with a worse prognosis. Improvement in outcome for higher-risk patients to date can largely be attributed to intensification of conventional chemotherapy.[14] The reported outcomes by the Children's Cancer Group (CCG) 1961 trial in three time periods, 1983–1988, 1989–1995, 1996–2002 and over the three intervals showed 10-year event-free survival (EFS) for Rome/NCI standard risk and higher risk B-precursor patients was 68% and 58%, 77% and 63%, and 78% and 67%.[15] Hence, our institution has adopted this protocol for the treatment high risk (HR) ALL.

Even with the risk-stratified and more intensive frontline therapy, 20-25% of children with ALL still relapse. The treatment of patients with relapse ALL remains unsatisfactory, with suboptimal re-induction remission rates and poor long-term overall survival rates ranging from 15-50%. We have adopted the Memorial Sloan-Kettering-New York II (MSK-NY-II) protocol for the ALL with relapse to the bone marrow or extramedullary (testicles or CNS) or a combined marrow and extramedullary relapse. Pilot study of the MSK-NY-II protocol showed in a median follow-up of 54+ months, the event-free survival (EFS) rate was 86%±10%. Disease-free survival (DFS) rate at 48 months was 93%. The estimated 4-year EFS rates for the high-risk and average-risk patients were 83±14% and 93 **%** respectively.[16]

The advent of intrathecal therapy as CNS prophylaxis has changed the paradigm of ALL treatment and has remarkably decrease cases of meningeal leukemia. This was further enhanced with systemic therapy using high dose methotrexate. However, a large number of patients at would still develop relapses, which usually is isolated to extramedullary sites, most commonly in the CNS, testicular, or ocular locations.[17] The treatment philosophy of intensive systemic therapy with anti-leukemic drugs that penetrate the CNS plus delayed CNS radiation used by Pediatric Oncology Group (POG), has resulted in significant improvements in outcome for patients with isolated CNS relapse of ALL. Previously, most studies had reported EFS rates below 50%. This shift in treatment philosophy resulted from the realization that most failures after isolated CNS relapse occurred in the bone marrow. Therefore, POG designed a regimen that intensified systemic therapy for 12 months while delaying radiation. The overall 4-year event-free survival (EFS) of the POG 9412 trial for the precursor B-cell patients with CNS relapse is at 70.1%±5.8%.[18] With the improvement in the survival using POG 9412 trial for isolated CNS relapse, we have adopted this protocol in our setting.

The management of ALL has drastically changed over the years and numerous protocols had been developed both for high income and low income countries. Treatment is optimally tailored to each individual patient's risk of failure so that chances for cure can be maximized, while unnecessary toxicity can be avoided.[14] With the application of these international protocols to our setting, this study was conducted to review the overall survival rate at our institution to assess the effectiveness of application of such protocols among our patients.

OBJECTIVES

General Objective

The general objective is to determine the survival of children 1-18 years old with acute lymphoblastic leukemia treated at a tertiary referral center for children from January 2012 to December 2016.

Specific Objectives

1. To describe the demographic and clinical characteristics of children diagnosed with ALL based on Rome/NCI Criteria, as to: a) age b) sex c) geographic region d) initial white cell count e) initial CNS status f) remission status post-induction g) FAB morphology/immunophenotype

2. To determine the overall survival (OS) and event free survival (EFS)

3. To determine the proportion of post-induction remission failure and relapse

4. To describe the sites of relapse and time to relapse (whether less than 18 months or more than 18 months) from diagnosis

5. To identify the causes of death

6. To assess the associated risk between treatment outcomes with risk classification and occurrence of relapse and mortality

METHODOLOGY AND STATISTICAL ANALYSIS

This was a retrospective cohort study conducted at the Philippine Children's Medical Center from January 2012 to December 2016.

Approval by the Philippine Children's Medical Center Institutional Review Board was obtained for this retrospective analysis. Medical Charts (in-patient and out-patient) of the patients newly diagnosed with ALL age 1 to 18 years old who underwent treatment at the Philippine Children's Medical Center from January 2012 to December 2016 were reviewed.

The following data were collected: demographic characteristics (age, sex, and geographic location), criteria based on Rome/NCI Criteria: a) initial white cell count b) initial CNS status c) status post-induction (whether remission or failure) d) FAB morphology/immunophenotype; the proportion of remission failure, relapse (time to relapse from diagnosis whether less than 18 months and more than 18 months, sites of relapse), and the cause of death.

The primary outcomes of 5-year OS and EFS among children ages 1-18 years old newly diagnosed with ALL standard risk treated with a modified version of the Berlin-Frankfurt-Münster/Hong Kong Acute Lymphoblastic Leukemia (BFM95/HKALL97) protocol, ALL high risk treated with Children's Cancer Group CCG 1961, and ALL relapse patients treated with Memorial Sloan Kettering New York MSK NY II protocol or Isolated CNS relapse Children's Oncology Group POG 9421 were determined.

The associated hazards between treatment outcomes with clinical profile and occurrence of mortality were also evaluated.

ALL is diagnosed when 25% lymphoblasts or more in the bone marrow aspirate will be present using FAB classification or using immunophenotyping (flowcytometry). Cytogenetics by karyotyping was not done on all our patients due to the high cost of the test and unavailability at our institution. Cerebrospinal fluid analysis was done on all patients for staging. Minimal residual disease evaluation was done at the end of induction phase 1A by flowcytometry.

Details of the treatment protocols are provided in the appendix. In the BFM95/HKALL97 protocol, the first part of induction chemotherapy comprised of four drugs and lasted 5 weeks. The second part comprised of 4 weeks of cytarabine arabinoside with intrathecal chemotherapy and 2 doses of high-dose cyclophosphamide. The consolidation phase included four 2-weekly courses of high-dose methotrexate (1 g/m^2). The delayed intensification commenced at week 22 after diagnosis (re-induction phase). Reinduction further enhanced treatment outcome, suggesting that the increased dose-intensity of other drugs—such as asparaginase—led to the noted improvement.[19] Daily mercaptopurine and methotrexate every week constitute the backbone of continuation regimens for the maintenance therapy.[20]

The ALL patients classified under high risk category were given the CCG 1961 protocol. Children with high-risk are treated with four or more drugs for remission induction for a more intensified regimen.[19] If marrow blasts remain $\geq$5% at the end of consolidation or patients experienced relapse during treatment, Memorial Sloan Kettering New York MSK NY II protocol were instead given. For those who developed isolated CNS relapse, they were shifted to isolated CNS relapse POG 9461 protocol.

Trimethoprim-sulfamethoxazole combination was given to all patients twice daily for three days per week from the start of the chemotherapy treatment up to three months after completion of chemotherapy as prophylaxis against *Pneumocystis jerovici* pneumonia.

Bone marrow response was evaluated at the end of induction phase 1A. Complete remission (CR) was defined as less than 5% blasts in the bone marrow by flowcytometry or BMA status of M1 by morphology, the absence of leukemic blasts in blood and CSF, and no evidence of localized disease. Resistance to therapy (remission failure) was defined as not having achieved complete response by the end of the induction phase. Relapse was defined as recurrence of 25% or more lymphoblasts in the bone marrow and/or localized leukemic infiltrates at any site.

Statistical methods employed were summary statistics (means, SD, frequency, percentages) for socio-demographic information and clinical characteristics. The Kaplan-Meier survival analysis was used to estimate EFS and OS. Censored observations were included and applied to the patients who abandoned treatment and to the group still alive and event-free. Univariate and multivaraite analysis was done using Cox regression proportional hazard.

RESULTS

A total of four hundred and forty seven medical charts were reviewed. Four hundred and thirty five patients were included in the study, twelve patients were excluded, of which six were infantile type of leukemia (age less than 1 year old) and the other six were failure of induction. Table 1 shows the demographic and clinical characteristics of the subjects. The mean age at diagnosis was at 6.6 years ± 4.3 standard deviation. There were more boys than girls at a ratio of 1.4:1. Majority of the patients were categorized under standard risk ALL at 60.7% of the total subjects and 39.3% were high risk ALL. Initial white blood cell count at diagnosis has a mean of 43.16 (0.5 - 502.3) x 10^9/L. According to immunophenotyping, the greater proportion of the population were Pre-B cell ALL at 88.3%, followed by T-cell ALL at 10.6%, biphenotypic 0.9%, and mature B cell 0.2%. CNS status on diagnosis showed CNS involvement in only 1.8% of the population. Failure of induction was seen in 6 out of 447 total patients at 1.3%. Overall outcome showed 63.7% live patients, 16.8% abandonment, and 19.5% dead. This illustrates an overall remission rate of 80.9% at the time of data collection and 19.1% developed relapse. For the duration from diagnosis to relapse, the group who developed early relapse (less than 18 months) showed 54.2% while the group who developed late relapse (more than 18 months) was 45.8%. The duration from relapse to death showed mean of 244.6 (38 – 527) days. As to the status of the relapse group, 7.2% had completed treatment and presently in remission, 63.9% deaths, the 27.7% were currently on-going treatment and in remission, and 1.2% on oral metronomics therapy. The causes of death reported showed majority died from septic shock 63.5%

Table 1. Clinical Profile of the patients with Acute Lymphoblastic Leukemia diagnosed at Philippine Children's Medical Center Cancer and Hematology Center from January 2012- December 2016

Characteristic	All population (N = 435)	Standard Risk Group (N = 264)	High Risk Group (N = 171)
	Frequency (%); Median (range); Mean ± SD	Frequency (%); Median (range); Mean ± SD	Frequency (%); Median (range); Mean ± SD
Age (years)	6.6 ± 4.3	5 ± 2.4	9.5 ± 4.8
Age 1-10 years old	340 (78.2)		
Age >10 years old	95 (21.8)		
Sex			
Male	257 (59.1)	143 (54.2)	114 (66.7)
Female	178 (40.9)	121 (45.8)	57 (33.3)
Locality			
Region 1	14 (3.2)	9 (3.4)	5 (2.9)
Region 2	5 (1.3)	4 (1.5)	1 (0.6)
Region 3	84 (19.3)	52 (19.7)	32 (18.7)
Region 4	114 (26.2)	62 (23.5)	52 (30.4)
Region 5	22 (5.1)	13 (4.9)	9 (5.3)
Region 6	5 (1.1)	2 (0.8)	3 (1.6)
Region 7	4 (0.9)	3 (1.1)	1 (0.6)
Region 8	6 (1.4)	2 (0.8)	4 (2.3)

Characteristic	All population (N = 435)	Standard Risk Group (N = 264)	High Risk Group (N = 171)
	Frequency (%); Median (range); Mean ± SD	Frequency (%); Median (range); Mean ± SD	Frequency (%); Median (range); Mean ± SD
Region 9	1 (0.2)	1 (0.4)	-
CAR	2 (0.5)	1 (0.4)	1 (0.6)
NCR	178 (40.9)	115 (43.6)	63 (36.8)
Risk Classification			
Standard Risk	264 (60.7)		
High Risk	171 (39.3)		
White Blood Cell Count (x 10^9/L)	43.16 (0.5 – 502.3)	11.9 (0.8 – 49.4)	63.61 (0.5 – 502.3)
Immunophenotyping			
Pre-B Cell ALL	384 (88.3)		
T-Cell ALL	46 (10.6)		
Mature B Cell	1 (0.2)		
ALL Biphenotypic	4 (0.9)		
CNS Status on Diagnosis			
CNS 1	401 (92.2)	252 (95.5)	149 (87.1)
CNS 2	1 (0.2)	-	1 (0.6)
CNS 3	7 (1.6)	-	7 (4.1)
Not done	26 (6.0)	12 (4.5)	14 (8.2)
Bone Marrow status Post-Induction			
Remission (M1 marrow)	401 (92.2)	251 (95.0)	150 (87.7)
Not done	34 (7.8)	13 (4.9)	21 (12.3)
Overall Outcome			
Alive	277 (63.6)	192 (72.7)	85 (49.7)
Abandonment	73 (16.8)	30 (11.4)	43 (25.1)
Dead	85 (19.5)	42 (15.9)	43 (25.1)
Present Status			
Remission	352 (80.9)	218 (82.6)	134 (78.4)
Relapse	83 (19.1)	46 (17.4)	37 (21.6)
Relapse as to Location			
Bone Marrow	51 (61.4)	25 (54.3)	26 (70.3)
CNS	27 (32.5)	17 (37.0)	10 (27.3)
Testicular	1 (1.2)	1 (2.2)	-
Multiple sites	4 (4.8)	3 (6.5)	1 (2.7)
Bone Marrow, testicular	1 (25.0)	1 (33.3)	-
Bone Marrow, CNS, Orbital	1 (25.0)	1 (33.3)	-
Bone Marrow, CNS	1 (25.0)	1 (33.3)	-
Bone Marrow, CNS, testicular	1 (25.0)	-	1 (100)
Duration from Diagnosis to Relapse			
Less than 18 months	45 (54.2)	21 (45.7)	24 (64.9)
Bone Marrow	27 (60.0)	11 (52.3)	17 (70.8)
CNS	14 (31.1)	8 (38.1)	6 (25)
Multiple sites	3 (6.7)	2 (9.5)	1 (4.1)
More than 18 months	38 (45.8)	25 (54.3)	13 (54.1)
Bone Marrow	25 (65.8)	16 (64.0)	9 (69.2)
CNS	11 (28.9)	7 (28.0)	4 (30.8)
Multiple sites	1 (2.6)	1 (4.0)	-
Testicular	1 (2.6)	1 (4.0)	-
Duration from Relapse to Death (months)	8.2 ± 9.4	14.8 ± 15.7	8.3 ± 9.8
Status of the Relapse Group			

Characteristic	All population (N = 435)	Standard Risk Group (N = 264)	High Risk Group (N = 171)
	Frequency (%); Median (range); Mean ± SD	Frequency (%); Median (range); Mean ± SD	Frequency (%); Median (range); Mean ± SD
Remission			
Dead	6 (7.2)	6 (13.0)	-
On Treatment	53 (63.9)	23 (50.0)	30 (81.1)
Palliative	23 (27.7)	16 (34.8)	7 (18.9)
	1 (1.2)	1 (2.2)	-
Causes of Death			
ARDS	6 (7.1)	3 (7.1)	3 (7.0)
Septic Shock	54 (63.5)	28 (66.7)	26 (60.5)
Respiratory Failure	3 (3.5)	1 (2.4)	2 (4.7)
Dengue Shock	1 (1.2)	1 (2.4)	-
Intracranial Bleed	10 (11.8)	4 (9.5)	6 (14.0)
Cardiogenic Shock	1 (1.2)	-	1 (2.3)
Multiple Organ Dysfunction	4 (4.7)	2 (4.8)	2 (4.7)
Syndrome (MODS)			
Unknown	6 (7.1)	3 (7.1)	3 (7.0)

Based on the Kaplan-Meier survival analysis, the 5 year OS for acute lymphoblastic leukemia (figure 1) and EFS (figure 2) rates were 65.3% and 62.8%, respectively. The 5 year OS for standard risk ALL was 68.8% and for high risk patients was 50% (figure 3). The 5 year OS for the patients in remission was 83.7% while for those who had relapse was 21.1% (figure 4).

Figure 1. 5 year Overall Survival of children with ALL diagnosed between 2012 to 2016

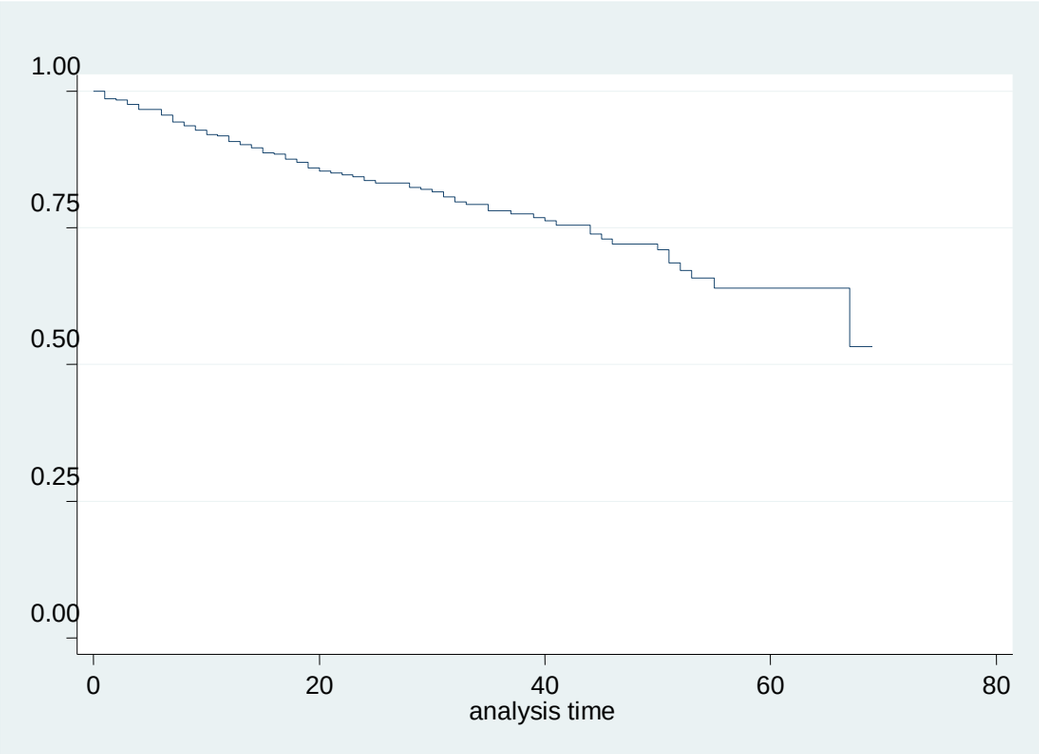


Figure 2. 5 year Event Free Survival of Children with ALL diagnosed between 2012 to 2016

