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Welcome to the first issue of The PCMC Journal during these pandemic times!

As before, the articles chosen for this issue are those which won during the residents and fellows research for a during the past year. The great disruptions to work and hospital operations during this year have been the main reason for the delay in coming out with this first issue.

As always, too, we try to look at the silver lining behind the great gray cloud of COVID. And it is that during this pause we were able to organize important research activities such as a manuscript writing workshop given by no less than the president of the Philippine Association of Medical Journal Editors, Dr. Jose Lapena, and a meta-analysis workshop. Hopefully these will help prepare us to be better equipped for our future research endeavors given our new realities.

Here's to a more productive rest of 2020!

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CONTENTS

PSYCHOSOCIAL SCREENING USING PEDIATRIC SYMPTOM CHECKLIST IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

WILMA N. DE LEON, MARIA EVA I. JOPSON, MARILOU ABIERA

ABSTRACT

BACKGROUND: Leukemia is the most common malignant neoplasm in childhood, with Acute Lymphoblastic Leukemia (ALL) comprising 71% of cases. Patients undergo intensive course of treatment and complications, making them at risk for psychosocial difficulties. The Pediatric Symptom Checklist (PSC) is a validated psychosocial screening tool for the identification of emotional, cognitive, and behavioral problems in children. It uses subscales to identify impairments in attention, internalizing, and externalizing behaviors.

OBJECTIVE: To screen the psychosocial status of pediatric patients with ALL using the PSC. It aimed to correlate a positive PSC score with factors such age, gender, and on-going chemotherapy.

METHODS: The study design is cross-sectional. Participants were asked to answer the PSC which is a 35-item questionnaire. Total scores were calculated and interpreted based on set cut-off scores.

RESULTS: A total of 87 patients with ALL were included in the study. The PSC was able to identify 16 patients (18%) with psychosocial problems. The patients had concerns related to the internalizing subscale, followed by attention and externalizing subscales. There was no association between age, sex, duration of diagnosis, and on-going chemotherapy with the presence of psychosocial issues in patients with ALL.

CONCLUSIONS: In this study, the prevalence of psychosocial issues in patients with ALL is 16%. Screening patients using the PSC can help in the early detection of psychosocial issues among children with ALL.

RECOMMENDATIONS: A separate study which focuses on both patients and families' psychosocial status is recommended to get an overall picture of the effect of cancer and its treatment. Screening in several points during the course chemotherapy can also be done in future studies.

KEYWORDS: Acute Lymphoblastic Leukemia; Psychosocial screening; Pediatric Symptom Checklist

INTRODUCTION

Mental health includes emotional, psychological, and social well-being that is important in every stage of life, from childhood, adolescence, and through adulthood.[1] Worldwide, 10-20% of children and adolescents experience mental disorders with half of the cases begins by the age of 14. [2]

Children with chronic conditions have a greater risk of having poor mental health and developing a psychological comorbidity compared to those children without chronic conditions.[3] This highlights the increasing need for investigation into the effects of these conditions on life-long mental health and wellbeing.[4] Addressing mental health during clinic visits is important for all pediatric patients especially those with chronic conditions.[3]

Leukemia is the most common malignant neoplasm in childhood accounting for approximately 31% of all malignancies that occur in children younger than 15 years of age. Acute Lymphoblastic Leukemia (ALL) comprised 71% of these cases,[5] and in Metro Manila, ALL comprised 65% of all leukemias among children ages 0-14 years old.[6] Despite the improved survival rates, cancer still remains to be a life-threatening condition with major impact not only on the lives of the child but also the entire family.[7] Upon diagnosis of leukemia, pediatric patients and their families goes through an often lengthy, stressful, and intensive course of treatment as well as complications, making them at increased risk for new or exacerbated psychosocial difficulties.[8]

The American Academy of Pediatrics (AAP) Task Force on Mental Health provides guidance and tools to aid screening and identification of mental health issues in primary care practice. There are different screening tools to detect common psychosocial problems. The Pediatric Symptom Checklist (PSC), developed by Jellinek and Murphy (1986), is a validated psychosocial screening tool that aids in the identification of emotional, cognitive, and behavioral problems in children.[10,11,12,13] Factor analysis of the PSC has led to the validation of three subscales for use in the identification of attention, internalizing and externalizing problems. [31]

At present, there are only two studies that screen patients with chronic illness for psychological dysfunction using the PSC. One of these studies revealed that PSC had adequate sensitivity and specificity when applied to pediatric neurology patients compared to a lengthier Child Behavior Checklist (CBCL) in identifying patients with psychological issues.[15] Stoppelbein used PSC in patients with insulin-dependent diabetes mellitus and sickle cell disease. This supports the empirical use of the PSC in screening patients for psychosocial dysfunction in a tertiary care pediatric setting. No similar studies, however, has been done locally or abroad on ALL patients. This study utilized the PSC to patients with ALL in a tertiary care setting in order to identify possible psychosocial and mental health issues among this population.

Significance of the Study

The use of PSC, although not diagnostic, can be a useful tool for pediatricians in the early detection of psychosocial and behavioral problems in patients with chronic illnesses such as ALL. If left unaddressed, such problems may worsen the child's medical condition as well as the disease management in general, further compromising their quality of life. Early detection will lead to an early referral to a specialist for further psychiatric or psychological assessment. Initiation of early intervention for such psychosocial problems can improve not only the patients' mental health status but also their families. It can also reduce financial burden caused by medical complications brought about and exacerbated by these problems. The use of subscales can assist pediatricians on which domains or subscales to focus on to identify what psychosocial disorders affect patients with ALL. This will be of benefit to psychologists and psychiatrists to guide them in their assessment and interventions.

OBJECTIVES OF THE STUDY

General Objective

This study aimed to screen the psychosocial status of pediatric patients with Acute Lymphoblastic Leukemia using Pediatric Symptom Checklist.

Specific Objectives

Specifically, the study aimed to:

1. Determine the prevalence of psychosocial issues among patients with ALL using PSC.
2. Identify in what subscales the subjects scored highest.
3. Identify whether factors such age, gender, and an on-going chemotherapy, are associated with positive PSC.

MATERIALS AND METHODS

The research design of this study is cross-sectional. The study included primary caregivers of patients with ALL. Convenience samplings was used in choosing eligible subjects and were screened based on the following inclusion criteria:

- Caring for patients diagnosed with ALL of:
    - Any subtype and stage
    - Ages 3 to 17 years
    - May or may not be undergoing chemotherapy at the time of the study
    - Being seen at the outpatient department (pay or service) or admitted in the ward
- May be a parent or non-parent
- Should be with the patient most days of the week (at least 5 days a week) both at home or in the hospital
- Responsible for taking care of the patient's basic needs, physical health, and emotional well-being for at least 6 months

Caregivers of patients diagnosed with psychiatric disorders and neurodevelopmental delay were excluded in the study.

The research protocol was submitted for review and approval of the Institutional Review – Ethics Committee (IR-EC) and commenced only upon final approval from the board. Primary caregivers of admitted and outpatients diagnosed with ALL seen at the Cancer and Hematology Center of a tertiary government hospital were recruited and screened for eligibility based on the set inclusion criteria. A written consent was then secured from all the participants who agreed to be part of the study.

The PSC was administered in a private cubicle in the outpatient department of the Cancer and Hematology department to provide privacy to the participants while answering the questionnaires. The participants were asked to answer the PSC. This is a validated screening tool widely used in research and clinical settings to help identify children with psychosocial issues. It has been translated and validated in multiple languages and all forms are available online for free. The Filipino version was downloaded from the website: *http://www.massgeneral.org/psychiatry/services/psc_home.aspx* and was used in this study. It took only 5 to 10 minutes to complete the questionnaire. The PSC – Filipino version which consists of 35 items that are rated as "*Hindi* (Never)", "*Paminsan-minsan* (Sometime)" or "*Madalas* (Often)" were scored 0, 1, and 2, respectively. The total score was calculated by adding together the score for each 35 individual items, with a total score ranging from 0 to 70. If one to three items are left blank, a score of 0 is given. If four or more items are left black, the questionnaire was considered invalid.