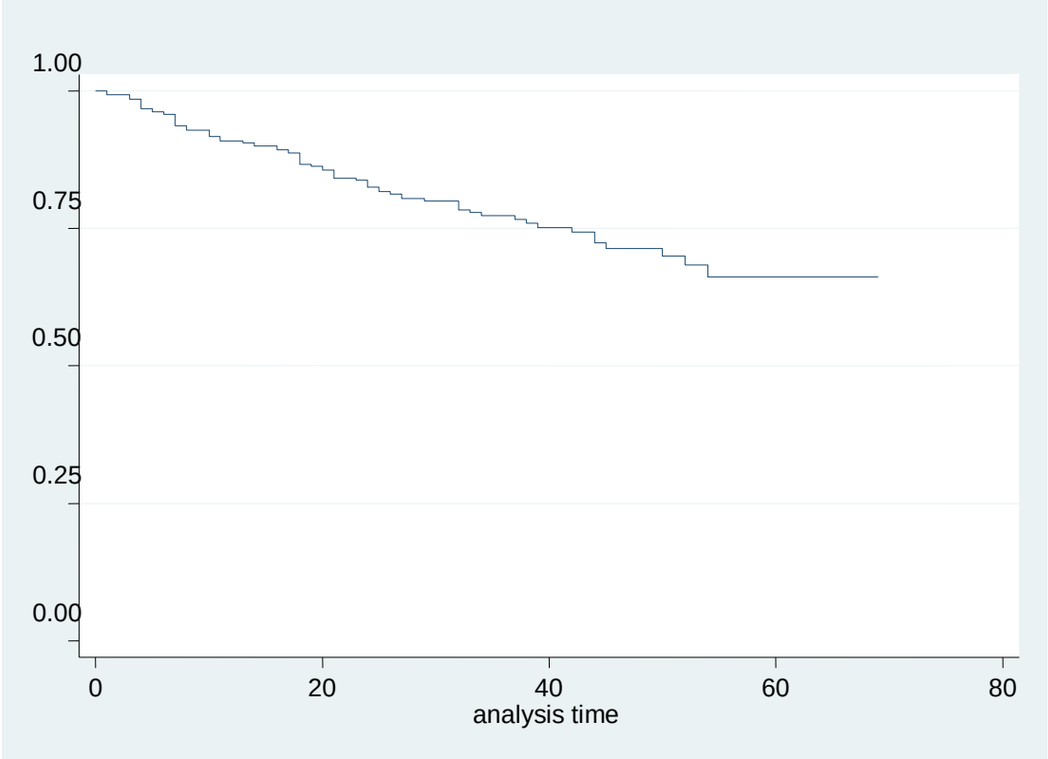


Figure 3. Overall Survival based on Risk Stratification of Children with ALL

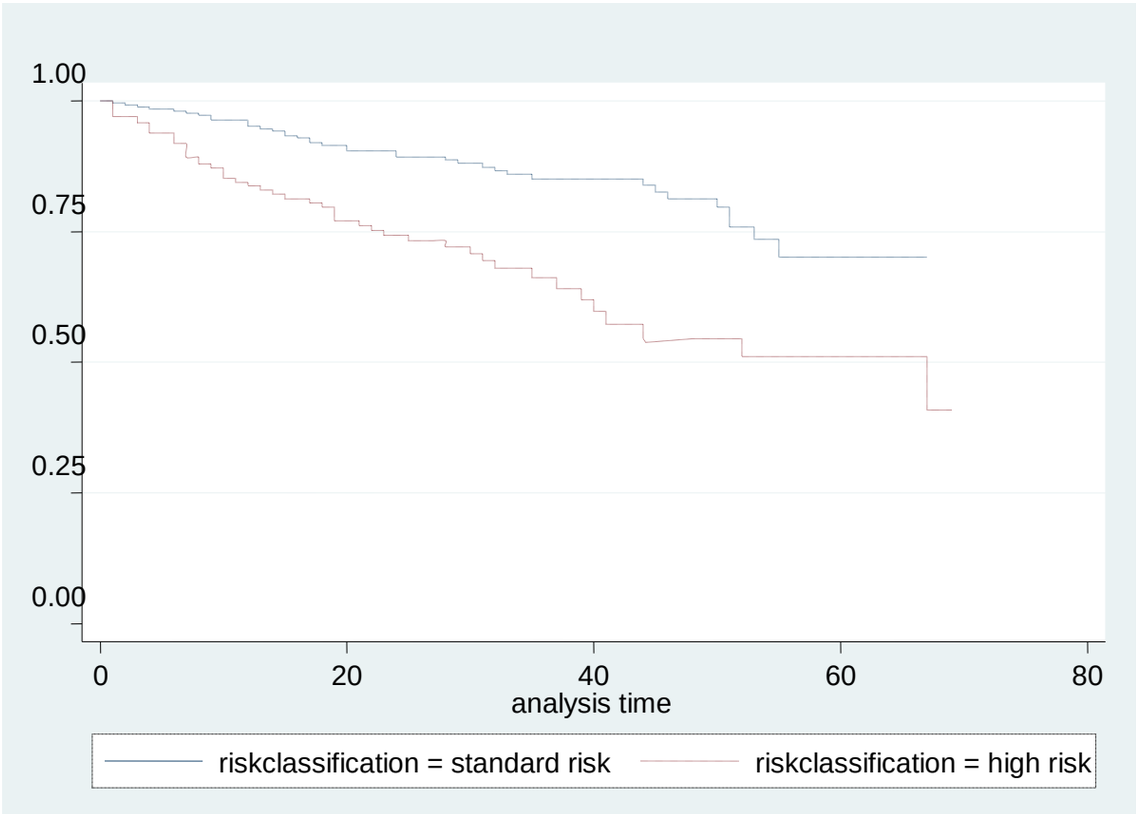
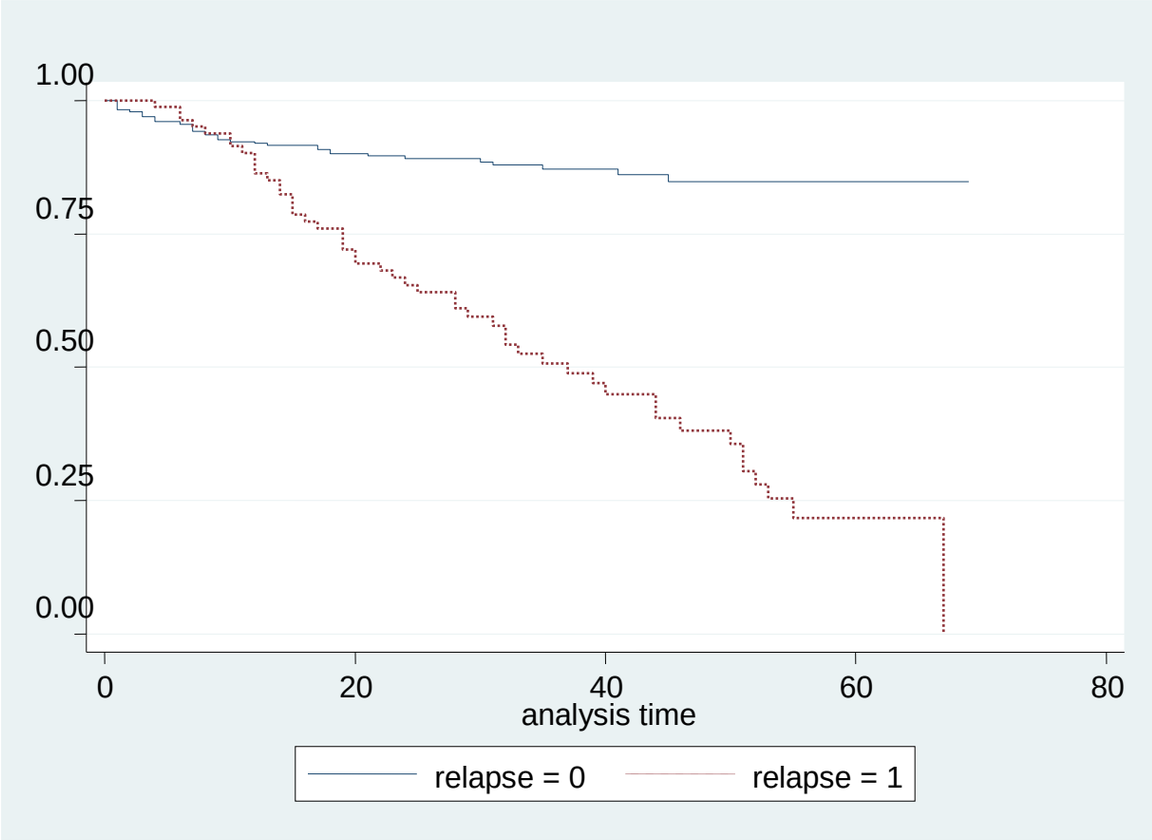


Figure 4. Overall Survival of children with ALL on Remission versus Relapse



Univariate and multivariate Cox proportional hazards regression in Table 3 revealed WBC count at diagnosis, risk classification, and immunophenotyping have a significant prognostic impact for development of relapse. Age and gender was reported with no prognostic significance.

Table 2. Factors Associated with Relapse

Variable	Univariate		Multivariate	
	Hazards Ratio	P-Value	Hazards Ratio	P-Value
Age	0.85	0.486	-	-
Gender	1.25	0.245	-	-
Risk Classification	3.52	0.000	3.08	0.000
WBC count on Diagnosis	1.00	0.000	1.07	0.025
Immunophenotype	2.88	0.000	2.09	0.028

Univariate and multivariate Cox proportional hazards regression in Table 2 revealed WBC count at diagnosis, risk classification, immunophenotyping, and development of relapse have a significant prognostic impact for mortality. Age and gender was reported with no prognostic significance

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Table 3. Factors Associated with Rate of Mortality

Variable	Univariate		Multivariate	
	Hazards Ratio	P-Value	Hazards Ratio	P-Value
Age	0.98	0.435	0.93	0.011
Gender	1.30	0.232	-	-
Risk Classification	2.62	0.000	2.98	0.000
WBC count on Diagnosis	1.00	0.000	1.00	0.034
Immunophenotype	2.51	0.001	1.91	0.037
Relapse	4.97	0.000	4.52	0.000

DISCUSSION

Patterns of cancer care vary across countries of different income levels. Countries also have different capabilities for cancer care, depending on resource availability. Combined successes in cancer prevention, early detection, screening, and treatment have resulted in a reduction in overall cancer mortality rates in some more developed countries, predominantly as a result of declines in the incidence and/or mortality from a number of specific types of common cancer. [22]

The Philippines belonged to the LMIC for which a lot of barriers to screening, diagnosis, and treatment of childhood cancer have been a predicament. These barriers occur at all steps. Patients and parents may not be aware of signs and symptoms of childhood cancer, may rely on nonmedical forms of treatment, and may not have the transportation or money to travel to a primary care facility. If the patient arrives to the primary care, personnel may not be trained to recognize childhood cancer, laboratory and diagnostic imaging equipment may not be available to screen for cancer, and the patient or clinic may lack money to pay for necessary testing and treatment. Similar barriers make access to tertiary care and correct diagnosis problematic.[1] Hence, survival against childhood cancer during the past 2 decades was scarce.

In 2006, the Philippine Children's Medical Center created an innovative demonstration project to raise public awareness about the curability of childhood cancer as well as introduced to the community how to recognize the early signs of cancer to prevent delay in diagnosis, to catch them early and to treat them timely. Six years later, in 2012, the number of the newly diagnosed childhood ALL compared to the study of Galano has increased by 75% (111 newly diagnosed patients with ALL from 2003 to 2007 compared to 447 newly diagnosed cases from 2012 to 2016). The better public awareness of the first signs of cancer and the ability of health care professionals to diagnose the disease has efficiently changed the paradigm.

Earlier, inequities to treatment occurred in the Philippines as only those who can afford the treatment will survive and those that belonged to the lower income group did not receive treatment at all. Recognizing the need of the country to support the treatment of childhood ALL, the Department of Health in 2009 began sourcing chemotherapeutic drugs to some of the government hospitals so those who were less fortunate can have a chance for cure, this was the Acute Lymphoblastic Leukemia Medicine Access Program (ALL MAP). The Philippine Health Insurance Corporation (PhilHealth) in July 2012 launched the 'Z benefit' package for ALL with the aim to not just cover the hospital expenses but also ensure totality of care and attainment of better health outcomes. With these medical assistances from the government, the survival rate changed dramatically from 32.3% (from the DOH Rizal Cancer Registry) to 65.3% (OS reported in this study).

The improvement in the survival of childhood ALL is mainly due to the adoption of modifications in therapy based on individual pharmacodynamics and pharmacogenomics, risk-adapted therapy and improved supportive care.[23] One of the great achievements of pediatric oncology in recent decades is the refinement of risk stratification systems, allowing for an assessment of the aggressiveness of a particular child's cancer and for treatment intensity to be matched to disease risk, thereby reducing both under-treatment and overtreatment.[24] Stratification into risk groups is based on a range of clinical, biological and genetic features, such as age and gender, WBC count at diagnosis, immunophenotypic, cytogenetic and molecular characteristics, and early medullar response to induction therapy.[25]

Although age of less than 1 year old and more than 10 years old as well as the male gender were considered in the NCI/Rome Criteria as high risk, results in this study showed no significant prognostic impact, this was in parallel with the Lituania study.[26] Likewise, in an eight year study done in 160 patients in Bulgaria, sex and age were found to be not significant prognostic factor for the development of relapse and death.[27] A study done in El Salvador also showed comparable results.[28] Similar results were also noted in a study done by Dujua and Galano.[7,12] Hossain analyzed 14192 children in the Surveillance Epidemiology and End Results (SEER) data during 1973–2009 which showed significant variability in pediatric ALL survival by age at diagnosis. In a multivariable Cox proportional hazard model stratified by year of diagnosis, those diagnosed in age groups 1–4, 5–9, 10–14, and 15–19 years were 82%, 75%, 57%, and 32% less likely to die compared to children diagnosed in infancy, respectively. Male gender showed hazards ration of 1.29 at p-value of <0.0001.[29]

In this study, out of 435 subjects, 95 (21.5%) showed WBC count of more than 50,000/mm^3, out of this 95 subjects 37 (38.9%) showed high risk immunophenotype. Twenty seven subjects (28.4%) were more than 10 years of age. From among the subjects with elevated WBC count of more than 50,000/mm^3, outcome showed 46 (48.4%) alive out of 95, the 18 (18.9%) abandonment and 31 (32.6%) dead. Cox regression analysis showed significant hazards ratio with WBC count on diagnosis which is compatible with the reports of other studies. Hazard analysis done in Lithuania revealed WBC at diagnosis to have a significant prognostic impact for an event.[26] The results were compatible with the study in Bulgaria for developing relapse and death.[27] In a study among Filipino children by Dujua, WBC count was insignificant to lead to relapse which was in parallel with the results in a study by Galano.[7,12]

According to risk classification by the NCI/Rome Criteria, high risk patients have significantly lower survival compared to the standard risk patients. Cox regression analysis in this study showed significant risk for mortality rate. This was compatible with the results seen in the Bulgarian study with events leading to relapse and death.[27] Similar results were seen in the study by Dujua with p-value of <0.001 risk for relapse.[12]

Significant prognostic factor that lead to mortality was seen in patients with immunophenotype T-cell ALL, biphenotypic ALL, and mature B cell ALL. Similar results were seen in the study by Hossain for T-cell ALL.[30] While in the study of Dujua, p-value was not significant at 0.740.

In this study 19.1% of the subjects developed relapse. Among the relapsed patients, 31.0% were reported with WBC more than 50,000/mm^3, 11.5% were of high risk immunophenotype, and age of more than 10 years old were seen in 19.5%. In a study by Galano relapse showed significant hazard for rate of mortality.[7] Very early relapses are those that occur within 18 months of initial diagnosis. The clinical behavior of early relapse is aggressive with less than a third survived. However, about 50% of patients with late relapse will survive. An isolated bone-marrow relapse indicates a worse prognosis than combined marrow and extramedullary relapse which, in turn, is worse than isolated extramedullary relapse.[30] Out of the 83 patients who relapsed, there were 54.2% who developed relapse in less than 18 months, 79.1% of from this early relapsers died within 455.5 $\pm$ 532.5 days, while for the group who relapsed more than 18 months 45.8% comprised this group, 51.4% among the late relapsers died within 1266 $\pm$ 546.6 days in this study.

Survival rates of childhood ALL in this study were inferior compared to those reported in the Western countries. The 5 year OS in this study was however similar to other LMIC such as Thailand showing OS of 67.2% in study by Seksarn among 486 children from 12 institutions.[31] The study in Brazil done last 2000-2005 showed an OS of 62.4%[32], Brazil belonged to the upper middle income countries. However, this was not comparable to the results in the study of Dujua among Filipino children with the 5 year OS of 86.94%. The difference with the treatment protocol in the Modified BFM95/HKALL97 with the study of Dujua was that they utilized methotrexate of 2g/m^2 for their standard risk ALL during the consolidation phase. Being a part of the LMIC group, we modified the methotrexate dose at 1g/m^2 in consolidation phase for our standard risk ALL, as most of our patients cannot afford the high cost of the drug as well as the methotrexate assay levels. In the BFM95 ALL study, they utilized methotrexate dose of 5g/m^2, which was modified with the HK ALL97 study using 2g/m^2, results of the HK ALL97 in 171 patients showed 4 year OS of 86.5%. According to Pui, the best dose of methotrexate depends on the leukemic cell genotype and phenotype and host pharmacogenetic and pharmacokinetic

variables. Methotrexate at 1–2 g/m^2 is adequate for most patients with standard risk ALL. The fairly low accumulation of methotrexate polyglutamates in blast cells with either *TEL-AML1* or *E2A-PBX1* fusion suggests that patients with these genotypes could also benefit from an increased dose of methotrexate. However, mega doses of methotrexate do not seem necessary for patients with ALL.[24]

One of the possible reasons for the lower survival of our patients compared to international trials could be due to presence genetic aberrations that are high risk for treatment failure or relapse. The advent of fluorescent in situ hybridization and molecular diagnostic techniques allow the detection of these cytogenetic abnormalities. However, these are not routinely done in our setting due to its high cost. Adverse genetic abnormalities include *MLL* rearrangements and hypodiploidy < 44 chromosomes.[24] A number of structural abnormalities that convey worse prognosis include chromosome band 11q23; translocations involving proto-oncogenes on chromosome 8, 9, and 22; translocation of the MYC proto-oncogene from chromosome 8 to an immunoglobulin gene, either the heavy chain on chromosome 14 or the light chains on chromosome 2 and 22, respectively; the Philadelphia (Ph) chromosome, with its t(9:22)(q34;q11) translocation; and translocation t(1:19)(q23;p13) found in cytoplasmic immunoglobulin M-positive pre-B-cell ALL.[33] Furthermore, several of the alterations that most often emerge at relapse are also associated with poor treatment outcomes when present at diagnosis—eg, deletions of *IKZF1*, *CDKN2A*/*CDKN2B*.[34]

Another possible cause for the decrease survival is the delay in the treatment. The cause is either due to the patient or family's decision to suspend treatment without medical advice or due to hematologist's decision to suspend treatment. In our institution, the main reasons of the patient and their family for the delays in the treatment and non-adherence to the protocol schedule is due to financial constraints from lack of funds for travel, medications and food allowance, no adult travel companion available to escort the child to the hospital for their treatment, and unavailability of transportation for the patients living in far flung areas of the country. Undue interruptions from the side of the hematologist are due to presence of moderate to severe infections, low absolute neutrophil counts, low platelet count of less than 50 x 10^9/L, and elevated liver transaminases during maintenance phase. A study done in Brazil regarding compliance with the treatment protocol mentioned that the reason for interruption included decreased leukocyte and/or neutrophil count, elevated aminotransferases, upper respiratory tract infections, bronchitis and other reasons not specified.[35] They found out that the reasons for undue interruption of chemotherapy by physicians included aminotransferase below levels pre-established by the protocol for adjusting the chemotherapy doses, and leukopenia and neutropenia, with values above the cutoff levels in the protocol. They found out that the longer the "appropriate" suspension of chemotherapy, the lower the likelihood of relapse. For graphical display, the investigator dichotomized the variable into two strata: children with less than or more than 2% of "appropriate" chemotherapy interruption. This interruption equals a two-week break for children who completed the whole of the maintenance phase. The probability of EFS for the group with less than 2% of interruption was 33.3 ± 13.6%. For the group with more than 2% of interruption, the EFS was 80.3% ± 5.1%.[35] Strict adherence to treatment protocols and rigorous monitoring of both the doctors and patients will contribute to better treatment results.

The occurrence of treatment abandonment, as often observed in LIC/LMIC, is of major concern because it prevents the correct administration of the full treatment regimen to the child with cancer and affects the effectiveness of the treatment and prevents observing the patient's final state. Many reasons for abandonment have been cited, including a lack of financial resources, poor disease comprehension, cultural factors, belief in alternative medicines, fear of treatment toxicity, inadequate care on the part of health care workers, and decreased awareness of aid programs.[36] Abandonment in our center was noted to be high in 2012 at 44.4%, then in 2013 it decreased to 15.1%, in 2014 abandonment rate was noted at 10.7%, in 2015 at 10.5% and in 2016 at 9.9%. In 2013, the patient navigation program for the ALL MAP was launched in the country with the aim to track and monitor patients, direct patients to resources, and provide compassion and empathy to help them understand their disease. Abandonment rate has declined since 2013 owing to the navigation program. Hence, further improvement on patient tracking, counseling and education among cancer centers should be strengthened to improve patient compliance.

Febrile neutropenia is one of the most serious hematologic toxicity seen in cancer

patients receiving chemotherapy. Delay in treatment due to infections contributes to low survival. Timely and effective supportive care is critical for the successful treatment of ALL. Indeed, the intensity of treatment for ALL must be appropriate for the level of supportive care that is available.[37] Indiscriminate adoption of high-intensity treatments from developed countries is inappropriate, without a commensurate level of supportive care. Over-treatment beyond the limits of supportive-care capabilities can lead to excessive induction death and high abandonment rates.[38] In this study, induction death was 1.4% (6 out of 435) of which 50% is due to septic shock followed by 16.7% due to respiratory failure, 16.7 % due to intracranial bleed and 16.7% due to cardiogenic shock. Currently in countries with basic, and even limited resources, the induction death rate is approximately 30%, exceeding even the total cumulative risk of relapse.[39] Deaths from infection and bleeding are most common. In one study from Northern India, sepsis and bleeding accounted for 53.3% and 15.7% of deaths, with tumour lysis syndrome contributing to 6.3% of deaths.[40] Prevention of infection by simple means is a cost-effective strategy. Patients on chemotherapy should preferably be admitted to a separate ward away from those with infectious diseases. Hand hygiene is especially important to prevent cross infection. Hand-washing facilities with easy accessibility should be made available in the wards, or disinfectant hand gels can be placed at the bedside.[37] These measures are being followed in our institution. We also have an infectious control committee in the center that evaluates and monitor infection control practice and reviews the febrile neutropenia protocol based on the local bacterial sensitivity in the ward. Monthly meeting of the Infection Control Committee recognized the aspects and areas of improvement to maintain good infection control program.

The strength of the CCG 1961 protocol making it suitable for the high risk patients was the double delayed intensification phases. The reported outcomes from 1996 to 2002 for the CCG 1961 trial by Bhojani showed EFS of 71.3% $\pm$ 1.6%.[13] A study done by Nachman in ALL patients aged 16-21 using the same protocol, reported 5 year EFS of 68%.[41] In a study by Bleyer among adolescents and young adults using the CCG 1961 protocol, OS showed 77.5%.[42] The study of Galano showed 77.8% EFS for the high risk group. This study showed OS of 50% which has lower survival compared to the result of the trials mentioned. Factors that contributed to the lower survival include treatment interruption, lack of cytogenetics study to identify genetic aberrations that could contribute to being high risk for relapse and treatment failure, as well as abandonment. Abandonment rate identified in this study for high risk group was higher at 25.1% compared to standard risk ALL at 11.4%.

The 5 year OS for the patients on remission was 83.7% and for those who developed relapse was 21.1% which is comparable with the study done in Central America showing OS of 28.3% $\pm$ 1.9%. The median follow up time for the patients who did not experience another event was 1.9 years.[43] While in our institution, the median follow up time from diagnosis to death among the relapsed group showed 2.4 $\pm$ 1.5 years (relapsed in less than 18 months 1.2 $\pm$ 1.5 years and the group who developed relapse in more than 18 months 2.4 $\pm$ 1.5 years). In the multivariate analysis done in the Central America by Chan time to relapse of less than 36 months, CNS status at diagnosis, age and WBC count at diagnosis showed significant prognostic EFS.[33] This results were similar to the study done by Marjerrison in Central America showing in multivariable analysis, worse post-relapse survival was associated with age > 10 years, white blood cell count > 50 X 10^9/L, and positive central nervous system status at the original ALL diagnosis, relapse that was not isolated central nervous system or testicular, and relapse < 36 months following diagnosis.[39] Prognosis after relapsed is poor but a substantial number of those who relapsed more than 18 months from the time of diagnosis showed prolonged survival compared to the early relapsers.

CONCLUSION

Cure rates for childhood ALL has improved remarkably over the past 50 years, as many treatment protocols have been developed and succeedingly modified with the goal of multimodal principle of synergistic effect with the least toxicities. The present study summarized the survival rate of childhood ALL in a single state tertiary treatment center for childhood cancer.

The 5-year overall and event-free survival rates were lower than those reported for developed countries but is comparable with reports of other LMICs. This outcome will serve as a framework for future improvements. Prognostic factors for relapse and mortality such as WBC count at diagnosis, risk classification, and immunophenotyping are comparable with other studies. Relapse has a significant prognostic impact for mortality. Development of accessibility to care, increase

awareness, early detection and resources at hand should be achieved. Improvement in the follow up protocol to prevent delays in the treatment, patient education to prevent non-compliance and psychosocial support, to developed better supportive care, and expand facilities should be given emphasis to further improve survival and prevent relapse.

Outcome for relapsed ALL remains poor hence, better chemotherapy regimen for improving survival should be studied. Various protocols for relapse have been studied but reported OS range from 25-30% with increase toxicities reported in these trials. Infection is a frequent and serious problem in cancer patients on chemotherapy. Effective supportive care is critical to successful treatment. Prevention of infection by simple means such as good hand hygiene should be emphasized to prevent delay in treatment due to infection. Employment of cytogenetic testing as part of diagnostic risk classification should be perform to recognize the group that are high risk so more intensified treatment protocol will be offered to increase survival. Overall, the adopted treatment protocols for childhood ALL in this institution showed acceptable results as survival has remarkably improved compared to the report in 2010 taken from the population based registry in DOH Rizal Cancer Registry at 32.3% to the present 65.3% OS in this study.

Future studies to evaluate the different relapsed protocol (MSK-NY-II for bone marrow and multiple site relapse and POG 9431 for isolated CNS relapse) adopted in the center should be done to facilitate better understanding of outcomes for relapse. Options such as hematopoetic stem cell transplant and immunotherapy should also be studied.

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BRONCHODILATOR CHALLENGE TEST USING THE TIDAL RAPID THORACO-ABDOMINAL COMPRESSION TECHNIQUE AMONG INFANTS AGED 6-24 MONTHS WITH RECURRENT WHEEZING

MA. LALLAINE G. COLUMNA, MD, CRISTAN Q. CABANILLA, MD

ABSTRACT

BACKGROUND: A definite diagnosis of asthma during infancy is difficult. Asthma Predictive Index (API) is used to predict asthma at school age, but does not determine who among these actually have asthma.

OBJECTIVES: This study aims to determine the bronchodilator response of infants with recurrent wheezing compared with normal control.

METHODOLOGY: This cross sectional study included asymptomatic subjects aged 6-24 months with history of recurrent wheezing and age/sex matched controls. After sedation with chloral hydrate (Odan) at 50-75 mg/kg, a bronchodilator challenge test was performed with single dose 400 mcg salbutamol (Ventolin) MDI inhalation delivered via a spacer (Philips Respironic OptiChamber Diamond). Baseline and 15 minutes after salbutamol inhalation Maximum Flow at Functional Residual Capacity (V'maxFRC) were determined using MasterScreen Paed/BabyBody Option Squeeze version 8.0. ANOVA and Pearson chi-square were used for the statistical analysis of data.

RESULTS: Sixty-nine infants (23 previous wheezers and positive API, 23 previous wheezers with negative API and 23 controls) were included. There was a significant difference in the post bronchodilator challenge test V'maxFRC between wheezers with positive API and controls (p= 0.047). There was no significant difference in other parameter among groups.

CONCLUSION AND RECOMMENDATION: Absolute values of V'maxFRC post bronchodilator challenge using the Tidal Rapid Thoracoabdominal compression technique may be used to identify current asthma among asymptomatic infants with recurrent wheezing. Further studies with patient follow-up are recommended to assess response to treatment.

KEY WORDS: Recurrent wheezing, Bronchodilator challenge test, Tidal Rapid Thoraco-abdominal compression technique

INTRODUCTION

A. Statement of the problem:

Wheezing in infancy is a common clinical problem (1). A definite diagnosis of asthma in the young age group has been challenging as it can be based largely on symptom patterns combined with a careful clinical assessment of family history and physical findings. It is also difficult to make a confident diagnosis of asthma in younger children because episodic respiratory symptoms such as wheezing and cough were also common without asthma, particularly in those 0-2 years old (2,3). In the year 2000, the Asthma Predictive Index (API) was developed using data in the Tucson Children's respiratory study to predict asthma at school age among those children with recurrent wheezing in the first 3 years of life. A positive stringent API score by the age of 3 years was associated with a 77% chance of active asthma from aged 6-13 years; children with a negative API score at the age of 3 years had less than 3% chance of developing active asthma during their school years (3). Using the API however only aids in predicting asthma later in life but does not determine at hand who among those infants with recurrent wheezing actually have or does not have asthma.

B. Significance of the study:

This study aimed to identify the presence of bronchodilator responsiveness among asymptomatic infants with history of recurrent wheezing. By being able to identify early on the reversal of an obstructive profile which is highly suggestive of asthma, therapies can be initiated for the secondary prevention of respiratory morbidity.

C. Review of Literature

Infant lung function (ILF) testing has evolved from a research technique into a diagnostic tool (5). It has been useful in the

early diagnosis of lung diseases (6), in serial monitoring of disease progression (7,8) and may improve the efficacy of therapeutic interventions (9). It was in the 1980s when prototypes of the infant pulmonary testing has been developed and was later enhanced in the mid 1990s (10,11). Series of standards for its use has been published in the year 2000 by the European Respiratory Society and American Thoracic Society. BabyBody-plethysmographic measurement reference values for Chinese and Taiwanese infants has also been published in 2017 (12,13). Relatively, the machine has been new in the Philippines and this study also aimed to establish reference data for Filipino infants.

Partial expiratory flow volume (PEFV) maneuvers obtained by the rapid thoracoabdominal compression technique have been used to assess airway function in infants (14). In this method, the result was expressed as the forced expiratory flow at the resting lung volume taken from the tidal breath before the inflation was applied and termed the forced expiratory flow at functional residual capacity, or V'maxFRC.

Because of the doubts about the stability of functional residual capacity and the apparently large intra-subject variability of VmaxFRC, an alternative technique was developed in which lung volume was first inflated several times to 20–30 cm H2O before inflating the compression jacket at the raised lung volume produced by these inflations. This technique generated a complete maximal forced expiratory flow volume (MEFV) curve (15) and allowed the measurement of parameters of expiratory flow at known proportions of the functional vital capacity as well as timed expiratory volumes such as the forced expiratory volume in the first 0.5 sec (FEV0.5) analogous to parameters obtained by standard spirometry in older children and adults.

In 98 healthy infants aged 1–69 weeks, the relationship between V'max FRC and the parameters derived from the MEFV curve in the same infants was compared.They noted that the VmaxFRC was most closely related to the forced expiratory flow at 85% of FVC (FEF 85) but with considerable variation between subjects (16). However , the study mentioned that if strict quality control criteria was applied, forced expiratory flows measured using Rapid Tidal Compression (RTC) were more variable than those measured using the Raised Volume Rapid Thoracic Compression (RVRTC) technique. By ensuring that RTC was performed during quiet sleep with steady end-expiratory levels, checking that the selected curves over lie the descending portion of the flow volume curve and ensuring an adequate driving pressure, the potential variability caused by an unstable FRC and lack of flow limitation can be minimized.

In another study done by Bar-Yishay et. al., the V'maxFRC derived from the partial expiratory flow volume maneuver was compared with expiratory flows and timed expiratory volumes derived from the MEFV curve in infants with a variety of respiratory problems. The study found out that despite the wide variety of diseases and the wide range in respiratory in airway function there was a good correlation between V'maxFRC and either FEF 75 or FEF 85. It further mentioned that a normal V'maxFRC virtually excludes abnormal lung function measured by more sophisticated methods like raised volume (17).

To illustrate whether there was an association between wheezing and bronchial responsiveness in infants, a study by Stick et. al. showed that the median V'max FRC of the wheezy group was 100.0 ml/S (95% CI:79 to133ml/s) compared with 182.0 ml/s (95% CI: 147 to 237 ml/s) for the normal group ($p<0.01$) The median difference in Vmax FRC between the wheezy infants and the control infants was-76ml/s (95%CI:-135 to -20mlls). There were no differences between the two groups with regards to the other baseline measurements of respiratory function. Despite the large difference in V'maxFRC between the two groups of infants, the geometric mean of the wheezy infants (1.8 mg/ml) was not significantly different from that of the normal infants (2.3 mg/ml). The data only indicate that recurrently wheezy infants do not have increased airway responsiveness to histamine compared with normal infants (18).

Similarly, Prendeville et.al. studied the effect of nebulized salbutamol on the bronchial response to nebulized histamine in five wheezy infants aged 3-12 months. The response to doubling concentrations of up to 8g/l of histamine was assessed by the change in maximum flow at FRC (V'maxFRc), measured by flow-volume curves produced during forced expiration with a pressure jacket.The concentration of histamine were required to provoke a 30% fall in V'max FRC (PC30) was measured. All of the infants responded to low concentrations of histamine during control tests before and after nebulised saline (mean PC 30 107 and 0-51g/l). On a separate day there was a similar response to histamine before salbutamol, but after salbutamol the response was completely abolished up to the maximum

concentration of histamine in all subjects. Thus wheezy infants have highly effective Beta adrenoceptors in the intrathoracic airways (19).

In a recent study by Shavit et. al., they evaluated the bronchodilator response of infants with recurrent wheezing or coughing and an obstructive profile on infant pulmonary function test. The study also assessed whether the existence of a positive response can help predict the course of the illness in early childhood. The study included 60 infants and results showed that 53% of whom demonstrated bronchodilator responsiveness defined as a mean post bronchodilator Vmax FRC exceeding the upper limit of the prebronchodilator confidence interval. Follow up data was then gathered after 2 years. It found out that infants in the responsive group had a significantly higher frequency of physician visits for wheezing than the non responders (3 mean visits/yr vs. 1.5) and had a higher likelihood of having received asthma medication in the last year of the follow up period (84% vs 50%). Also, at the end of the follow up period, more parents in the responsive group reported continued respiratory disease (71% vs 22%) (20).

II. OBJECTIVE OF THE STUDY:

General Objective:

The main objective is to determine if there is a significant difference in the bronchodilator response among group of asymptomatic infants with recurrent wheezing who fulfilled the criteria of the API, compared to those who did not fulfill the API and those normal healthy infants using the rapid thoracic compression technique.

Specific Objectives:

1. One of the specific objectives is to determine if there was a significant difference in the pre-bronchodilator V'maxFRC and post bronchodilator V'maxFRC among groups.

2. The second objective is to determine if there was a significant difference in the percent change of V'maxFRC post bronchodilator challenge test among groups.

III. METHODS

This is a cross sectional study. Asymptomatic infants ages 6 months to 24 months seen at Philippine Children's Medical Center and those from the local health centers were recruited in this study.

Sample Size computation

Sample size was computed as follows:

$$n = \frac{(Z_{L+\beta})^2 (SD)^2}{E^2}$$

$Z_{L=}$ 95% confidence level = 1.96
Z = 80% power of the study = 1.28
SD = standard deviation of the VmaxFRC:

$$\frac{0.94 + 0.7}{2} = 0.86$$

E= measure of effect, that was, difference in Vmax FRC

$$= -2.00 - (-1.36) = 0.64$$

$$= \frac{(1.96+1.28)^2 (0.86)^2}{(0.64)^2}$$

$$= 23$$

The number of samples collected was computed using 95% level of confidence and 80% power of the study. At least 19 subjects were needed to detect a 0.64 difference in the VmaxFRC among groups. A 20% allowance was added to account for lost to follow up subjects. A total of 23 subjects per group was needed.

Subject Sampling:

Infants with a history of recurrent wheezing with or without the API and those normal healthy infants with no previous episode of wheezing were considered for inclusion.

The following were excluded: [a] any episode of upper and lower respiratory tract infection in the past 2 weeks prior to recruitment, and [b] with a significant co-morbid conditions affecting the respiratory system such as a physician-diagnosed congenital heart disease, presumptive interstitial lung disease, gastroesophageal reflux disease, upper airway obstruction, tracheoesophageal fistula, rib cage anomaly, kyphoscoliosis, history of prematurity (born <36 wks), cleft lip and palate and neurologic conditions such as seizure disorder and cerebral palsy.

Subjects were divided into three groups: Group 1 were Infants with recurrent wheezing who had a positive API; Group 2 were Infants with recurrent wheezing who did not fulfill the API, and Group 3 were normal healthy infants who never had an episode of wheezing and did not also fulfill the API. Informed consent was obtained prior to the study conduct.

To control for the influence of environmental temperature on respiratory pattern, room temperature was maintained between 20-25 C. The lights were also dimmed to encourage sleep. The equipments were checked before the test to avoid technical faults.

All infants were weighed, and their length were measured at the time of test. Feeding was also withheld at least 4 hours prior to testing. Vital signs such as cardiac rate, respiratory rate, temperature and oxygen saturation were recorded. Subjects were then sedated to facilitate positioning of the face mask and application of the jacket for thoracoabdominal compression. Chloral hydrate (Odan) 100mg/ml Syrup was given at 50 mg/kg per orem to facilitate moderate sedation (21).

Infants who woke up during the study conduct was given a smaller second dose of chloral hydrate at 25 mg/kg (max dose of 100 mg/kg) (22). However, infants who already achieved adequate volume curves were not resedated. Subjects with failed sedation and those who fail to have a technically acceptable manoeuvre after 3 trials were excluded in this study.

After the infants were sedated, a baseline measurement of the V'maxFRC using the rapid thoracoabdominal compression technique was obtained using the MasterScreen^{TM} Paed/BabyBody Option Squeeze version 8.0. The ATS/ERS statement on its current practice guidelines was used in this study. Measurements were made with the infant lying supine and the neck and/or shoulders supported in the midline in slight extension and the position was stabilized using a neck roll (23).

Partial expiratory flow volume curves were produced by wrapping a jacket around the infant's chest and abdomen. The infant's chest was wrapped in a suitably sized jacket. Small jacket size (Green in color) was used for infants weighing 8-13 kg; extra small (Blue) for 4-8 kg and extra extra small (yellow) for 2-4 kg (24). The outer expansive part of the jacket was firmly wrapped, while still being able to insert two adult fingers between the inner inflatable part and the infant's sternum. The mask was then placed with a silicon putty used to ensure that it was leak-free.

The jacket wrapping around the infant's chest and abdomen was inflated at the end of tidal inspiration to force expiration. An initial inflation pressure of 3 kPa (30 cm H20) was selected with the machine and applied at the end of tidal inspiration. A single squeeze maneuver was performed ensuring that the jacket remained inflated through out the entire expiration to be able to determine the flow at functional residual capacity (*V'max* FRC). The resultant changes in air flow were recorded through a pneumotachometer (PNT) attached to the face mask through which the infant breathed. The jacket pressure was subsequently increased by increments of 1 kpa until further increases did not elicit any further increase in forced expired flow at FRC. Three to five squeezes was performed at the first estimate of optimal pressure.

Once the optimal pressure has been determined with its corresponding V'maxFRC, a confirmatory determination of this pressure was done by decreasing at one pressure below and increasing at one pressure above it. If on confirmatory determination of the pressure the flows increased compared to the initial determination, subsequent incremental increase by 1 kpa was done until an airflow limitation was achieved. The determined pressure was then used after a bronchodilator challenge.

After the baseline V'max FRC has been determined, a bronchodilator challenge done using salbulatol inhalation. Infants were given Salbutamol (Ventolin) MDI 100 mcg/ inhalation, 4 puffs via a spacer (Philips Respironics OptiChamber Diamond) with face mask (25). After 15 minutes of salbutamol inhalation, a repeat rapid thoracoabdominal compression technique was taken. Vital signs such as cardiac rate, respiratory rate, temperature and oxygen saturations was monitored every 30 minutes until the patient was fully awake. Infants were only sent home when they were already active and were able to sustain wakefulness.

Outcome/ assessment, Data collection method, Instrument/s used

The MasterScreen^{TM} Paed/BabyBody Option Squeeze version 8.0 was used in this study (See figure 1). V'maxFRC was determined pre and post bronchodilator challenge test. It was reported as the absolute value in mL/s. The best value which is the highest flow from a technically acceptable curve (See figure 2) was reported, provided it is within 10% or 10mL/S (whichever is greater) of the next highest value. The mean of the three to five technically satisfactory curves was also made available as a measure of the intra-subject variability.

Criteria for acceptability of the flow volume curve were as follows: there should be no evidence of leak during data collection; the rapid rise time at start of forced expiration with the peak forced expiratory flow being attained before 30% of tidal volume has been expired; length of the jacket compression time sufficiently long enough to fully complete forced expiration; forced expiration should have a smooth curve and continue beyond FRC (See Figure 2). Three technically acceptable maneuvres were required (25).

Plan for Data Processing and Analysis

ANOVA was used to determine whether there was a significant difference in the values of V'maxFRC pre and post bronchodilator challenge among groups. Pearson Chi-square was also used to compare if there was a significant difference in the percent change pre and post bronchodilator challenge.