The total score indicates whether a child has impairment in psychosocial functioning. For children and adolescents ages 6 through 17, a cutoff score of 28 or higher indicates psychological impairment. For children ages 3 to 5 and those who are not attending school, score on elementary school related items 5, 6, 17, and 18 were ignored and the total score was based on the remaining 31 items. The cutoff score for this group was 24 or higher. The result for each subscale was interpreted as follows:

- A score of greater or equal to 7 in the attention subscales signified impairment in attention.
- A score of greater or equal to 5 in the internalizing subscale signified impairment with anxiety or depression.
- A score of greater than or equal to 7 in the externalizing subscale signified impairments with conduct.

A positive score on the PSC suggests the need for further evaluation by a qualified health or mental health professional. Patient characteristics were summarized using frequencies and proportion. PSC and subscale scores were determined for each patient and summarized using mean and standard deviation. The rates of positive screening in the PSC and each subscale were also computed. Simple and multiple logistic regression analysis were done to determine which patient characteristic was associated with positive screening in the PSC. The significance level was set at 95% and all analyses were done using STATA14.

The study was started only upon approval by the IR-EC. The entirety of the study was explained to the parent/ guardian participants. These include the significance of the study, the procedure, the benefits, and the confidentiality. Participating in the study was voluntary and the parents/ guardians were enrolled in the study only when they consented. Answering of the questionnaires was at the convenience of the parents/ guardians, and of the patients to make sure that the study did not interfere with the patients' treatment or consultation. All private patients who participated in the study were included upon the approval of their attending physicians. The participants were given the option to withdraw from the study at any given point in time. Upon withdrawal, his/her input was not counted as valid and participation was completely terminated. Whatever information that has been gathered during the period of participation was kept confidential.

Participation in the study was completely free of charge and no monetary compensation was given for participation. Whatever information gathered from the participants was used solely for the purpose of the study and for advancement in health education and counseling.

The primary investigator, research assistant, and encoder were the only ones who had access to the gathered data. All documents including the questionnaires answered by the subjects was kept in a secured box labeled as confidential and was stored in the office of the Cancer and Hematology Center. All documents will be shredded and disposed two months after the completion of the final paper.

All patients who scored positive for mental health issues were identified including drop outs. The results of the screening test were discussed to the participants and their doctors. The importance of further evaluation for psychiatric disorders and the need for a psychiatric consult were explained. We coordinated with the Child Neuroscience Center to facilitate referral of patients who screened positive with PSC for further assessment and management.

RESULTS

Eighty-seven (87) patients with ALL were included in the study. The patients age ranged from 3-17 years with a mean age (± standard deviation) 7.43 ± 3.56 years. There are more males (65.5%) than females (34.5%). The mean duration of diagnosis (± standard deviation) was 21.98 ± 19.31 months. Sixty-eight or 78.2% of the children are not attending school.

Table 1 shows the chemotherapy status of the children. Majority or 90.8% of the patients included in the study are receiving chemotherapy. Of the 79 patients with on-going chemotherapy, 31% are on induction phase, 17.3% on consolidation phase, and 42.5 % are on maintenance phase.

Table 1. CHEMOTHERAPY STATUS OF ALL PATIENTS IN THE STUDY

Status	Frequency	Percentage (%)
With Chemotherapy	**79**	**90.8**
Induction Phase	27	31.0
Consolidation Phase	15	17.3
Maintenance Phase	37	42.5
Without Chemotherapy	**8**	**9.2**
TOTAL	**87**	**100**

Nineteen or 22% of the parent/ guardian participants of the study have the perception that their child has some form of psychosocial problem. Of these, 16 or 18% of the patients perceived to have a psychosocial problem, truly screened positive with the PSC (Figure 1). All the patients who screened positive with PSC were also perceived by their parents/ guardians to have a psychosocial problem.

A patient with a positive score was interpreted as having psychosocial issues. The highest score recorded was 39, obtained from one patient. Seven or 43.8% are females and nine or 56.3% are males. Of the 16 patients with psychosocial issues, 15 are on chemotherapy.

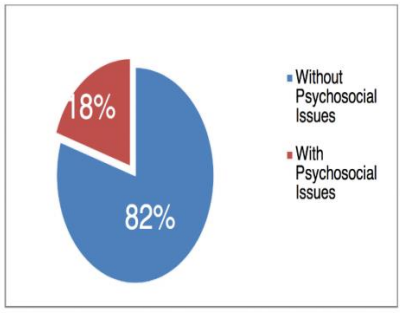


Figure 1. Proportion of ALL Patients With and Without Psychosocial Issues by PSC

A total of 16 (18%) patients with ALL scored positive with PSC. Positive score was interpreted as having psychosocial issues. Of these 16 patients who scored positive, only eight patients had positive subscale scores. Internalizing subscale screens for depression and anxiety while externalizing subscale screens for conduct disorder, oppositional defiant disorder, and rage disorder among others. Attention subscale, on the other hand, requires evaluation for Attention Deficit/Hyperactivity Disorder (ADHD).[14]

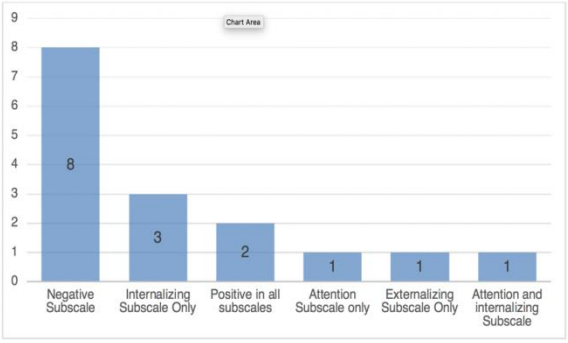


Figure 2. Distribution of ALL Patients with Psychosocial Issues Based on Subscales

Two patients scored positive in all three subscales, one patient scored positive for both attention and externalizing subscales, one patient scored positive for both attention and internalizing subscales, three patients scored positive to internalizing subscales only, and one patient scored positive to attention subscale only (Figure 2). The remaining 8 patients did not score positive in any of the three subscales. Internalizing subscale has thegreatest number of patients who scored positive followed by attention subscale, and externalizing subscale.

Table 2 shows the mean and median PSC subscale scores of the patients in the study. The internalizing impairment subscale is the highest mean score followed

by attention impairment. The externalizing impairment subscale is the lowest at 1.53. The six patients identified to have internalizing impairments were diagnosed to have ALL and ranged from 6 to 33 months from time of diagnosis.

Table 2. The PSC Subscale Scores Among ALL Patients

Subscale	Mean Score	Median Score
Internalizing	**2.72** ± 2.41	2.00
Impairment	**2.46** ± 2.06	2.00
Attention Impairment		
Externalizing Impairment	**1.53** ± 1.63	1.00

Using logistic regression, a p-value <0.05 is considered to have to have a significant association between patient's characteristics and the presence of psychosocial issues. Based on the analysis of data, there was no association between age, sex, duration of diagnosis, and on-going chemotherapy with a positive PSC score as seen in Table 3.

Table 3. Association of Age, Gender, and Chemotherapy status with Presence of Psychosocial Issues.

Factors	Psychosocial Issues		Odds Ratio	CI	p value
	Present	Absent			
Mean Age (years)	8.13	7.27	1.063	0.915 – 1.235	0.423
Sex					
Female	7.0 (43.8)	23.0 (32.4)	1.781	0.567 – 5.596	0.323
Male	9.0 (56.3)	48.0 (67.6)			
Mean Duration of Diagnosis	18.25	22.82	0.987	0.956 – 1.018	0.394
Chemotherapy status					
With chemotherapy	15.0 (93.8)	64.0 (67.6)	0.499	0.053 – 4.707	0.543
Without chemotherapy	1.0 (6.3)	7.0 (32.4)			