Ethical Considerations

Since infants were sedated in this study, careful assessment and monitoring were done for their safety. Pre sedation assessment included physical examination, observation of vital signs and any other physical findings. Resuscitation equipment such as bag with oxygen, suction apparatus, catheters and emergency kit were also made available. Subjects were also monitored continually with pulse oximetry until they were fully awake. Infants were only released home following sedation until they were fully arousable and capable of swallowing. In addition, parents were also advised that the infant maybe drowsy and unsteady for several hours and should not be left unattended.

IV. Results:

There were 114 infants recruited, but only 84 were initially enrolled (had no parental consent (n=19), history of recent respiratory tract infection (n =8), prematurity (n=1), cleft lip and palate (n=1) and gastroesophageal reflux disease (n=1)). Among 84 infants, 10 infants did not complete the study due to failed sedation and 5 who completed the study did not produce acceptable flow-volume loops. A total of 69 infants completed the study and were included in the final statistical analysis. They were then divided into three groups: Group 1 were infants with recurrent wheezing who had a positive API (n=23) ; Group 2 were infants with recurrent wheezing who did not fulfill the API (n=23), and Group 3 were normal healthy infants who never had an episode of wheezing and did not also fulfill the API (n=23).

The demographics are shown in Table 1. There were no significant difference among groups in terms of their age, gender, length and weight.

Table 1. Demographic Profile

		Group 1[a] n = 23	Group 2[a] n = 23	Group 3[a] n = 23	p-value
Age (mo)		16.83 ± 6.38	17.83 ± 4.68	14.96 ± 5.46	0.213 (NS)[b]
Gender	Female	14 (60.9%)	11 (47.8%)	16 (69.6%)	0.319 (NS)[c]
	Male	9 (39.1%)	12 (52.2%)	7(30.4%)	
Length (cm)		77.46 ± 9.52	78.24 ± 6.92	78.59 ± 7.88	0.891 (NS)[b]
Weight (kg)		12.14 ± 14.23	9.70 ± 1.11	9.17 ± 1.67	0.437 (NS)[b]

a – Mean ± sd or count (%)
b – using ANOVA F-test
c – using Pearson Chi-square

Table 2 shows the comparison of the pre-bronchodilator challenge and post bronchodilator challenge test determination of V'max FRC among groups. There was no significant difference in the pre-bronchodilator challenge determination of V'maxFRC in terms of its best, mean and median values. The V'maxFRC post bronchodilator challenge test was also significantly higher in infants with recurrent wheezing fulfilling the API compared to those without API and normal infants with values of 164.3, 142.61 and 123.87 respectively. On further analysis, there was a significant difference between infants with recurrent wheezing fulfilling the API when compared to a group of normal infants.

Table 2. Pre-bronchodilator Challenge and Post Bronchodilator Challenge Test V'max FRC determination

	Group 1[a] n = 23	Group 2[a] n = 23	Group 3[a] n = 23	p-value
Pre-bronchodilator Challenge				
Best V'maxFRC	152.30 ± 61.43	149.13 ± 55.34	127.13 ± 49.91	0.256 (NS)[b]
Mean V'maxFRC	137.02 ± 53.59	132.24 ± 49.32	113.51 ± 48.85	0.258 (NS)[b]
Median V'maxFRC	138.24 ± 55.16	133.33 ± 47.30	115.80 ± 49.33	0.295 (NS)[b]
Post Bronchodilator Challenge Test				
V'maxFRC	164.30 ± 59.65	142.61 ± 54.38	123.87 ± 48.05	0.047*[b]

a – Mean ± sd or count (%)
b – using ANOVA F-test
c – using Pearson Chi-square
* – significant at the 0.05 level of significance

Table 3 shows the comparison of the percent change in V'max FRC post bronchodilator challenge test among groups. Percent change was the difference between the best V'maxFRC value pre-bronchodilator and post bronchodilator challenge. The difference was then divided by the baseline (pre-bronchodilator) V'maxFRC value and multiplied by 100. Group 1 had a mean percent change of 13.44 $\pm$ 38.62 while groups 2 and 3 had -2.41 $\pm$ 22.43, -1.64 $\pm$ 11.86 respectively. Using the anova test, there was no significant difference in the mean percent change in V'max FRC when compared among groups (p= 0.083).

Table 3. Percent Change in V'max FRC Post Bronchodilator Challenge Test

	Group 1 n = 23	Group 2 n = 23	Group 3 n = 23	p-value
Post Bronchodilator Challenge Test				
Mean absolute values of V'max FRC Change from baseline	12.00 ± 45.80	-6.52 ± 35.53	-3.26 ± 15.64	0.162 (NS)
V'max FRC Change 95% CI	(-7.80, 31.80)	(-21.89, 8.84)	(-10.02, 3.50)	
% Change from Best V'maxFRC	13.44 $\pm$ 38.62	-2.41 $\pm$ 22.43	-1.64 $\pm$ 11.86	0.083 (NS)
% Positive responders	13 (56.5%)	9 (39.1%)	9 (39.1%)	0.392 (NS)

* – significant at the 0.05 level of significance

DISCUSSION:

Maximum flow at functional residual capacity (V'max FRC) has been used as an index of intrathoracic airway function (26). Using the rapid thoracoabdominal compression technique, bronchodilator responsiveness can now be demonstrated in asymptomatic infants as it can reproduce a flow-volume curve like in older children and adults. Physiologically, a decrease in airway calibre brought about by bronchodilation should decrease airway resistance thus producing higher flows.

To achieve a successful measurement using the tidal rapid thoracoabdominal compression technique, generally, a sedation is required. Sedation does not affect the phlethysmographic result measurements of infants but in fact facilitates the child to be in a quiet sleep essential for a reproducible measure of V'maxFRC. Out of the 84 infants who were included in this study, there were 10 infants who were not able to complete the test due to failed sedation. The onset of action of chloral hydrate and the duration of sleep were unpredictable (between 15-90 minutes) (27). The time required to obtain an informed consent, assessment of the infant, time for the infant to fall asleep and duration of the test may require a parent to spend around 3 - 4 hours at the pulmonary laboratory. It actually limited their willingness to stay and some refused to have their child be given an additonal second dose or come back to have the test repeated. Due to the bitter taste of chloral hydrate, infants had a tendency to cry or spit out which probably was also one reason why other infants had failed sedation. Others had a light sleep prior to the study conduct making them less susceptible to sedation. No other adverse events were noted upon sedation of these infants. To facilitate sedation, parents should be reminded and advised that infants should be sleep deprived.

Morever, there were 5 infants who were excluded due to unacceptability of the loops due to the following reasons: early inspiratory effort during the forced expiratory phase, flow distortion due to narrowing or closure of the glottis or larynx during forced expirations and fluctuations in the expiratory signal which may reflect presence of secretions mobilized during the maneuvers. Considerable caution has been required to interpret such loops due to a marked natural physiologic variability between infants. Proper positioning and handling of secretions must then be observed.

In a previous study by Shavit et. al. they have found out that bronchodilator responsiveness can help predict early childhood respiratory morbidity. In this study, there was a significant difference in the V'maxFRC values between infants with recurrent wheezing fulfilling the API compared to normal infants (164.30 ± 59.65 vs 123.87 ± 48.05). This only implies that these values may be used to identify the wheezy infant suffering from asthma at an early age.

The recurrent wheezy infants were group into two groups, those fulfilling and not fulfilling the API. As mentioned in the previous literature, infants not having the API have a less than 3% chance of developing asthma at the age of 3. This study aimed to identify current asthma in this small number of infants. However, there was no significant difference found between infants with recurrent wheezing not fulfilling the API when compared to normal infants. This finding suggests that the API still has a value to predict asthma in the young age group. Also, since there was no positive response in this group of infants (Group 2), it was assumed that the cause of the recurrent wheezing was not due to bronchial hypereactivity but to other more common causes such as in viral infections. The pre-bronchodilator values of V'max FRC among groups were also not statistically significant as infants, irregardless of the API, has a comparable baseline smooth muscle tone.

However, the absolute values obtained postbronchodilator challenge also has a wide range making it as one limitation of the study. There was actually an overlap of values between infants with recurrent wheezing and normal infants. Infants who will be identified to have a positive bronchodilator response can actually be just normal infants and vice versa. The mean percent change post bronchodilator challenge between groups was also not statistically significant ($p = 0.083$) probably because of this wide range of values (*Group 1= 13.44 ± 38.62; Group 2= -2.41 ± 22.43; Group 3 = -1.64 ± 11.86)*. It was noted in the previous studies that infants less than 1 year of age actually has a wider range of responses with mean percent changes in their spirometric values significantly higher compared with those infants older than 1 year of age (28). In this study, no subgroup of infants in terms of their age was made.

Furthermore, there was also a large intra subject variability in the determined V'maxFRC values. In this study, there was only one determination made of the V'maxFRC post bronchodilator challenge. To

minimize the observed variability, three determinations should also have been made.

It should also be taken into consideration that infants both in the wheezy and normal groups have varied responses to a bronchodilator challenge test. There were only 13 (56.5%) infants who had a positive response in group 1 and there were 9 (39.1%) in groups 2 and 3. Although there were more infants with a positive API who had bronchodilator responsiveness, it was not still statistically significant. It is also important to note that a normal infant can still have some degree of responsiveness. This can be supported by previous study where normal infants were responders with their spirometric measurements significantly increased after an inhalation of a beta 2 agonist (28). However, it was noted in their study that in those responders, they had a signifi2acantly higher percentage of mothers who smoked during pregnancy compared with the non responders. However, in this study, history of maternal smoking was not accounted for to those infants who had a positive response.

Aside from the positive responses elicited in the different groups, there were also a number of infants with a decline in forced expiratory flow rate after salbutamol inhalations. This finding has been similiar to a study by Prendeville et. al. where there were infants with paradoxical response to salbutamol inhalations which can be explained by the relative effect of bronchodilator drugs on airway compliance (by altering smooth muscle tone) and on airway calibre. An increase in airway compliance due to a decrease in airway smooth muscle tone will tend to diminish maximum flow rates at low lung volumes. If the intrathoracic airway calibre did not improve by bronchodilator treatment, then the net effect of these drugs would be little or no improvement in overall airway resistance or lung volume during quiet breathing but a decline in end expiratory flow rates during forced expirations (26).

The action of salbutamol actually has adverse effect in most of the infants . Clinical success in bronchodilator treatment may be explained by reversal of airway narrowing due to an excessive smooth muscle tone (26). If the cause of the airway narrowing is due to inflammation or edema such as in a viral infection which is common is this age group, then any reduction in airway smooth muscle tone may have an adverse effect of increasing airway compliance and hence cause a decrease in flow.

Careful monitoring should be done in infants when therapies such as giving salbutamol inhalations can have varied responses. Using the tidal rapid thoracoabdominal compression technique, bronchodilator responsiveness can be assessed. Asthma therapies can be initiated for the secondary prevention of respiratory morbidity to those who have a positive response. It can also help in monitoring the response to asthma therapies and aid in the plan for management in infants with recurrent wheezing. For infants who may have a paradoxical response to salbutamol, careful monitoring is essential. Parents can be educated that one common cause of recurrent wheezing in infancy can be still viral infections which may not benefit with asthma therapies.

CONCLUSION AND RECOMMENDATION:

There was a significant increase in the values of V'max FRC post bronchodilator challenge in infants with recurrent wheezing who fulfills the asthma predictive index compared to normal infants. Since there was no statistical difference in the mean percent change postbronchodilator challenge test from the baseline, it is recommended that only the absolute values in the post bronchodilator challenge can be used to identify asthma in infancy. However, due to the wide range of absolute values, accurate identification of asthmatics from those who are not is limited. The large variability of values should also be minimized probably by doing at least three technicaly acceptable determination of V'maxFRC post bronchodilator challenge. This study recommends to make a subgroup analysis among infants younger and older than 1 year of age. Maternal smoking as a risk factor should also be taken into consideration.

To further assess response to treatment, further studies to be made should also include a follow-up for patients who were initiated with asthma therapies.

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COMPARISON OF THE ANXIETY LEVELS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND THEIR WELL SIBLINGS USING THE CHILD DRAWING: HOSPITAL MANUAL"

EFRAIM P. CULMINAS, MD, ANGIE SIEVERT-FERNANDEZ, MD,
MICHAEL M. RESURRECCION, MD

ABSTRACT

OBJECTIVES: The study aims to determine and compare the anxiety of children with acute lymphoblastic leukemia (ALL) and their well siblings based on Child drawing: Hospital manual and to identify factors associated with the level of anxiety.

METHODS: A prospective cross-sectional study was done in tertiary pediatric hospitals which included children aged five to eleven years old diagnosed with ALL and their well siblings.

RESULTS: A total of forty dyads of participants were studied. ALL patients presented higher anxiety scores than their siblings, but this was not statistically significant. There is a weak direct correlation between overall anxiety scores of ALL patients and their siblings ($p = 0.017$). There is insufficient evidence for an association between select clinical factors with anxiety scores. The linear regression model explained 49.77% in the variation of the anxiety scores but was not statistically significant.

CONCLUSIONS: There is a direct correlation between overall anxiety scores of ALL patients and their siblings. There is also a positive association with larger family size and child's response to sibling's illness. Larger families are likelier to have a healthier environment. The study also showed low to average anxiety levels among participants which may be related to quality of care and support given by the institution and inherent resiliency of the family.

RECOMMENDATIONS: Future research should aim to develop programs in partnership with families and other social support groups and explore the effectiveness of these interventions. Further studies should examine other possible cultural and psychodynamic factors prevalent in Filipino Family.

KEY WORDS: Anxiety, Siblings, Children, Chronic illness, Acute Lymphoblastic Leukemia, Child Drawing: Hospital Manual

INTRODUCTION

The burden of cancer cannot be underestimated. It is a major public health concern worldwide. Cancer is an enormous global health burden, toughing every region and socioeconomic groups. Today cancer accounts for about 1 in every 7 deaths worldwide more than HIV/AIDS, tuberculosis and malaria combined. More than 60% of cancer deaths occur in low- and middle-income countries, many of which lack the medical resources and health systems to support the disease burden. Moreover, the global cancer burden is growing at an alarming pace of about 21.6 million new cancer cases in 2030. It is foreseen that 13.0 million cancer deaths are expected to occur due to the growth and aging of the population.[1]

Acute Lymphoblastic leukemia (ALL) is a chronic disease. In the Philippines there is a growing number of young children diagnosed with life limiting illnesses. A 2016 survey conducted by the Philippine Cancer facts found that some 3,500 Filipino children are diagnosed with cancer yearly.[3] Children with chronic illnesses are required with repeated long-term visits to the hospitals. These children are at a greater risk of developing mental health or social adjustment problems, generally resulting in increase in levels of negative affect, higher rates of depression, suicidal behavior and distress.[4]

Siblings of children with cancer experience mental and social adjustment.[5] The disruption and turmoil created by these cancers reach beyond the diagnosed child to impact the entire family. Parents become highly distressed and their need to attend to the ill child at the hospital or at home may make them physically and emotionally unable to fully attend to the needs of their healthy children.[6] It is no surprise, then that siblings within these families are at risk

for emotional, behavioral, and academic problems. Given the level of disruption that childhood cancer causes for families, it is important to understand the consequences of these diseases for siblings and develop feasible interventions to reduce their distress and promote their adjustment.[7]

Determining the degree of anxiety of children with ALL and their sibling will give us an idea of its severity and help to find innovative ways for appropriate interventions that may help to address their psychosocial distress and foster their resilience and mental health.

This study intends to look at the level of anxiety of school-aged children with life limiting illnesses and their siblings using children's drawings, specifically, the Child Drawing: Hospital (CD:H) manual. It hypothesizes that children with ALL and their well siblings have significantly greater level of anxiety than the general population. There is very minimal research conducted specifically on the impact of a hospital-based program that addresses the psychosocial needs of pediatric chronically ill patients and their siblings. Moreover, this paper aims to help guide future policy maker to develop programs that will help reduce the burden of cancer for the family and siblings of children with cancer. This paper will help physicians accurately measure and monitor the degree of anxiety their children experience. This study hopes to add to existing knowledge on the literature on the significance of determining levels of anxiety in children with chronic illnesses as well as their siblings.

GENERAL OBJECTIVE

The general objective of this study is to determine and compare the anxiety level of children with Acute Lymphoblastic Leukemia and their well siblings based on Child Drawing: Hospital manual.

SPECIFIC OBJECTIVES

This study specifically aims:

1. To identify the factors associated with the level of anxiety of Children with Acute Lymphoblastic Leukemia and their well siblings in terms of socioeconomic characteristics, support systems, clinical status and duration of illness from the time of diagnosis.

2. To correlate level of anxiety of children with Acute Lymphoblastic Leukemia and their well siblings with the following demographic features such as age, gender, education (private/public school), socioeconomic status; support systems, clinical status and duration of illness from the time of diagnosis.

METHODOLOGY

A prospective cross-sectional design was done among chronically ill patients with Acute Lymphoblastic Leukemia and their well siblings. The Child Drawing: Hospital manual by Clatworthy, Simon, and Tiedeman was used to assess the level of anxiety.[8]

Patient included in this study are children who were diagnosed with Acute Lymphoblastic Leukemia within six months or longer prior to the conduct of the study with no developmental delays or concerns; the child is between 5-11 years old and able to follow instructions; seeking medical consult at the Hematology-Oncology center out-patient unit and private clinic of Hema-oncology specialist of different institutions; the child participates voluntarily; and with informed consent by the parents and assent by the child as deemed necessary.

Siblings of children with ALL with no illness and developmental concerns or delays; aged 5-11 years old; able to follow instructions; participates voluntarily; and informed consent was given by the parents and assent was, likewise, given by older children.

The study was conducted at the out-patient department of Cancer and Hematology Center of the Philippine Children's Medical Center (PCMC) and private clinics of Hema-oncology specialist of different institutions.

Study Procedure

The research protocol was submitted and approved by PCMC IRB-EC prior to study implementation. Research eventuation was conducted among members of the research team. An informed consent was obtained from parents and guardians and assent from children ages 7-11 years old. Parents or guardians of eligible subjects were fully informed of the nature of the study, and, the process of data gathering. A checklist of inclusion and exclusion criteria was also accomplished. Primary information which include age, gender, socioeconomic status and the duration of illness from the time of diagnosis were obtained by the investigator.

The study was conducted in a quiet room free from any distractions and medical procedures. Two instruments were used for the study; the Sociodemographic Questionnaire and

the Child Drawing: Hospital manual. The index patient and the corresponding sibling were subjected to the sociodemographic Questionnaire and Child Drawing: Hospital manual (CD:H).

The CD:H, developed by Clatworthy, Simon, and Tiedeman, was used to measure the participants' level of anxiety. This instrument was specifically made as a means of measuring the emotional status of the hospitalized school-aged child. It was designed to assess hospitalized children's anxiety from the child's point of view. Specifically it was developed as a means to produce an instrument that is nonthreatening to children; with an element of fun; appropriate to the child developmental level; easily administered; and scored with a scientifically sound mechanism. This manual contains three parts: Part A contains 14 items scored on a scale of 1 to 10, with 1 indicating the lowest level of anxiety and 10 the highest level; Part B is an eight items portion presumed to be pathological indices; and Part C is a gestalt rating that calls for an overall response by the scorer to the child's anxiety as expressed in the picture on a 1 to 10 scale. A score of 11 indicates coping or low anxiety, whereas a score of 10 indicates disturbance or high anxiety.[23]

The instrument consisted of an 8.5 x 11-inche blank white sheet of paper and a box of eight crayons (red, purple, blue, green, yellow, orange, black, and brown). The child was asked to "draw a picture of a person in the hospital". The scoring of the tool is based on the theoretical foundations of drawings as a projective measure of children's states of anxiety.[23]

The child doing the drawing was asked to sit on a table of an appropriate height. The researcher then handed the piece of paper to the child at an angle for the child to determine the placement of the drawing on the paper. A box of crayons was opened exposing all of the colors available. The crayons were the only tool allowed to make the drawing (e.g., no pencils were used).

The child was instructed as follows: "Please draw a picture of a person in the hospital." The person administering the CD: H observed the child to be sure that the child was able to attend to the task. In the event that the child becomes distracted, the directions were again repeated, and the child was encouraged to participate. Some children asked questions when they were unsure of themselves; when they were suspicious of the situation; or when compulsiveness, neatness, or concreteness interfered with the task of completion. These questions were responded to either with the original instructions or with clarifications that were congruent with the given instructions and have not influenced the child to respond in one way or the other. The children prompted not to add parts or color to the drawing. As the child had indicated verbally or by gesture that he or she is finished, the drawing and crayons were collected. No time limit was given. The drawings were labeled on the backside of the paper with the child's age, gender and birth date.