DISCUSSION

One of themajor tasks of childhood involves achieving healthy development and functioning in physical, cognitive, emotional, and psychosocial domains. Studies have shown that childhood chronic illness, including childhood malignancies like leukemia, can impair psychosocial functioning and development.[45]There have been inconsistent findings with regard to psychosocial impairments in patients with cancer in general. One study showed that most patients with leukemia suffered from significant psychiatric morbidity – with older age, female gender, and parental psychopathology as risk factors.[27]Another study showed that children in remission from ALL have on average significantly more problems regarding mental health and psychosocial adjustment as compared with health controls.[46]These two studies however are in contrast with another study by Nazari et al wherein behavioural problems among the ALL cases are significantly less frequent than the healthy peers.[47] In the present study, no comparison was done between patients with ALL and healthy peers. However, this is the first study that measured the prevalence of psychosocial issues among patients with ALL in a tertiary government hospital in the Philippines. A prevalence of 16% among the participants showed that screening might play a role in identifying psychosocial issues in patients with ALL. Using a simple validated screening tool like the PSC can help clinicians in identifying patients who are at risk.

Studies on the externalizing impairments among children with cancer have also been inconsistent. Some studies concluded that significant numbers of children have behavioral problems in the childhood cancer population as compared with healthy controls and that they have higher risks for displaying behavioral difficulties.[50] These findings were not consistent with one study done by Michalowski et al, wherein they compared the emotional and behavioral symptoms in three groups: a) children with acute leukemia; b) children with blood dyscrasia; and c) children evaluated or treated in a pediatric outpatient service. In this cross–sectional study, children with leukemia did not differ from the two other groups regarding symptoms of externalization. [51]

There are few studies that correlate attention problems with cancer. One of these studies, reported on longitudinal change in neurocognitive function and predictors of neurocognitive outcomes 2 years after completing therapy for ALL. The results showed that survivors of childhood ALL remain at elevated risk for attention problems that impact real-world functioning.[52]Of those who screened positive using PSC, 5 patients had impairment in either externalizing or attention subscales. All these patients who screened positive for PSC will require further evaluation and management by a child psychologists or psychiatrist. With the use of PSC subscales, certain psychosocial impairments were identified, and these can assist in the evaluation of these patients. However, a bigger study using PSC in conjunction with other validated psychosocial tools may produce a more sensitive and accurate assessment.

We also noted the association of positive PSC with age, sex, duration of diagnosis, and on-going chemotherapy in this study. The nature of the onset and course of the illness, the potential fatality of the illness and the degree of incapacitation are important factors in understanding the impact of chronic illness in general. In patients with ALL, chemotherapy has a significant impact on the psychological status of both patients and their parents with high prevalence of low self-esteem in children and high degree of stress in their parents. [53]However, there was no association between on-going chemotherapy and the presence of psychosocial issues in patients with ALL. The same holds true with age, sex, and duration of diagnosis. The innate nature of Filipinos of being optimistic and resilient might be factors that aid both patients and their families in battling cancer.

CONCLUSION AND RECOMMENDATIONS

This study used the Pediatric Symptom Checklist to screen patients with Acute Lymphoblastic Leukemia in a tertiary government hospital in the Philippines. The PSC was able to identify 16% of patients with ALL to have psychosocial issues. The internalizing subscale has the highest mean score, followed by attention subscale, and externalizing subscale with the lowest mean score. There is no relationship between age, sex, duration of diagnosis, and on-going chemotherapy with the presence of psychosocial issues in patients with ALL.

Screening patients may be necessary for early detection of psychosocial issues among children with ALL.

We recommend using PSC as a screening tool in a broader population of patients with cancer – including those with other types of leukemia and tumors. Testing in several points during treatment or chemotherapy can also be done so as to better establish the role of chemotherapy in the psychosocial aspect of health of patients with cancer.Future studies which focus not only on the patients psychosocial status but as well as the parents and family psychosocial status may be necessary to get an overall picture of the effect of cancer and it's treatment in the smallest unit of the community.