The drawings of the children were scored using the CD:H manual, by three raters. The first rater has a doctor's degree in Counseling Psychology, is a Certified Counseling and Developmental Psychologist from the Psychological Association of the Philippines and is likewise a Certified Child Life Specialist from the Child Life Council, USA. The second rater has a master's degree in Family Life and Child Development, with years of experience as a child life specialist. The third rater is the Executive Director of Kythe Foundation Inc., with a master's degree in psychology and a Certified Child Life Specialist.

The third rater was consulted if the first two raters were unable to determine the score. Inter-rater reliability was determined using Spearman's correlation.

The Children's drawings were interpreted using the CD:H manual, which has acceptable validity and reliability. Using the manual, the drawing is scored in three parts and includes a total score depicting the child's level of anxiety and was analyzed by a Psychologist.

Part A contained 14 items and was scored on a scale of 1 to 10, with 1 indicating the lowest level of anxiety and 10 the highest level. These items were 1. Person: Position; 2.Action; 3. Length of Person; 4. Width of Person; 5. Facial Expression; 6. Eyes; 7. Size of Person to Environment; 8. Color: Predominance; 9. Color: Number Used; 10. Use of Paper; 11. Placement; 12. Strokes: Quality; 13. Hospital Equipment; and 14. Developmental Level.

Part B was scored by giving additional points for the presence of any of eight items presumed to be pathological indices. These items included: 1. Omission: 1 Part; 2. Exaggeration of a Part; 3. Deemphasis of a Part; 4. Distortion; 5. Omission: 2 or more parts; 6. Transparency; 7. Mixed Profile; and 8. Shading.[26]

Part C was a gestalt rating that called for an overall response by the scorer to the child's anxiety as expressed in the picture on a 1 to 10 scale. A score of 11 indicates coping or low anxiety, whereas a score of 10 indicates disturbance or high anxiety.

A total score was obtained by adding the scores of the three sections, with the range of possible total scores from 15 to 290, with higher

numbers indicating more anxiety. Table 1 shows the range of Child Drawing: Hospital manual scores and its corresponding qualitative description on the level of anxiety. Data were checked for completeness, accuracy and consistency. The score of the drawings was encoded and analyzed.

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables. Median and range was used for ordinal variables. Mean and SD for interval/ratio variables. Paired sample t-test and Wilcoxon Signed Ranks test was used to compare item and scale scores. All valid data was included in the analysis. Spearman's correlation coefficient was used to determine the correlation between the patient's and sibling's anxiety scores. Simple and multiple linear regression analyses were performed, after checking that it meant for statistical assumptions required for these analyses. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

Ethical Considerations

The protocol of this study adhered to the ethical principles set out in relevant guidelines, including the Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, and National Ethics Guidelines for Health Research. The study protocol was submitted and approved by the Institutional Review Board- Ethics Committee.

RESULTS

A total of 40 dyads of children with ALL and their siblings was included in this study. Our patients' socio-demographic profile is presented in Table 1. Majority, eighty eight percent of ALL fathers were employed. In comparison, 75% of ALL, mother were unemployed. The percent of the patients have a monthly per capita income equal to 140% (C3). Forty five percent of the family resides in the National Capital Region.

Table 1. Sociodemographic Profile of Parents of Leukemia Patients and their Siblings

	Frequency (%); Mean ± SD; Median (Range)
Father's occupation	
Employed	35 (87.50)
Unemployed	2 (5)
Don't know	2 (5)
Deceased	1 (2.50)
Mother's occupation	
Employed	10 (25)
Unemployed	30 (75)
Socioeconomic status	
C1	0
C2	1 (2.50)
C3	29 (72.50)
Indigent	0
Pay	10 (25)
Region	
NCR	18 (45)
Region 1	1 (2.50)
Region 3	8 (20)
Region 4A	11 (27.50)
Region 5	1 (2.50)
Region 6	1 (2.50)
Transferred place of residence	4 (10)

The ALL patients had a mean age of 7.65 ± 1.94 years. Sixty five percent of ALL were male. The siblings had a mean age of 8.4 ± 1.89 years. Majority, 60% were female (Table 2).

As seen in table 3, thirty five percent of Leukemia patients are second born, 30% were first born and 17.5% were third born. In comparison, the well siblings of ALL patient were second born (40%), 38% were first born and 7.50% were third born.

Table 2. Age, Sex and Birth Order of Leukemia Patients and their Siblings

	Patients (n=40)	**Siblings (n=40)**
	Frequency (%); Mean ± SD; Median (Range)	
Age (years)	7.65 ± 1.94	8.4 ± 1.89
Sex		
Male	26(65)	16 (40)
Female	14(35)	24 (60)
Birth ordinal position		
1	12(30)	15 (37.5)
2	14(35)	16 (40)
3	7(17.50)	3 (7.50)
4	3(7.50)	4 (10)
5	2(5)	1 (2.5)
6	2(5)	1 (2.5)

There were twenty three percent each of ALL B-cell and ALL standard included in the study. Twenty three percent of the study subjects were in maintenance phase of treatment and three percent were being monitored (Table 3).

Table 3. Diagnosis and clinical status of 40 leukemia patients

Time since diagnosis (months)	28 (6 – 109)
Diagnosis	
ALL	20 (50)
ALL B-cell	9 (22.50)
ALL isolated CNS	1 (2.50)
ALL Standard	9 (22.50)
ALL T-cell	1 (2.50)
Clinical status	
ALL 4th cycle	1 (2.50)
ALL Bone Marrow relapsed	1 (2.50)
ALL chemo	2 (5)
ALL Maintenance	23 (57.50)
ALL consolidation	1 (2.50)
ALL induction	2 (5)
ALL intensification	1 (2.50)
ALL Monitoring	3 (7.50)
ALL Relapsed	2 (5)
ALL Off-chemo	2 (5)
ALL MSK	2 (5)

Comparative analysis of the 14 items in Child Drawing: Hospital manual part A showed that the number of color used was significantly higher among ALL patients (P Value 0.029). The other item showed insufficient evidence to demonstrate a difference in scores between ALL patients and their well siblings (Table 4).

Table 4. Comparative Analysis of Child Drawing: Hospital Manual Part A of 40 dyads of Leukemia Patients and their Siblings

	Patients (n=40)	**Siblings (n=40)**	***P* value**
	Median (Range)		
Person position	2 (1 – 10)	2 (1 – 10)	0.567
Action	5 (1 – 10)	5 (1 – 10)	0.724
Length of person*	3 (1 – 10)	3 (1 – 10)	0.090
Width of person	7 (1 – 10)	6 (1 – 10)	0.383
Facial expression	4.5 (1 – 10)	4 (1 – 10)	0.552
Eyes	7 (1 – 10)	7 (1 – 10)	0.378
Size of person to environment	2.5 (1 – 9)	1 (1 – 10)	0.291
Color predominance	6 (1 – 10)	8 (1 – 10)	0.548
Color number used	3 (1 – 10)	2 (1 – 10)	**0.029**
Use of paper	2 (1 – 9)	1.5 (1 – 9)	0.287
Placement	1 (1 – 8)	1 (1 – 10)	0.371
Stroke quality	3 (1 – 7)	3 (1 – 7)	0.474
Hospital equipment	3 (1 – 10)	3 (1 – 6)	0.161
Developmental level	5 (2 – 10)	5 (1 – 10)	0.502

Statistical test used: Wilcoxon Sign Rank Test

Comparative analysis of Child drawing: Hospital manual Part B score between ALL patients and their siblings showed no significant difference (P Value >0.05). However, it was noted that shading, omission of 2 or more parts, omission of one body part, and exaggeration are observed in both ALL patients and their siblings (Table 5).

Table 5. Child Drawing: Hospital Manual Part B Scores of 40 dyads of Leukemia Patients and their Siblings

	Patients (n=40)	**Siblings (n=40)**	***P* value**
	Median* (Range), [number of children]		
Omission: 1 part	5 [n=12]	5 [n=13]	-
Exaggeration of a part	5 [n= 8]	5 [n=10]	-
De-emphasis of a part	5 [n=5]	5 [n=1]	-
Distortion	10 (5 – 10) [n=7]	10 [n=2]	-
Omission: 2 or more parts	10, [n=20]	10 [n=	-
Transparency	0	0	-
Mixed profile	10 [n=1]	0	-
Shading	10 [n=35]	10 [n=35]	-

Comparative analysis of child's drawing: Hospital manual Part C showed no significant difference.

Table 6 outline the overall anxiety scores based on the Child Drawing: Hospital Manual. ALL patients have a mean score higher than the well siblings in all part of the manual. However, the result is not significantly different between the two groups with P value of 0.062.

Table 6. Overall Anxiety Scores based on the Child Drawing: Hospital Manual of 40 dyads of Leukemia patients and their Siblings

	Patients (n=40)	**Siblings (n=40)**	***P* value**
	Frequency (%); Mean ± SD; Median (Range)		
Part A (highest possible score is 140)	62.68 ± 18.53	57.68 ± 17.26	0.137‡
Part B (additional scores for pathologic items)	18.75 ± 6.86	16.5 ± 5.80	0.068‡
Part C (Gestalt, overall responses of scorer to the child's anxiety; highest possible score is 10)	5.83 ± 1.71	5.18 ± 2.06	0.084‡
Overall score	87.25 ± 22.19	79.35 ± 21.11	0.062‡
Interpretation			0.115ƨ
Very low	0	0	
Low	18 (45)	26 (65)	
Average	21 (52.50)	14 (35)	
Above average	1 (2.50)	0	
Very high	0	0	

Statistical tests used: ‡ - Paired sample t test; ƨ - Fisher's exact test

Statistical analysis was done to determine any association of ALL patient's anxiety score with selected clinical factors. Simple linear regression analysis showed insufficient evidence to demonstrate an association between select clinical factors (Table 7).

Table 7. Simple Linear Regression of Patient's Anxiety Score and Select Clinical Factors (n = 40)

	Crude Beta coefficient	95% Confidence Interval	P-value
Age	0.650	-2.96 – 4.26	0.718
Time diagnosis (months)	0.096	-0.21 – 0.41	0.532
Sex (Female)	-0.933	-15.79 – 13.92	0.899
Birth ordinal position			
1	(reference)	-	-
2	0.452	-17.36 – 18.27	0.959
3	-7.476	-29.01 – 14.06	0.485
4	-4.333	-33.56 – 24.9	0.765
5	-27.8333	-62.42 – 6.75	0.111
6	15.667	-18.92 – 50.25	0.364
Father's occupation			
Employed	(reference)	-	-
Unemployed	18.414	-15.24 – 52.07	0.274
Mother's occupation			
Employed	(reference)	-	-
Unemployed	-6.333	-22.82 – 10.15	0.442
Socioeconomic status			
C2	-41.7	-87.18 – 3.78	0.071
C3	-12.98	-28.88 – 2.92	0.107
Pay	(reference)	-	-
Region			
NCR	(reference)	-	-
Region 1	2.333	-44.07 – 48.74	0.919
Region 3	13.083	-6.11 – 32.28	0.175
Region 4A	3.970	-13.31 – 21.26	0.644
Region 5	-23.667	-70.07 – 22.74	0.307
Region 6	-23.667	-70.07 – 22.74	0.307
Transferred place of residence	-14.167	-37.69 – 9.36	0.230
Sibling's Total anxiety score	0.297	-0.35 – 0.63	0.078

Multiple linear regression showed insufficient evidence to demonstrate an association between ALL patient anxiety score and select clinical factors with anxiety scores. However, compared to first born, those who were born fifth have associated lower anxiety score. The model explained 50.28% in the variation of the anxiety scores, but was not statistically significant (p = 0.586)

Analysis of siblings' anxiety score and selected clinical factors was determined through simple linear regression. There is insufficient evidence to demonstrate an association between select clinical factors with anxiety scores (P value >0.05) (Table 8).

Table 8. Simple Linear Regression of Sibling's Anxiety Score and Select Clinical Factors (n = 40)

	Crude Beta coefficient	**95% Confidence Interval**	**P-value**
Sibling's Age	-2.527	-6.21 – 1.15	0.173
Sibling's sex (Female)	-2.899	-16.63 – 10.83	0.671
Birth ordinal position			
1	(reference)	-	-
2	3.857	-13.31 – 21.03	0.651
3	-9.214	-29.97 – 11.54	0.373
4	-14.17	-42.34 – 14.0	0.314
5	-1	-34.33 – 32.33	-.952
6	-15.5	-48.83 – 17.83	0.351
Father's occupation			
Employed	(reference)	-	-
Unemployed	-9.857	-41.1 - 21.38	0.526
Mother's occupation			
Employed	(reference)	-	-
Unemployed	4.333	-11.41 – 20.08	0.581
Socioeconomic status			
C2	-27.3	-71.84 – 17.24	0.222
C3	-10.02	-25.6 – 5.55	0.200
Pay	(reference)	-	-
Region			
NCR	(reference)	-	-
Region 1	34.278	-8.72 – 77.28	0.114
Region 3	13.903	-3.88 – 31.69	0.121
Region 4A	-0.995	-17.01 – 15.02	0.900
Region 5	-20.722	-63.72 – 22.28	0.334
Region 6	-8.722	-51.72 – 34.28	0.683
Transferred place of residence	9.611	-12.99 – 34.21	0.395
Patient's total anxiety score	0.268	-0.03 – 0.57	0.078

Analysis was performed to determine any association between siblings' anxiety score and selected clinical factors. The result showed insufficient evidence to demonstrate an association between select clinical factors with anxiety scores. The model explained 49.77% in the variation of the anxiety scores, but was not statistically significant (p = 0.508).

DISCUSSION

Sibling relationships are intense, complex and of infinite variety. It is widely accepted that siblings contribute enormously to family life. Unfortunately, children as siblings have largely been overlooked in most family health research in favor of the mother-child dyad. The resultant lack of understanding of the world of siblings becomes especially problematic when health professionals attempt to deliver true family-centered care to families with a chronically ill or disabled child.[27] Bank and Kahn highlighted the importance of the sibling relationship by asserting that siblings spent much more time together than any other family subsystem and that they are striking empathic with one another.[28]

This study compared the level of anxiety of children with ALL versus their well siblings using the Child Drawing: Hospital Manual. The result shows that on the average, ALL patients present higher scores than their well siblings. This however, were not statistically significant. Childhood chronic illness has long been thought to have a negative impact on the psychological functioning and behavior of the ill child that compared with healthy peers.[29]

Childhood chronic illness, affect not only the sick child but all the family members.[30] Coddington, in a survey of life events as etiology factors in childhood disease, found that sibling illness ranked as among the most stressful.[31] In several studies they concluded that these siblings were a "population at risk to experience psychological difficulties". [27,32,33] Similarly, the results of our study shows that there is a direct correlation between the overall anxiety scores of the ALL patients and their siblings. This means that the higher the score of the patients, the higher it is as well for the sibling, and vice versa. This is parallel to the result of the study done by Minuchin *et al* which showed that siblings usually share a common environment as well as their parents' attention.[34] The study also showed that siblings serve an important functions as socializers to one another, forming cohesive groups and reciprocating behavior on one another. In a study by Spinetta and Deasy-Spinetta, they concluded that siblings live through the experience with the same intensity as the patient.[35]

It was noted in this study that a lower anxiety level of ALL patient who were born fifth compared to those who were born first. This in relation to the family size wherein previous studies have shown that larger families is likely to have a healthier family environment as the burden of care is dispersed among several children.[35,36,37]

Studies have shown that anxiety levels are significantly affected by factors such as socioeconomic status, transfer of residence, educational attainment of the parents and the patients.[27,37,38] Farber suggested that a child's general life opportunities and social mobility are affected by having a chronically ill sibling.[38] Cairns et al., noted that the financial stress of having a child with cancer, may deprived parents and siblings to fulfill their basic needs as well as the luxuries of life.[39] They also suggested that the long-term needs of siblings may be slighted as parents focus on the draining tasks of the present. Moreover, it is interesting to note that a child's health problem may directly influence where the family will live. Families often move to be closer to treatment center or to find a better climate for the sick child.[40] Moving involves both financial and psychological stress that clearly affects healthy siblings.[31] However, this is not congruent in this study it showed that there is no significant correlations to selected clinical factors in relation to level of anxiety of children with ALL and their well siblings.

CONCLUSION

The Family is the primary social support system for children; however, childhood cancer disrupts family pattern and may interfere substantially with the family-based support that healthy siblings typically receive.[41] Parents of children with cancer report difficulty in attending to the needs of both their sick and healthy children.[5,12,13, 14]

This study showed there is a direct correlation between the overall anxiety scores of the ALL patients and their siblings. This means that the higher the score of the patients, the higher it is as well for the sibling, and vice versa. Moreover there is a positive association with larger family size and the child's response to a sibling's illness. The larger families is likely to have a healthier environment mainly because the burden of care is dispersed among several children.[35,36, 42]

The study also showed low to average anxiety levels among the participants which may be related to the quality of care and support given by the institution and inherent resiliency of the families included in the study.

LIMITATIONS OF CURRENT RESEARCH

It is recommended that a bigger sample be considered. We did not have a comparison group so we cannot determine if the absolute levels of anxiety experience by the siblings is significant compared to other general population. Furthermore, since we do not have longitudinal data, we cannot determine if patterns in amount of anxiety level as the disease condition progresses. Thus, future research may confirm a longitudinal relationship between social support and better functioning for siblings of children with cancer. Lastly, we did not present variation in our finding as a function of age or gender and other selected clinical factors, despite our sample size. These are important questions that may help guide future intervention or prevention programs to help support siblings of children with cancer.

Future research should aim to develop programs and pilot test in partnerships with families and other social support groups. Future research should explore the effectiveness of these interventions to assist the siblings of children with chronic illness. Future researchers should investigate further the impact of disease factors on psychological functioning of siblings. Further exploratory studies can be conducted in the future to examine other possible cultural and psychodynamics prevalent in the Filipino Family.

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CLINICAL EFFICACY OF CHLORHEXIDINE 0.12% SPRAY VERSUS CHLORHEXIDINE MOUTH RINSE ON PLAQUE CONTROL AND GINGIVAL HEALTH IN HEALTHY PEDIATRIC PATIENTS: A RANDOMIZED CONTROLLED TRIAL

MALIN A. MANDANAS, DMD, KARYL GRACE E. BAUTISTA, DMD

ABSTRACT

BACKGROUND: Difficulties in providing proper oral health hygiene is accentuated in special populations. Effective plaque control is necessary to minimize the potential risks of dental disease. Chlorhexidine (CHX) mouth rinse is an efficacious means of plaque control yet may be difficult to use..

OBJECTIVES: To compare the clinical efficacy of 0.12% CHX spray versus 0.12% CHX mouth rinse on existing supragingival plaque and gingivitis in a group of healthy pediatric patients.

METHODS: This is a randomized, controlled, single blind, open label clinical trial. Participants were assigned by simple randomization to: (1) Group A used 0.12 CHX mouth rinse, and (2) Group B administered 0.12% CHX spray, to be used for a period of 4 weeks or 28 days.

RESULTS: 28 children were included in the analysis. After 4 weeks of CHX use, there was no difference in the gingival status. Within the mouth rinse group, the plaque scoring index (from 3 to 2, p value =0.005) and the plaque severity index (from 0.65 to 0.51, p value =0.017) decreased. While in the spray group, only the plaque severity index had significant decrease (from 0.55 to 0.46, p value =0.019).

CONCLUSIONS: CHX spray delivery system is an efficacious method in decreasing plaque severity and is comparable to plaque reduction seen with the use of mouth rinse. The decrease/maintenance in gingival index values proves that there is no progress in gingivitis disease process.

RECOMMENDATIONS: CHX spray has been proven to reduce plaque severity and should be considered as an adjunct of oral hygiene maintenance for children.

KEY WORDS: chlorhexidine, plaque control, gingivitis

INTRODUCTION

In 2010, the World Health Organization (WHO) released a global overview of severe periodontitis (SP) citing it as the sixth-most prevalent condition affecting 10.8% or 743 million of the global population.[1]

The WHO Oral Health Global Data Bank describes the prevalence rates of the signs of periodontal disease i.e., gingival bleeding, periodontal pocketing, and loss of attachment. In that report, the consensus among adult populations in all regions of the world present gingival bleeding as highly prevalent; while advanced disease with periodontal pockets (>6 mm) affects ~10 to 15% of adults globally.[2]

According to the American Academy of Periodontology (AAP), the presence and persistence of bacterial plaque will initiate and propagate most forms of gingivitis. It has also been widely accepted that the presence of virulent microorganisms (i.e., *Actinobacilius actinomycetemcomitans* and Porphyromonas *gingivalis*) may initiate and lead into the progression of periodontitis. Plaque sample analysis from patients with severe levels of gingival inflammation reveals a progression of bacterial species that has the capacity to induce an inflammatory response. The change in gingival environment provides the environment for more virulent microorganisms within the plaque mass to flourish.[3]

The inability to control the periodontitis will subsequently lead to further destruction of periodontal tissues. Bone resorption and collagen destruction may occur leading to the tooth attachment loss.[3] Globally, it has been reported that dental caries and periodontal disease are the major causes of

tooth loss. It is estimated that 30% of people aged 65 – 74 years are edentulous.[9]
Therefore, various preventive oral health strategies have been recommended. Plaque control and regular periodontal maintenance have been prescribed. The AAP has prescribed a semi-annual periodontal maintenance for patients presenting with recurrent gingivitis without attachment loss.[4] Ensuring proper oral hygiene can decrease the burden of the risk of SP. The correction of inappropriate habits such as tobacco use, alcohol consumption, and an unhealthy diet has been emphasized by the WHO to reduce risk and improve periodontal health.[2] However, oral hygiene may not always be adequate due to the lack of patient compliance, insufficient motivation, impaired dexterity, and possibly by the hindrance of hard to reach areas in the mouth.[5]

Multiple over-the-counter products are available in the local market that address the need for anti plaque and anti gingivitis agents that will serve as an adjunct to periodontal health maintenance. These antimicrobial agents have been utilized to complement or replace mechanical oral hygiene measures. A meta-analysis of anti plaque and anti gingivitis agents conducted by Gunsolley (2006) concluded a strong evidence of anti plaque and anti gingivitis effects of 0.12% Chlorhexidine digluconate (CHX) mouthrinse.[6]

Multiple articles have reported that CHX has proven to have a broad-spectrum of anti-microbial activity.[5-7] Plaque inhibition by CHX is achieved by an immediate bactericidal action during the time of application. A prolonged bacteriostatic action is also noted due to the CHX being adsorbed to the pellicle-coated tooth surface.[8] The substantivity of CHX, which allows the antimicrobial to remain attached to the tissue for 8 – 12 hours,[5] makes it an ideal antiseptic for plaque inhibition as the minimum effective dose is reached despite few daily administrations.

Locally, CHX is available as an over-the-counter mouth rinse in the form of 0.12% and 0.20% concentrations. Both concentrations exhibit equal efficacy when used at appropriate similar doses.[10] The recommended use of CHX is by rinsing 15 mL of undiluted solution, morning and evening, after regular toothbrushing. CHX is available in different formulations: mouth rinses, gel, toothpaste, spray, varnish, and chewing gum.[10] In the local market, the public has access to various brands of CHX mouth rinse as an over-the-counter medicament. CHX gels and varnishes are available through the professional oral health care giver.

CHX is particularly suited for patients that are part of the special population: those who are developmentally disabled, medically compromised, and in the elderly population. The inability to efficiently use a toothbrush for plaque removal calls for an adjunct to plaque control. Loading CHX in an oral spray bottle provides a simple and quick way to deliver the necessary supplement to plaque control.[7,12]

Despite improvements in the oral health status in the world, underprivileged groups in the developed and developing countries still come across problems in the delivery of proper oral health care. People in special populations, i.e., home-bound or disabled individuals, and the frail elderly, are not sufficiently covered by oral health care.[2]

In a study of the oral health status of individuals with cerebral palsy (CP) by Al-Allaq (2015), oral health presents a significant challenge as people with CP are more prone to developing dental caries and periodontal disease. Due to the spasticity and uncontrollable movements, oral hygiene is difficult to perform[13]. Another study conducted by Guare (2004) concluded that children with CP had greater prevalence of periodontal disease in the primary dentition as opposed to healthy children.[14]

Practical protocols for the prevention of dental disease in patients with special needs have been recommended. Glassman et al. (2003) has prescribed a CHX regimen and has suggested the topical application with a swab or sponge applicator for those patients unable to rinse or expectorate the solution.[15] In the study by Francis et al. (1986), a comparison of three delivery methods of CHX in handicapped children concluded that respondents prefer the use of the CHX spray as a form of oral hygiene.[12] Locally, CHX is distributed as a cosmetic product which may be purchased as an over-the-counter medicament. The allowable concentration for commercial distribution is up to 0.3% of the active ingredient.[35] In the dental practice, practitioners carry concentrations of 1% CHX in gel form to use for in-office periodontal treatment, and not as an adjunct to oral hygiene maintenance.

This study aims to seek evidence – based support for the clinical efficacy of 0.12% CHX when delivered via spray. Since there are no known studies of CHX use in the pediatric population, this study will serve as a pilot study in the clinical efficacy of 0.12% CHX mouth rinse and spray among the pediatric population. Counting into consideration the

preferences of the primary caregiver of a special-needs patient, using CHX in spray-form may significantly improve the compliance in oral health maintenance.

This study may bring awareness to the general dental practitioner in providing appropriate preventive interventions for patients with specific needs. Difficulties in providing proper oral health hygiene is accentuated in special populations. Effective plaque control is necessary to minimize the potential risks of dental disease. It is the duty of the dental practitioner to instruct and recommend a practical regimen.

OBJECTIVES OF THE STUDY

4.1 General Objectives

To compare the clinical efficacy of 0.12% Chlorhexidine spray versus 0.12% Chlorhexidine mouth rinse on existing supragingival plaque and gingivitis in a group of healthy pediatric patients

4.2 Specific Objectives

a) To evaluate supragingival plaque formation using the Quigley-Hein Plaque Scoring Index (with Turesky Modification) before and after the use of 0.12% CHX spray and mouth rinse;
b) To assess the effectiveness of 0.12% CHX spray and mouth rinse on tooth surfaces with high plaque accumulations using the Plaque Severity Index;
c) To evaluate the condition of gingival tissues using the Modified Löe-Silness Gingival Scoring Index before and after the use of 0.12% CHX spray and mouth rinse;
d) To assess the effectiveness of 0.12% CHX Spray and mouth rinse on gingival sites that received high gingival index scores using the Gingivitis Severity Index;
e) To determine the incidence of the adverse effects seen when using 0.12% CHX spray and mouth rinse.

METHODOLOGY

The study is a randomized, controlled, single blind, open label clinical trial. Patients of the Philippine Children's Medical Center – Pediatric Dentistry Division were invited to participate in the study. A participant was assigned by simple randomization to one of two groups: (1) Group A will use 0.12 CHX mouth rinse according to the manufacturer's instructions, and (2) Group B will administer 0.12% CHX spray twice daily. The study was conducted for a period of 4 weeks or 28 days. The examiner was blinded to the regimen of the subjects.

Patients who received CHX mouth rinse or CHX spray were selected using simple random sampling technique by computer generated numbers.

The inclusion criteria for participation is as follows: a) able to obtain parental permission and give assent; b) aged 6 to 18 years old; c) does not have a systemic condition that could negatively influence oral health, and; d) have not been under antimicrobial treatment locally or systemically 4 weeks before or during the study period.

A total of 29 participants were able to meet the eligibility standards for participation.

Patients who received chlorhexidine mouth rinse or chlorhexidine spray were selected using simple random sampling technique by computer-generated random numbers. A computer-generated random numbers 0-9 was used to assign the treatment: chlorhexidine mouth rinse (Group A) was assigned to even numbers (0 is regarded as even) and the chlorhexidine spray (Group B) was assigned to odd numbers. The blocking design was used to ensure the equal allocation of treatment.

Examiner 1 assigned the subjects to the control (Group A – Mouth rinse) or test group (Group B – Spray). Examiner 2 was blinded to which group the subject was assigned to. Examiner 1 delegated instructions for both the spray and mouth rinse using visual aids (dental model / typodont). The subject was asked to demonstrate how they will practice the instructions before leaving the clinic to ensure utmost understanding. Examiner 1 dispensed the CHX (and tools ie. Spray bottle) and the prorated travel allowance to the subject / parent / legal guardian. A study monitor was assigned to conduct weekly over-the-phone monitoring to check the subjects' compliance with the instructions.

Group A – Rinse instructions were as follows: rinsing should be made twice daily, one after breakfast and one after dinner. 10 mL of undiluted solution shall be rinsed thoroughly and left in the mouth for 1 minute, after which, the excess fluids are to be expectorated. Rinsing shall be done after their normal oral hygiene maintenance routine.

Group B – Spray instructions were as follows: applications should be made twice daily, one after breakfast and one after dinner, using five bursts of spray at each application. The spray should be directed at the buccal surface of the teeth at the following areas: (1) Upper right posterior, (2) Lower right posterior, (3) Upper left posterior, (4) Lower left posterior, and (5) Anterior region, while making sure teeth are occluded. The solution is to be left in the mouth for 1 minute, after which the excess fluids are to be expectorated. Spraying shall be done after their normal oral hygiene maintenance routine.

This study was carried out from February 2018 to September 2018. Two examiners and one monitor conducted this study (Examiner 1, Examiner 2, Monitor). The Monitor recruited the subjects from the walk-in patients of the Pediatric Dentistry Division of Philippine Children's Medical Center.

During oral examination, baseline values of the plaque and gingivitis score were obtained. Baseline clinical measurements were determined by Examiner 2 whom received training in making clinical measurements for plaque accumulation and gingival inflammation. To ensure that the baseline values reflect the subjects' existing oral hygiene conditions, the subjects did not receive a baseline prophylaxis nor were their daily oral hygiene altered.

Plaque accumulation and gingival tissue condition were re-evaluated 4 weeks / 28 days after obtaining the baseline. To avoid inter-examiner variability, Examiner 2 (in blinded fashion) conducted the measurements of the subjects. A post-treatment oral prophylaxis was rendered to the subjects.

PCMC – Institutional Review Board has approved this study prior to implementation.

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables.

Independent/Paired sample T-test, and Fisher's exact/Chi-square test was used to determine the difference of mean, and frequency between groups, respectively

All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

The study included a total of 28 children in the analysis, 15 were assigned to Chlorhexidine mouth rinse and 13 to the spray. Figure 1 shows the phases of the randomized trial of the two groups. As to age and gender, both groups were comparable (Table 1).

Table 1. Demographic profile of healthy pediatric patients (n = 28)

	Chlorhexidine mouth rinse (n = 15)	**Chlorhexidine spray (n = 13)**	**P-value**
	Frequency (%); Mean ± SD; Median (Range)		
Age (years)	10.8 ± 2.83	13 ± 3.58	0.081*
Sex			
Male	7 (46.67)	6 (46.15)	0.978†
Female	8 (53.33)	7 (53.85)	
All	15 (100)	13 (100)	

*Statistical Tests Used: * - Independent t – test; † - Chi – square test*

Gingivitis and plaque condition for both treatment groups are noted in Table 2. As to gingival health, there are no difference between the two groups and no difference in its status after 4 weeks of chlorhexidine mouth rinse or spray use. Plaque scoring and severity index between two groups were also not statistically significant. Within the chlorhexidine mouth rinse group, the plaque scoring index (from three to two, p value =0.005) and the plaque severity index (from 0.65 to 0.51, p value =0.017) decreased after four weeks of use. While in the chlorhexidine spray group, only the plaque severity index had significant decrease after four weeks (from 0.55 to 0.46, p value =0.019).

Table 2. Evaluations of the plaque index and gingivitis index of healthy pediatric patients (n = 28)

	Chlorhexidine mouth rinse (n = 15)	Chlorhexidine spray (n = 13)	p-value*
	Mean ± SD		
Gingivitis Index			
Baseline	1 (0 – 1)	0 (0 – 1)	0.143
4th week	0 (0 – 1)	0 (0 – 1)	0.202
p – value‡	0.083	0.414	
Gingivitis Severity Index			
Baseline	0.27 ± 0.22	0.13 ± 0.13	0.057
4th week	0.18 ± 0.16	0.11 ± 0.13	0.222
p – value§	0.051	0.606	
Plaque Scoring Index			
Baseline	3 (2 – 4)	2 (2 – 4)	0.125
4th week	2 (1 – 3)	2 (1 – 3)	0.456
p – value‡	**0.005**	0.059	
Plaque Severity Index			
Baseline	0.65 ± 0.21	0.55 ± 0.17	0.178
4th week	0.51 ± 0.23	0.46 ± 0.22	0.534
p – value§	**0.017**	**0.019**	

*Statistical Tests Used: * - Independent t – test; ‡ - Wilcoxon Sign Rank test; § - Paired sample t – test*

Among all 28 children, there were four in mouth rinse group and one in spray group that presented with calcular deposits (p value=0.600) as seen in Table 3.

Table 3. Adverse events during Chlorhexidine use among Healthy Pediatric Patients (n=28)

	Chlorhexidine mouth rinse (n = 15)	Chlorhexidine spray (n = 13)	P-value
	Frequency (%); Mean ± SD; Median (Range)		
With adverse event	4 (26.67)	1 (7.69)	0.600
Calcular deposits	4 (100)	1 (100)	-

Statistical Test Used: Fisher's Exact Test

DISCUSSION

The study aimed to evaluate whether chlorhexidine spray was comparable to chlorhexidine mouth rinse in terms of plaque control and gingival health in the pediatric population. When prescribing practical protocols for the prevention of dental disease, a simple yet effective regimen should be considered. This study has shown that delivery of chlorhexidine through spray is comparable to chlorhexidine mouth rinse in terms of decreasing plaque severity. While there is no statistically significant decrease in the plaque index, gingivitis index, and gingivitis severity index in the spray group, it has not shown progression of the scores either. This implies some level of oral health maintenance with respect to plaque and gingival health control.

In a similar study by Burtner et al [24], chlorhexidine spray was added to the daily oral hygiene routine of institutionalized patients. The results of the four-week trial effected a decrease in plaque accumulation and an improvement in gingival health. However, due to the absence of the studies of CHX efficacy in the pediatric population, this study was necessitated to detect an effect in plaque control and gingival health. Another study

conducted by Clavero et al [25] showed that the use of chlorhexidine spray for 30 days also produced significant reductions in plaque and gingivitis scores. While our study has shown significant reductions in plaque severity of the spray group, the gingival indexes did not prove statistical significance. A possible explanation for this is that the population selected for the spray regimen had lower baseline gingivitis index scores compared to the control group. Hence, should there be a generalized decrease in gingivitis scores post – treatment, there will still be no statistical difference in the pre- and post – treatment scores. It should be noted also, that the gingivitis scores in the control group also did not yield a significant decrease. This result shows that there is a need for more aggressive oral hygiene measures (e.g. scaling and polishing of teeth, gingival curettage) prior to the use of an adjunct.

Neto et al [20] has performed an efficacy study, which had a similar experimental design to our study, comparing two different concentrations of chlorhexidine among dental students. Because of this special population, compliance to the regimen was easily controlled and assured. Our study has involved actual pediatric patients with parents and guardians that have an average or below average oral hygiene knowledge. Given this situation, real life concerns in achieving acceptable levels of oral hygiene has surfaced. Therefore, easy and uncomplicated preventive oral hygiene measures should be put in place on top of oral health education.

Even though no prior mechanical prophylactic treatment was performed on the subjects, plaque reduction or plaque severity decrease was observed. This proves that chlorhexidine is effective in preventing the formation of new plaque. The cause of the reductions may be attributed to the Hawthorne effect, wherein the participants of the study modify their behavior by working harder in response to their awareness of being observed.

Delivery of chlorhexidine as a spray allows a method of dispensing the drug in small, controlled doses. This diminishes the adverse effects commonly seen with the use of chlorhexidine. In this study, only 7% of the participants from the spray group has presented with adverse effects (i.e. calcular deposit formation) as opposed to the 27% of the participants from the control group.

The results of this study prove that delivery of chlorhexidine via spray is effective in reducing plaque severity and preventing the formation of new plaque. This provides dentists enough support to recommend this regimen to their patients in need of a supplement to their oral health maintenance. Also, this also provides more options for the special care population in oral health delivery. The use of an oral spray provides a simple, effective, rapid way to incorporate chlorhexidine in a patient's regimen.

For this study, monitoring of the subjects ended after the final administration of chlorhexidine and post – treatment follow up. Further research is recommended to check if there are residual beneficial effects that continued after the last dose. Also, it is recommended to conduct a study on program compliance to further establish the ease in utilization of the chlorhexidine spray.

CONCLUSION AND RECOMMENDATIONS

The simplified regimen of the chlorhexidine spray delivery system proves to be an efficacious method in decreasing plaque severity and is comparable to plaque reduction seen with the use of chlorhexidine mouth rinse. Although gingival health remains statistically unchanged in both mouth rinse and spray groups, the decrease in index values proves that there is no progress in gingivitis disease process in the pediatric population.

The use of chlorhexidine as a spray or rinse has proven to reduce plaque severity and should be considered as an adjunct for oral hygiene maintenance in the pediatric population whom are considered as part of the special population as well. However, providing mechanical prophylactic plaque and gingivitis control measures prior to chemical prophylactic means will provide maximal beneficial effects to the patient.

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A COMPARISON BETWEEN PENLIGHT AND OTOSCOPIC EXAMINATION OF THE EAR CANAL AND TYMPANIC MEMBRANE AMONG GRADE 1 STUDENTS

MAY CRISTINE L. OBANA, MD, CECILIA GRETCHEN NAVARRO – LOCSIN, MD, MARIA RINA REYES-QUINTOS, MD

ABSTRACT

BACKGROUND: In the Philippines, screening for ear problems especially in children at entry to school is usually undertaken by school nurses and teachers who typically do not have specialized instrumentation. The penlight has recently been employed as screening method in determing the possibilities of ear problems in public school communities. This study attempts to determine the accuracy of the penlight as an alternative method for screening to assess the common external ear abnormalities among Grade 1 students in an elementary school.

OBJECTIVES: 1. To compare the result of otologic examination using the penlight versus otoscopy in determining of common pediatric ear problems. 2. To determine the sensitivity, specificity and predictive values of penlight examination in the screening of ear canal and tympanic membrane for abnormal conditions among Grade 1 students.

METHODS: Otologic examination with the use of a penlight was carried out by the tranined nurse in ears of Grade 1 students and the results compared with those obtained from otoscopy done by an otolaryngologist. Presence of ear conditions such as cerumen, discharge, foreign body, tympanic membrane visualization, and an overall assessment were recorded in an Excel file. The examiners were both blinded with the findings.

RESULTS: Ninety-four students (188 test ears) with a median age of 6 years, ranging from 5 to 10 years, and a 1:1 sex distribution were included in the study. The result showed an excellent agreement (P<.001) between the penlight and otoscopic examination. The sensitivity and specificity were of 98.6% and 100%, respectively. The PPV is nearly 100% and NPV of 95.2% and and overall accuracy of 98.94%.

CONCLUSIONS: There is an excellent agreement between the nurse's findings and otolaryngologist's findings in examining the ear canal and tympanic membrane. The penlight has on overall accuracy of 98.94%, in identifying cerumen, discharge, foreign body and visualizing the tympanic membrane. Thus, this study shows that with trained nurse in otologic examination, the penlight is an effective screening in identifying common ear problem among children.

KEY WORDS: Penlight Examination, Otoscopic Examination, Ear Canal, Tympanic Membrane

INTRODUCTION

Detection of common childhood ear problems is vital in many educational programs. Correct identification of ear problems, such as cerumen, discharge, and eardrum perforation, is important since it can compromise hearing and may influence speech-language acquisition, academic performance, and personal-social adjustments.[1] Hearing loss in these conditions is caused by a conductive problem such that the sound waves do not reach the tympanic membrane, ossicles or inner ear. Screening, evaluation, treatment and referral in the primary care setting can reduce the degree and adverse effects of subsequent hearing loss in the pediatric population.