BIBLIOGRAPHY

1. Learn About Mental Health - Mental Health - CDC. (n.d.). Retrieved from https://www.cdc.gov/mentalhealth/learn/index.htm

2. Mental Health. (2019, June 20). Retrieved from https://www.who.int/mental_health/en/

3. Perrin, J. M., Gnanasekaran, S., &Delahaye, J. (2012). Psychological Aspects of Chronic Health Conditions. Pediatrics in Review, 33(3), 99–109. doi:10.1542/pir.33-3-99

4. Secinti, E., Thompson, E. J., Richards, M., &Gaysina, D. (2017). Research Review: Childhood chronic physical illness and adult emotional health - a systematic review and meta-analysis. Journal of Child Psychology and Psychiatry, 58(7), 753–769. doi:10.1111/jcpp.12727

5. Roberts, Iwan. (2017). Nelson's textbook of pediatrics (20th edn.), by R. Kliegman, B. Stanton, J. St. Geme, N. Schor (eds) : Elsevier, Philadelphia, 2016,

6. Laudico AV, Mirasol-Lumague MR, Medina V, Mapua, C, Valenzuela, F, and E. Pukkala. (2015) Cancer Facts and Estimates. http://www.philcancer.org.ph/wp-content/uploads/2017/07/2015-PCS-Ca-Facts-Estimates_CAN090516.pdf

7. Turk J Haematol. (2016) Dec; 33(4): 326–330. Published online 2016 Dec 1.

8. Kazak, A. E., Brier, M., Alderfer, M. A., Reilly, A., Fooks Parker, S., Rogerwick, S., … Barakat, L. P. (2012). *Screening for psychosocial risk in pediatric cancer. Pediatric Blood & Cancer, 59(5), 822–827.*

9. American Academy of Pediatrics (AAP) Task Force on Mental Health

10. Jellinek MS, Murphy JM, Burns BJ. (1986). Brief psychosocial screening in outpatient pediatric practice. J Pediatr. 1986;109:371-378.

11. Jellinek MS, Murphy JM, Little M, et al.(1999). Use of the Pediatric Symptom Checklist to Screen for Psychosocial Problems in Pediatric Primary Care (A National Feasibility Study). Arch PediatrAdolesc Med. 1999;153:254-260.

12. Jellinek MS, Murphy JM, Robinson J, et al. (1988). Pediatric Symptom Checklist: Screening school-age children for psychosocial dysfunction. J Pediatr. 1988;112(2):201-209

13. Murphy JM, Ichinose C, Hicks RC, et al. (1996). Utility of the Pediatric Symptom Checklist as a psychosocial screen to meet the federal Early and Periodic Screening Diagnosis and Treatment Standards: a pilot study. J Pediatr. 1996;129:864-869.

14. Gardner W. The PSC-17: (1999). A brief pediatric symptom checklist psychosocial problem subscales: A report from PROS and ASPN. Ambulatory Child Health. 1999;5:225-236

15. Anderson DL, Spratt EG, Macias MM, Jellinek MS, Murphy JM, Pagano M, Griesemer DA, Holden KR, Barbosa E. (1999). Use of the pediatric symptom checklist in the pediatric neurology population. PediatrNeurol. 1999 Feb;20(2):116

16. Stoppelbein, L et al. (2005). *Factor Analysis of the Pediatric Symptom Checklist with a Chronically Ill Pediatric Population.* Journal of Developmental & Behavioral Pediatrics, 26(5), 349–355.

17. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* 4 ed. Geneva; 2008

18. Chan, K.W. (2002). Acute lymphoblastic leukemia. CurrProblPediatrAdolesc Health Care 32:40-4

19. Laudico AV, Esteban DB, Tabafunda TM. (1998). Philippines, Manila and Rizal Cancer Registry, 1983-1992. In: International Incidence of Childhood Cancer, vol II, IARC Scientific Publications No. 144, ed. Parkin DM, Kramarova E, Draper GJ et al, 211-215. Lyon: IARC Press

20. Pui CH, Mullighan CG, Evans WE, Relling MV. (2012). *Pediatric acute lymphoblastic leukemia: where are we going and how do we get there?* Blood. 2012;120:1165–74.

21. Jeha, S., and Pui, C.H. (2009). Risk-adapted treatment of pediatric acute lymphoblastic leukemia. Hematol Oncol Clin North Am 23:973-990, v.

22. Sutherland A. M. (1956). *Psychological impact of cancer and its therapy*. Med. Clin. North Am. 40 705–720.

23. San Juan AF, Chamorro-Vina C, Mate-Munoz JL, Fernandez del Valle M, Cardona C, Hernandez M, et al. (2006). *Functional capacity of children with leukemia.* Int J Sports Med. 2008;29:163–7.

24. Caprino D, Wiley TJ, Massimo L. (2004). Childhood cancer survivors in the dark. Journal of Clinical Oncology. 2004;22:2748–50.

25. Leung W, Hudson MM, Strickland DK, Phipps S, Srivastava DK, Ribeiro RC, et

al. (2000). *Late effects of treatment in survivors of childhood acute myeloid leukemia.* Journal of Clinical Oncology. 2000;18:3273–9.

26. Schultz KA, Ness KK, Whitton J, Recklitis C, Zebrack B, Robison LL, et al. (2007). *Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study.* Journal of Clinical Oncology. 2007;25:3649–56.

27. Khalifa AS, Bishry Z, Tantawy AA, Ghanem MH, Effat SM, El Shahawy H, Ebeid FS. (2014). Hematol Oncol Stem Cell Ther. 2014 Jun;7(2):76-84. doi: 10.1016/j.hemonc.2014.01.002. Epub 2014 Mar

28. Efficace F, Novik A, Vignetti M, Mandelli F, Cleeland CS. (2007). *Health-related quality of life and symptom assessment in clinical research of patients with hematologic malignancies: where are we now and where do we go from here?* Haematologica. 2007;92:1596–1598.

29. Thabrew, H, McDowell H, Given K, Murrell, K. (2017). *Systematic Review of Screening Instruments for Psychosocial Problems in Children and Adolescents WithLongTerm Physical Conditions.* Global Pediatric Health Volume 4: 1–25

30. Murphy, J, Bergmann, P, Chiang, C, Sturner, R, Howard, B, Abel, M.,Jellinek, M. (2016). The PSC-17: Subscale Scores, Reliability, and Factor Structure in a New National Sample. Pediatrics Vol 138. No. 3

31. Massachusetts General Hospital. (n.d.). Retrieved from https://www.massgeneral.org/psychiatry/services/treatmentprograms.aspx?id=2088&display=scoring

32. Talavera-Icban A. *Utility of the Pediatric Symptom Checklist Translated in ilipino as a Screening Tool for Psychosocial Problems.* Angeles University Foundation Medical Center, Angeles City, Pampanga, Philippines, (2006). Unpublished.

33. Leiner MS, Shirsat P. (2005). *Improving Detection of Psychological Problems in a Hispanic Population Using a Pictorial Version of the PSC.* Developmental and Behavioral News. 2005;14(2).

34. Canceko-Llego, C, Castillo-Carandang, N and Rey, A. (2009). *Validation of the Pictorial Pediatric Symptom Checklist – Filipino Version for the Psychosocial Screening of Children in a Low-income Urban Community*. Acta Medica Filipina. Vol. 43 N0. 4

35. Liu J (2004). *Childhood externalizing behavior: theory and implications*. Journal of Child and Adolescent Psychiatric Nursing 17, 93–103.

36. Liu J., Chen, X., and Lewis, G. (2011). *Childhood internalizing behaviour: analysis and implications. Journal of Psychiatric and Mental Health Nursing, 18(10), 884–894.*

37. National Institute of Health. Attention Deficit Hyperactivity Disorder; 2016 Mar [cited 2017 Mar]. Available from: https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml.

38. Leiner, M. et al. (2010). *Sensitivity and specifity of the pictorial Pediatric Symptom Checklist for psychosocial problem detection in a Mexican sample.* Rev Invest Clin; 62 (6): 560-567

39. Terrone, G., et al. (2013). *The Pediatric Symptom Checklist as screening tool for neurological and psychosocial problems in a Paediatriccohorl of patients with coeliac disease.* Acta Pediatrica; 102 (7) p325-328

40. Han DH, et al. (2015). *The Korean Version of the Pediatric Symptom Checklist: Psychometric Properties in Korean School-aged Children.* J Korean Med Sci; 30 (8): 1167-74