In the Philippines, screening for ear problems in children at entry to school is usually undertaken by school nurses and teachers who typically do not have specialized instrumentation. The penlight has recently been employed as an screening method in determing the probability of ear problems in public school communities where the otoscope is not readily available.[15]

There is only one published research by Goloria-Cruz, et al., where they assessed the success of the training of the school nurses by the otorhinolaryngologist with regards to ear examination using a penlight in detecting signs of common ear conditions.[6] Further research is needed to guide future recommendations for a protocol in this area. This study attempts to determine the accuracy of the penlight as a screening method in routine otologic

examination to assess the presence of ear discharge, cerumen and perforated ear tympanic membrane among Grade 1 students in an elementary school.

OBJECTIVES OF THE STUDY

General Objective

- To determine the accuracy of penlight examination among Grade 1 students as to compare with using otoscope as reference standard.

Specific Objectives

- To compare the result of otologic examination using the penlight versus otoscopy in the screening of common pediatric ear problems.
- To determine the sensitivity, specificity and predictive value of penlight examination in the screening of ear canal and tympanic membrane conditions among Grade 1 students.

METHODOLOGY

The study aims to compare the penlight and the otoscopic results in examining the ear canal and tympanic membrane among Grade 1 students. A prospective, cross-sectional study was employed to answer the research problem.

The study was conducted at Sto. Cristo Elementary School located at Barangay Sto. Cristo, Quezon City. A total of 251 garde 1 students, divided in 6 sections, composed the Grade 1 class. The sample size of 85 participants (170 test ears) is the minimum number that achieves 80% power to detect a difference of 0.090 using a two-sided binominal test. The target significance level of 0.0500. These results assume that the population under the null hypothesis is 0.900.

Inclusion Criteria

All Grade 1 students with parental consent that are enrolled at Sto. Cristo Elementary School in Quezon City.

Exclusion Criteria

1. Patients not included in a Grade 1 class in an Elementary school.
2. Children with orocraniomaxillofacial disorders.
3. Children who are unable to complete the procedure due to lack of cooperation or for any other reason.

The participants from the Grade 1 class were selected by stratified random sampling. Out of six (6) sections, four (4) sections were randomly selected. A 30% margin was allotted for those who did not consent. A total of 110 consents were distributed equally among the 4 sections, and a total of 94 students with consent were included in the study, which exceeds the sample size of 85.

One nurse was trained in doing otologic examination using a penlight. Lectures were given in basic anatomy of the ear and common ear diseases. A proper and methodologic otologic examination was demonstrated and was reciprocated by a return demonstration.

Otologic Examination was conducted in two parts. In the first part, a trained nurse used a penlight to assess the ear canal and tympanic membrane. The penlight used is an Energizer metal penlight with bright LED light of 35 lumens, it is battery operated with 2 AAA batteries, and is readily available at local hardware stores at a reasonable price. The second part of the examination, was conducted by pediatric otolaryngology Fellow using a Welch-Allyn 3.5 V Halogen HPX Diagnostic Fiber-Optic Otoscope.

Features that determined relevant were assessed: presence of cerumen, foreign body, discharge, tympanic membrane condition, and an overall assessment was recorded. All findings were blinded to both examiners. Appropriate recommendations were given by the Pediatric Otolaryngology Fellow, to those with remarkable findings.

All the findings were inputted in an Excel Database and identification of abnormal or normal results were determined. Abnormal results constitutes findings in the ear canal such as cerumen, foreign body and discharge that may result in non-visualization of the tympanic membrane or a perforated tympanic membrane. Normal results are considered if unremarkable ear canal findings and visualized intact tympanic membrane.

The study was presented to the Institutional Review Board of the Philippine Children's Medical Center. The study commenced upon the approval of the IRB. No subject participated in the study without written documentation of informed consent.

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion was used for nominal variables, median and range for ordinal variables.

Kappa statistic was used to measure the agreement between penlight and otoscopy. Kappa values were interpreted according to guidelines adapted from Landis and Koch: 0.81-1.00, excellent; 0.61-0.80, good; 0.41-0.60, moderate; 0.21-0.40, fair; and < 0.20, poor.

Sensitivity, Specificity, NPV, PPV, and Likelihood Ratios was used to determine the diagnostic quality and accuracy of the penlight test as compared to otoscopy as a hearing screening tool among Grade I students.

All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA15.0 was used for data analysis.

RESULTS

Included in the study were 94 Grade 1 pupils with a median age of 6 (range 5-10) years and an equal distribution between sexes (Table 1).

Table 1. Demographic characteristics of Grade 1 students (n = 94)

	Frequency (%); Median (Range)
Age (years)	6 (5 – 10)
5	7 (7.45)
6	74 (78.72)
7	9 (9.57)
8	3 (3.19)
10	1 (1.06)
Sex	
Male	47 (50)
Female	47 (50)

Different otologic findings based on otoscopy and penlight visualizations are given in Table 2. The eardrums of children were either visualized intact (62-63% at right side, 66-68% at left side) or not visualized. Impacted cerumen was seen in more or less a third of children (37-38% at right side, 31-34% at left side).

Table 2. Diagnoses based on otoscopy and penlight (n = 94)

	Right Ear		**Left Ear**	
	Otoscope	**Penlight**	**Otoscope**	**Penlight**
	Frequency (%)			
Ear canal				
Unremarkable	20 (21.28)	21 (22.34)	21 (22.34)	21 (22.34)
Discharge	0	1 (1.06)	0	0
Wax/cerumen retained	36 (38.30)	35 (37.23)	43 (45.74)	40 (42.55)
Wax/cerumen impacted	36 (38.30)	35 (37.23)	29 (30.85)	32 (34.04)
Foreign body	2 (2.13)	2 (2.13)	1 (1.06)	1 (1.06)
Tympanic membrane				
Not visualized	36 (38.30)	35 (37.23)	30 (31.91)	32 (34.04)
Visualized perforated	0	0	0	0
Visualized intact	58 (61.70)	59 (62.77)	64 (68.09)	62 (65.96)

The kappa coefficients for ear canal, and tympanic membrane findings on either side all indicated excellent agreement (P<.001) between the two modes of otologic visualization (Table 3).

Table 3. Agreement between otoscopy and penlight

	Agreement	Kappa Coefficient	Interpretation	P-value
Ear canal				
Left	93.62	0.902	Excellent agreement	**<.001**
Right	93.62	0.904	Excellent agreement	**<.001**
Tympanic membrane				
Left	95.74	0.904	Excellent agreement	**<.001**
Right	94.68	0.887	Excellent agreement	**<.001**

With otoscopy as a gold standard, penlight testing had high sensitivity and specificity to detect clinically abnormal or remarkable otologic findings in children. Among patients who had remarkable findings, we have a 98.6% probability that the penlight test will turn positive (sensitivity). Among patients with normal findings, we have nearly 100% probability that the penlight test will be negative (specificity). When penlight test is positive, we have nearly 100% probability that otoscopy is positive (PPV). When penlight test is negative, we have 95.2% probability that the patient is otoscopy negative (NPV). Overall, the accuracy of penlight testing in detecting remarkable or abnormal ear findings is 98.94%. Positive likelihood ratio cannot be computed because none of those were normal on otoscopy had abnormal findings on penlight test. Students who are otoscopy positive are approximately 99% less likely to yield a negative penlight result (LR-) (Table 4).

Table 4. Diagnostic accuracy of penlight test as compared to otoscopy (n = 188 ears)

	Otoscope		Total
Pen light test	Abnormal/remarkable	Normal/unremarkable	
Abnormal/remarkable	146 (77.76)	0	146 (77.66)
Normal/unremarkable	2 (1.06)	40 (21.28)	42 (22.34)
Total	152 (80.85)	36 (19.15)	188 (100)

Sensitivity (Sn)	98.6 (95.2 – 100)	Positive LR	-
Specificity (Sp)	100 (91.2 – 100)	Negative LR	0.01 (0 – 0.05)
PPV	100 (97.5 – 100)	Accuracy	98.94 (96.21 – 99.87)
NPV	95.2 (83.8 – 99.4)		

Subgroup by left and right ears, but likely unimportant as subgroup analyses:

Table 4.1 Diagnostic accuracy of penlight test as compared to otoscopy – left ear

	Otoscope		Total
Pen light test	Abnormal/remarkable	Normal/unremarkable	
Abnormal/remarkable	73 (77.66)	0	73 (77.66)
Normal/unremarkable	1 (1.06)	20 (21.28)	21 (22.34)
Total	74 (78.72)	20 (21.28)	94 (100)

Sensitivity (Sn)	98.6 (92.7 – 100)	Positive LR	-
Specificity (Sp)	100 (83.2 – 100)	Negative LR	0.01 (0 – 0.09)
PPV	100 (95.1 – 100)	Accuracy	98.94 (94.21 – 99.97)
NPV	95.2 (76.2 – 99.9)		

PPV, positive predictive value; NPV, negative predicted value; LR, likelihood ratio

Table 4.2 Diagnostic accuracy of penlight test as compared to otoscopy – right ear

	Otoscope		Total
Pen light test	Abnormal/remarkable	Normal/unremarkable	
Abnormal/remarkable	73 (77.66)	0	73 (77.66)
Normal/unremarkable	1 (1.06)	20 (21.28)	21 (22.34)
Total	74 (78.72)	20 (21.28)	94 (100)

Sensitivity (Sn)	98.6 (92.7 – 100)	Positive LR	-
Specificity (Sp)	100 (83.2 – 100)	Negative LR	0.01 (0 – 0.09)
PPV	100 (95.1 – 100)	Accuracy	98.94 (94.21 – 99.97)
NPV	95.2 (76.2 – 99.9)		

PPV, positive predictive value; NPV, negative predicted value; LR, likelihood ratio.

DISCUSSION

The goal of the study was to be able to compare the result on the effectiveness and accuracy of the penlight with an otoscope, in examining the ear canal and tympanic membrane among Grade 1 students.

The result of the study showed an excellent agreement between a penlight, used by a trained nurse, and an otoscope, used by an otolaryngologist, in identifying cerumen, discharge, foreign body and tympanic membrane. This indicates that with a trained nurse in otologic examination, penlight is an effective screening method in examining the ear canal and the tympanic membrane for common pediatric ear problems. With otoscope as a gold standard in otologic examination, a penlight has a high sensitivity and specificity to detect ear findings in among Grade 1 students.

In the introduction, it discussed the importance of hearing screening and ear care in school children. It has been shown that in the developed countries, there already legislations and policies implemented that initiates and

conducts hearing screening and ear care among school children. This includes trained personnels and appropriate devices, that are readily available. In the Philippines, the use of penlight was introduced in the study of Gloria-Cruz, et al., where they have showed that there is a good agreement between the nurses' penlight examination and the otolaryngologists' otoscopic examination. However, the study did not achieve the ideal sample size to be able to state a more statistical generalization. In this study, it yielded an excellent agreement in the two modes of examination. The lack of inter-observer variability between nurses and a more focused set of subjects may have contributed to a more superior result in this study. The agreement between otoscopy and penlight in examining the ear canal in terms of identifying cerumen, whether it is retained or impacted, were both statistically significant in both studies, however, no foreign body were noted on the former. The agreement in visualizing the tympanic membrane also has a significant outcome, in terms of normal ear canal and retained cerumen with intact tympanic membrane. Non-visualized tympanic membrane findings are consistent with findings of impacted cerumen.

A comprehensive literature search did not show any studies about the accuracy of using a penlight in otologic examination. In this study, the penlight has 98.6% sensitivity in detecting an abnormal finding in the otologic examination. However, it is only limited in identifying the presence of cerumen, foreign body, discharge and non-visualized tympanic membrane. In patients with normal findings, the penlight has 100% specificity that is limited in determining unremarkable findings of the ear canal and identifying an intact tympanic membrane. However, among the subjects, none were identified to have a perforated tympanic membrane that may tell if it can be identified using a penlight.

As part of the hearing screening program for school children, the examination of the ear must be readily available. The study expected that the nurse is equipped with the knowledge and the skill in otologic examination. With an overall accuracy of 98.94%, the penlight, in comparable to an otoscope, is a good screening tool in examining the ear canal and tympanic membrane. This maybe beneficial to those areas such as barangay health center, school clinics and such, that has limited budget in acquiring an otoscope; since a penlight is cheap, readily available and easy to use.

The study is limited in examining the ear canal in identifying the presence of cerumen, foreign body and discharge. Since none of the subjects had a finding of perforated tympanic membrane, the study was limited in visualizing the tympanic membrane and identifying if it is intact. Also, the subject population consists only of Grade 1 students with a median age of 6 (range 5-10) years. Thus far, the conclusion of may be limited to the study population studied. With these limitations, it is recommended to conduct further study in identifying perforated tympanic membrane using penlight. It is also important to determine the youngest age that will permit screening with a penlight, as well as the possibility of training the teachers in areas where there are lack of nurses.

CONCLUSION

The study showed that there is an excellent agreement between the nurse's findings and otolaryngologist's findings in examining the ear canal and tympanic membrane. The penlight has on overall accuracy of 98.94%, in identifying cerumen, discharge, foreign body and visualizing the tympanic membrane. Thus, this study shows that a trained nurse in otologic examination may use the penlight effectively as a screening tool in identifying common ear problem among Grade 1 students.

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THE EFFICACY OF SINGLE DOSE INTRAVENOUS DEXAMETHASONE vs PLACEBO COMBINED WITH CAUDAL BLOCK ON POSTOPERATIVE ANALGESIA IN CHILDREN UNDERGOING OUTPATIENT UROLOGIC SURGERY: A PROSPECTIVE, DOUBLE-BLIND, RANDOMIZEDSTUDY

SHEILA BIANCA M. SANTY, MD, MARICHU D. BATTAD, MD, JANETTE F. PASCUAL, MD

ABSTRACT

BACKGROUND: Pain in the pediatric age is more difficult to assess and treat. Inadequate pain management may produce anxiety and trauma in children and affect not only the surgical outcome but the child's overall quality of life and recovery. Advances in various perioperative techniques to provide optimal analgesia continually grow especially in the outpatient setting where there are a significant number of pediatric patients. Caudal block is easy to perform and can be used in combination with general anesthesia. It provides excellent analgesia but is often short-lived. Dexamethasone is a potent synthetic glucocorticoid with anti-inflammatory and anti-emetic properties. The exact mechanism for its analgesic action is said to be related to its strong anti-inflammatory action.

OBJECTIVES: The study aims to determine and compare the anxiety of children with acute lymphoblastic leukemia (ALL) and their well siblings based on Child drawing: Hospital manual and to identify factors associated with the level of anxiety.

METHODOLOGY: This is a prospective, double-blind, randomized study that included sixty-four patients, aged 3 - 12 years old, ASA I and II, scheduled for outpatient urologic surgery under combined general and regional caudal anesthesia. Patients were randomized into two groups: Group D received 0.5mg/kg (maximum of 16mg) single dose intravenous dexamethasone in 5mL volume and Group P received the same volume of saline after the start of surgery when successful caudal block was determined. Postoperative pain scores using the Wong-Baker Faces Pain Rating Scale and vital signs were monitored at the PACU at hourly intervals until discharge. The time to first rescue analgesic and the total analgesic consumption given at home for forty-eight hours were recorded.

RESULTS: Group D showed significantly longer block duration and time to rescue analgesic and lesser analgesic consumption.

CONCLUSION: A single dose intravenous dexamethasone combined with caudal block effectively prolongs duration of caudal block and time to first rescue analgesic and lessens analgesic consumption in children undergoing outpatient urologic surgery.

INTRODUCTION

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". It is a common problem encountered after surgery in the postoperative care unit (PACU) and at home after patient's discharge.

Pain in the pediatric age is more difficult to assess and treat. It has been reported that up to forty percent (40%) of children feel moderate to severe postoperative pain and in seventy five percent (75%) of patients, pain is undertreated. Inadequate pain management may produce anxiety and trauma in children and affect not only the surgical outcome but the child's overall quality of life and recovery.

Advances in various perioperative techniques to provide optimal analgesia continually grow especially in the outpatient setting where there are a significant number of pediatric patients. The use of local anesthetic would infiltration, oral or intravenous nonsteroidal anti-inflammatory drugs (NSAIDs), like acetaminophen, ibuprofen and ketorolac, and opioids all reduce postoperative pain but their use has been limited by undesirable side effects in children undergoing outpatient surgery. Side effects and toxicity of NSAIDs are mainly related to gastrointestinal and renal effects and hypersensitivity. Common side effects of opioid administration

include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression.

Regional anesthesia is also effective for postoperative pain relief and caudal block is the most widely used pediatric regional technique. It is easy to perform and can be used in combination with general anesthesia. It provides excellent analgesia but is often short-lived. Adjuncts to caudal anesthesia including dexmedetomidine and fentanyl have been tried successfully but have also been limited by undesirable effects.[i]

Dexamethasone is a potent synthetic glucocorticoid with anti-inflammatory and anti-emetic properties. It is indicated and used in various conditions, from allergic states to endocrine, gastrointestinal, hematologic, neoplastic, nervous, renal, pulmonary and rheumatic diseases. As an anti-emetic, its role in preventing postoperative nausea and vomiting (PONV) when used alone or in combination with ondansetron has already been documented though the mechanism is unclear. The exact mechanism for its analgesic action is also unclear though it is said to be related to its strong anti-inflammatory action from suppression of tissue bradykinin or nerve ending neuropeptide production, inhibition of phospholipase, alterations in lymphocytes, inhibition of cytokine expression and stabilization of the cellular membrane. A single dose administration of dexamethasone is safe while long-term consumption is associated with side effects such as increased risk of wound infection, delayed wound healing, adrenal suppression and glucose intolerance.

Dexamethasone administration has been shown in international studies to have small but significant analgesic benefit in the postoperative period because of lesser pain scores and longer block and time to rescue analgesia. Unlike other drugs used to extend analgesia among postoperative patients, dexamethasone does not produce sedation, urinary retention or vomiting. Its use for postoperative analgesia is a new area of research. Caudally administered dexamethasone has also resulted in reduced postoperative pain and effects have been found to be similar when given intravenously. This study will determine if a single dose intravenous dexamethasone combined with caudal block augment postoperative analgesia in children undergoing outpatient urologic surgery.

The management of postoperative pain in children is an essential but challenging task. The mainstay of treatment is still pharmacotherapy. Studies on the potential analgesic property of dexamethasone are limited and inconsistent. There is no available data locally and no consensus on its routine use especially in children. The results of this study will largely benefit our patient population in terms of rendering them pain free for an extended period of time. Adequate analgesia will improve recovery and will have an impact on patient and parental satisfaction. It will also reduce costs and length of hospital stay.

OBJECTIVES OF THE STUDY

General Objective

To determine the efficacy of single dose intravenous dexamethasone vs placebo combined with caudal block on postoperative analgesia in children 3 – 12 years old undergoing outpatient urologic surgery in the Philippine Children's Medical Center from July 2017 to May 2018.

Specific Objectives

1. To determine if there is a reduction in postoperative pain scores in children 3 - 12 years old undergoing outpatient urologic surgery given single dose intravenous dexamethasone vs placebo using the Wong-Baker Faces Pain Rating Scale

2. To determine the duration of caudal block in children 3 - 12 years old undergoing outpatient urologic surgery given single dose intravenous dexamethasone vs placebo

3. To determine the time to first dose of rescue analgesic in children 3 – 12 years old undergoing outpatient urologic surgery given single dose intravenous dexamethasone vs placebo

4. To determine total analgesic consumption in children 3 - 12 years old undergoing outpatient urologic surgery given single dose intravenous dexamethasone vs placebo

METHODOLOGY

The research protocol was presented to the Division of Pediatric Anesthesia and Institutional Review Board (IRB) by the investigator and a written approval to conduct the research was secured. Sixty-four patients, aged 3 - 12 years old, ASA I and II, scheduled

for outpatient urologic surgery under combined general and regional caudal anesthesia were included in this prospective, double-blind, randomized study. Patients with contraindications to regional anesthesia, allergies to any medications used in the study and failed caudal blocks were excluded. Patients who develop complications intraoperatively and require admission were managed and treated accordingly and were also excluded from the study.

A preoperative evaluation of subjects was done and detailed informed consent/assent forms and ASA fasting guidelines were provided to all patients. The investigator presented the study by using language appropriate for laymen.

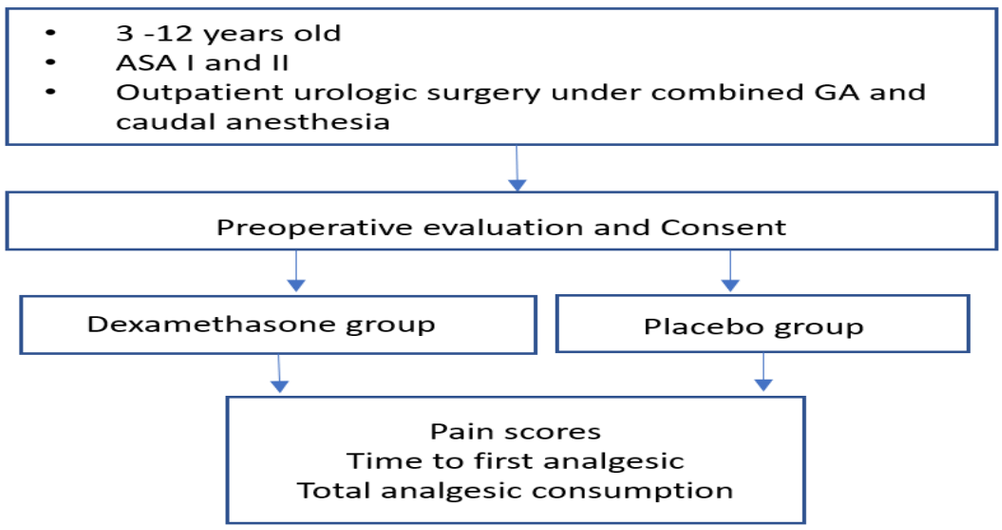
Subjects were randomly assigned to either Dexamethasone (D) group or Placebo (P) group using computer-generated random numbers. Randomization was done by an anesthesiologist who is not participating in the study. Treatment assignment were placed in sealed envelopes and were opened by another anesthesiologist who handled the case. He/She prepared and administered the drugs according to allocation. The patients and primary investigator were blinded to the allocation.

Standard monitoring was applied once the patient arrived in the operating theater. All patients were induced with Sevoflurane 6% in 100% oxygen by face mask. Venoclysis with normal saline solution was started once a patent line was placed and patients received intravenous Atropine 0.01-0.02 mg/kg and Fentanyl 2ug/kg. Anesthesia was maintained with Sevoflurane adjusted according to clinical signs (arterial pressure or heart rate within 20% of baseline), by face mask or an appropriately sized laryngeal mask airway (LMA). A caudal block was then performed in the left lateral decubitus position, using a 5cm, short-beveled, Gauge 23 needle. Bupivacaine 0.2% (1mL/kg, maximum of 20mL) was injected after identification of the right space. Surgery was allowed to begin ten minutes after performing the caudal block. Once surgery has started and a successful caudal block was determined, patients in Group D received 0.5mg/kg (maximum of 16mg)[ii] single dose intravenous dexamethasone in 5mL volume and patients in Group P received the same volume of saline. During surgery, electrocardiogram, heart rate and pulse oximetry were continuously evaluated and non-invasive blood pressure determined every five minutes. At the end of surgery, 100% oxygen was given and patients were extubated.

Postoperatively, patients were transferred to the PACU where their vital signs and pain scores using the Wong-Baker Faces Pain Rating Scale were monitored by a nurse blinded to the study, at hourly intervals until discharge. Emergency drugs and equipment were available at the PACU: Ephedrine 5 mg or fluid bolus of 10-20mL/kg for hypotension, Atropine 0.02mg/kg for bradycardia, patient and airway repositioning with oxygen support via face mask or ambubag for oxygen desaturation, Metoclopramide 0.2 mg/kg for nausea and vomiting, effective warming and documentation of temperature for shivering and oral Paracetamol 15mg/kg for pain.

A patient with a score of nine and above (≥9) on the Post-Anesthesia Discharge Scoring System were discharged. The primary caregivers and children were taught the Wong-Baker Faces Pain Rating scale prior to discharge. The investigator provided a written discharge instruction that was uniform for all patients. The primary caregiver was provided a form to record for forty-eight (48) hours the time and the pain score when their child complains of pain, the time the first rescue analgesic was given, and the total analgesic consumption given at home. Oral paracetamol15mg/kg was the take home analgesic. The investigator gathered the data collection forms on follow up of the child at the Surgery outpatient department two weeks after surgery.

Figure 1. Methodology Algorithm



Sample size was computed using G*Power 3.1. Using results from the study of Arbi et. al. wherein pain scores of children assessed using the Wong-Baker Faces Scale showed that pain scale in patients given intravenous dexamethasone have mean pain score of 1.9±2.0, whereas those given placebo have mean pain score of 3.5±2.2, a total sample size of sixty-four patients (32 per group) with 10% allowance for dropouts will be included in the study to achieve 80% power and two-sided 5% level of significance.

The investigator monitored the following data:

1. Demographics and intraoperative characteristics
2. Postoperative pain score using the Wong Baker Faces Pain Rating Scale
3. Time to first dose of rescue analgesic
4. Total analgesic consumption

Pain scores, time to first rescue analgesic and total analgesic consumption were recorded in the PACU, and in day 1 and day 2 postoperatively at home. Each primary caregiver was given instructions to lessen the risk of unnecessary confusion or mistakes. Data collected are presented in Tables 1 and 2.

For this study, mean and standard deviation were used to summarize the Wong-Baker Faces Pain Rating scale scores between patients given single dose intravenous dexamethasone and placebo. Mann-Whitney Test was used to compare the two groups, while Friedman test was used to determine if there is a significant reduction in each group. Meanwhile, mean and standard deviation was also used to summarize the time to first dose of rescue analgesic in patients given single dose intravenous dexamethasone and placebo group. Independent t-test was used to compare the two groups. For categorical data, such as gender and ASA classification, Fisher's exact test was used to compare the two groups. Statistical tests were performed using SPSS version 20, under 5% level of significance.

The study was conducted to determine the efficacy of single dose intravenous dexamethasone vs placebo combined with caudal block on postoperative analgesia in sixty-four children, aged 3-12 years old, undergoing outpatient urologic surgery in the Philippine Children's Medical Center from July 2017 – May 2018. The study only used a single intravenous dose of dexamethasone and utilized data gathered by the caregiver for forty-eight hours. The investigator did not evaluate potential adverse effects of dexamethasone that will require laboratory testing.

The research underwent approval from the Ethics Committee - Institutional Review Board of the Philippine Children's Medical Center. Written consent/assent forms were obtained and participation in the study was purely voluntary and without financial compensation. Patient data and information, and interventions and results were kept with utmost confidentiality and anonymity.

An adverse reaction that developed in one patient postoperatively was reported and recorded accordingly. The patient had an exacerbation of asthma and was treated with appropriate medications without delay and withdrawn from the study.

RESULTS

A total of sixty-four patients were recruited to the study but two were excluded. One had an asthmatic attack postoperatively and one was lost to follow up so data from sixty-two patients were analyzed. Mean age is 5.27 years (range, 3 to 12), composed of 46 (74.2%) males and 16 (25.8%) females. Mean weight is 19.92 Kg (range, 10 to 47.5). Most of them are classified as 1 in the ASA classification scale, with 51 (82.3%) patients and only 11 (17.7%) are in ASA II. The mean duration of surgery is 47.26 minutes (range, 5 to 149). Demographics and intraoperative characteristics of the two groups did not significantly differ.

Table 1. Demographics and Intraoperative Characteristics

	Treatment Group		*p*-value
	Dexamethasone	Placebo	
Number of Patients	31	31	
Age (years)	4.84 ± 2.21	5.71 ± 2.66	0.166
Gender: Male	20 (64.5%)	26 (83.9%)	0.146
ASA Classification: I	26 (83.9%)	25 (80.6%)	1.000
II	5 (16.1%)	6 (19.4%)	
Weight (Kg)	18.14 ± 6.79	21.70 ± 9.09	0.085
Duration of Surgery (mins)	42.87 ± 33.10	51.65 ± 30.81	0.284

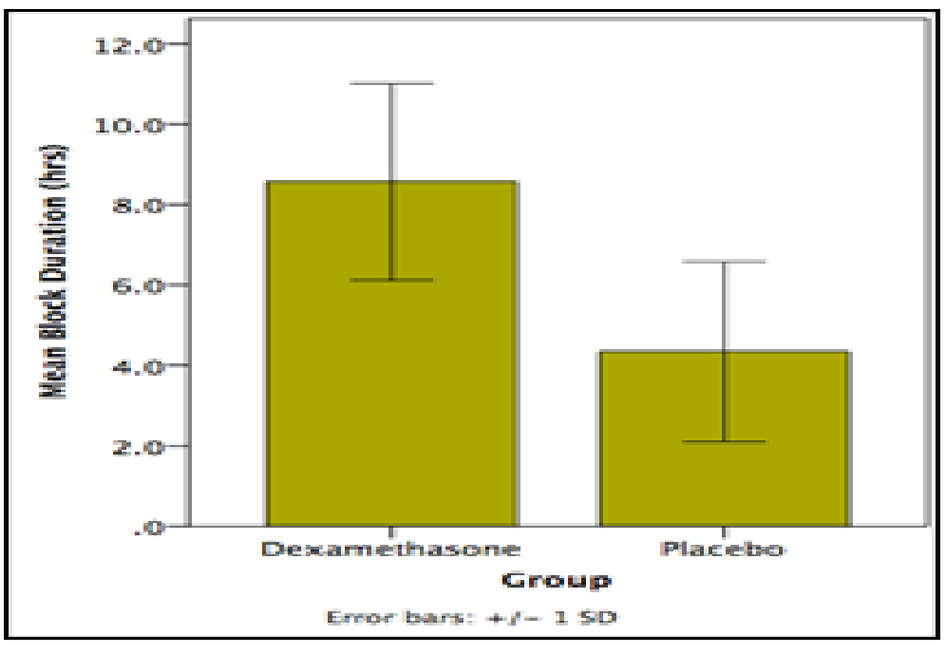
Values expressed as mean ± SD.

Table 2. Block Duration, Length of Time to First Rescue Analgesic, Total Analgesic Consumption and Pain Scores

	Treatment Group		
	Dexamethasone	**Placebo**	***p*-value**
Block Duration (hours)	8.57 ± 2.45	4.34 ± 2.24	<0.001
Time to First Rescue Analgesic (hours)	8.88 ± 2.01	4.50 ± 2.20	<0.001
Total Analgesic Consumption	0.39 ± 0.56	3.26 ± 1.15	<0.001
Pain scores	0.57 ± 2.79	2.17 ± 2.79	<0.001

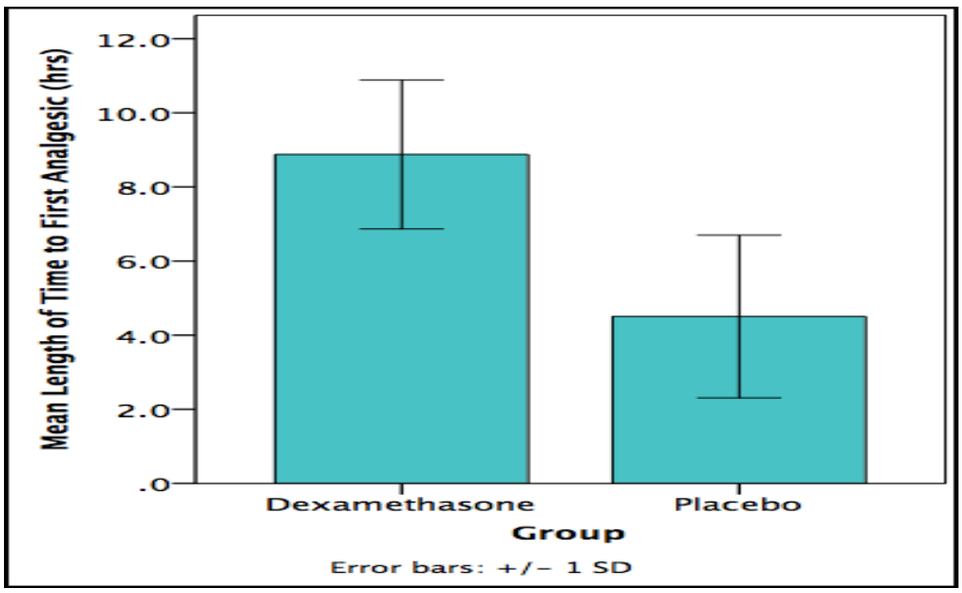
Values expressed as mean ± SD.

Figure 3. Mean Block Duration



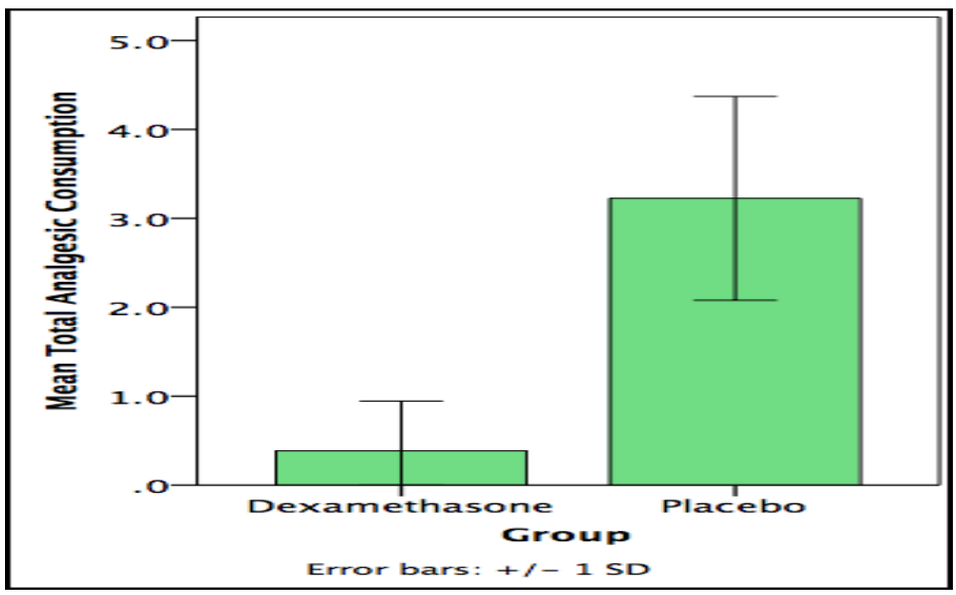
There was no failure of caudal blocks noted in any of the patients. It is evident that the mean duration of analgesia (block duration) of patients treated with dexamethasone is significantly higher (p<0.001) than the placebo group. This shows that the duration of analgesia of patients treated with dexamethasone is longer by 4.23 hours [$CI_{95\%}$: 3.02 to 5.41].

Figure 4. Mean Length of Time to First Analgesic



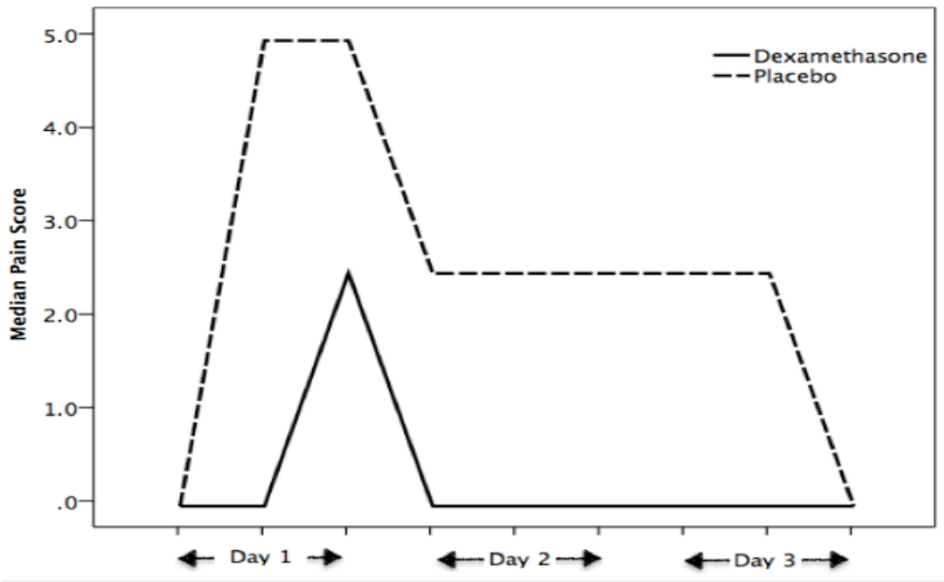
None of the children in both groups needed rescue Paracetamol in the PACU. Thirty-one (31) patients in the placebo group, while 11 patients treated with dexamethasone had been given Paracetamol. It was evident that among the patients, the mean length of time to first rescue analgesic of patients treated with dexamethasone is significantly longer (p<0.001) than the placebo group, indicating that on the average, patients treated with dexamethasone had longer time to first rescue analgesic by 4.38 hours [$CI_{95\%}$: 2.85 to 5.90].

Figure 5. Mean Total Analgesic Consumption



Moreover, patients treated with dexamethasone had significantly less (p<0.001) mean number of total analgesic consumption versus the placebo group, which shows that at an average, the number of total analgesic consumed by those treated with dexamethasone is less by 2.85 [$CI_{95\%}$: 2.38 to 3.30].

Figure 6. Median Pain Scores



It was also evident that the pain scores of both groups significantly increased on day 1 (p<0.001) and decreased until day 3 (p<0.001). But overall, the pain score of patients treated with dexamethasone is significantly less (p<0.001) than patients in the placebo group.

DISCUSSION

The study demonstrated that the use of single dose intravenous dexamethasone (0.5mg/kg) with caudal block prolonged block duration and time to first rescue analgesic and decreased postoperative pain and total analgesic consumption, compared with caudal block alone. This finding is comparable to the studies done by Bangash, Arbi and Hong et. al. which also reported prolonged postoperative pain relief in patients given dexamethasone in combination with caudal block. In the study by Bangash et al. mean duration of analgesia was ten hours. Patients who were given dexamethasone along with caudal block were rendered pain free for a longer period of time than those who received caudal block alone. In the study by Hong et al., the incidence of rescue fentanyl and acetaminophen was significantly lower in children who received dexamethasone compared to those who received placebo. Pain scores were lower and the time to giving of first analgesic was also significantly longer. In the study by Arbi et al., pain scores were less, there is prolonged time to first rescue analgesia, and less frequent Paracetamol administration among patients in the dexamethasone group than in the placebo group.

The proposed mechanism of prolonged pain relief demonstrated in the studies is the powerful inflammatory and long duration of action of dexamethasone. The analgesic mechanism is not yet fully understood but is believed to be because of inhibition of synthesis of the cyclooxygenase isoform-2 in peripheral tissues and in the central nervous system resulting in reduction in prostaglandin production. Another possible mechanism is abolishment or suppression of inflammatory cytokine release with its subsequent nociceptive effects. Dexamethasone does not cause sedation, vomiting or urinary retention rather it has anti-emetic property and has been used for prevention of postoperative nausea and vomiting. This property is via prostaglandin antagonism, serotonin inhibition in the gut and release of endorphins. In the study, none of the patients had nausea and vomiting and there was no incidence of systemic complications such as hypotension, bradycardia and respiratory depression.

CONCLUSION AND RECOMMENDATIONS

In conclusion, a single dose intravenous dexamethasone in combination with caudal block effectively prolongs block duration thus reducing postoperative pain, prolongs time to first analgesic and lessens analgesic requirement.

Further investigations are warranted to determine the optimal dexamethasone dose associated with the longest duration of analgesia. The study was just limited to forty-eight hours and the primary caregiver was the only assessor of pain and maybe subject to bias. Studies on the efficacy of dexamethasone for other types of surgical procedures is also recommended.

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