41. Castro et al. (2016). *Utility of New Spanish RQC and PSC in Screening with CBCL Validation.* Psychiatry Q; 87 (2): 343-53

42. Rukabyarwema, et al. (2019). *Behavior Problems in Physically Ill Children in Rwanda.* Journal of Developmental and Behavioural Pediatrics. Retrieved from https://insights.ovid.com/crossref?an=00004703-900000000-99172

43. Reijneveld, SA, et al .(2006). *Use of the Pediatric Symptom Checklist for the detection of psychosocial problems in preventive child health care.* BMC Public Health. Vol 6: 197

44. Institute of Medicine (US) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting; Adler NE, Page AEK, editors. Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs. Washington (DC): National Academies Press (US); 2008. 2, Consequences of Unmet Psychosocial Needs. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK4008 September 12, 2019

45. Huff, Marlene B.; McClanahan, Kimberly K.; and Omar, Hatim A. (2010). "Chronic Illness and Mental Health Issues". Pediatrics Faculty Publications. 109.

46. Reinfjell, T., Lofstad, G.E., Nordahl, H.M., Vikan, A., &Diseth, T.TH. (2009). *Children in remission from acute lymphoblastic leukaemia: mental health, psychosocial adjustment and parental functioning. European Journal of Cancer Care, 18(4), 364–370.*

47. Nazari, S., Koupaei, M. T., Shafiee, A., Kashani, Z. H., Bahraminia, E., Ansari, M., &Alipour, A. (2014). Emotional/Behavioral problems in children with acute lymphoblastic leukemia: a case-control study. *International journal of hematology-oncology and stem cell research*, *8*(2), 14–20.

48. Leavey, P., Germann, J., Leonard, D., Stuenzi, T., LeVieux, J. & Stewart,

S.(2013). *Depression and anxiety (DA) in children within one year of a cancer diagnosis*.Journal of Clinical Oncology 2013 31:15_suppl, 10064-10064

49. Sawyer, M., Antoniou, G., Toogood, I., & Rice, M. (1997). Childhood cancer: A two- year prospective study of the psychological adjustment of children and parents. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(12), 1736-1743.

50. Olson, A.L., Boyle, W.E., Evans, M.W., & Zug, L.A. (1993). Overall function in rural childhood cancer survivors: The role of social competence and emotional health. *Clinical Pediatrics, 32*, 334-342.

51. Michalowski, Mariana &Ketzer, C &Daudt, L & Rohde, Luis. (2001). Emotional and behavioral symptoms in children with acute leukemia. Haematologica. 86. 821-6.

52. L. M. Jacola, K. R. Krull, C.-H. Pui, D. Pei, C. Cheng, W. E. Reddick, H. M. Conklin. Longitudinal Assessment of Neurocognitive Outcomes in Survivors of Childhood Acute Lymphoblastic Leukemia Treated on a Contemporary Chemotherapy Protocol. *Journal of Clinical Oncology*, 2016;

53. Sherief, L. M., Kamal, N. M., Abdalrahman, H. M., Youssef, D. M., Alhady, M. A. A., Ali, A. S., … Hashim, H. M. (2015). *Psychological Impact of Chemotherapy for Childhood Acute Lymphoblastic Leukemia on Patients and Their Parents. Medicine, 94(51), e2280.*

CORRELATION OF ULTRASOUND MEASUREMENT OF INFERIOR VENA CAVA TO AORTA DIAMETER RATIO WITH HEMATOCRIT LEVELS AND SEVERITY OF SHOCK AMONG CHILDREN WITH DENGUE FEVER SEEN AT THE EMERGENCY ROOM OF A TERTIARY GOVERNMENT HOSPITAL

CHARISSE JOY M. LIM, MELLINOR A. ANG, CRISTAN Q. CABANILLA, MICHAEL SALVADOR CABATO

ABSTRACT

BACKGROUND: Severe dengue is a leading cause of serious illness and death, and intensive supportive care is the most important aspect of management. Before fluid resuscitation, a baseline hematocrit is obtained, and frequent monitoring of the complete blood count is needed.

OBJECTIVE: To determine the correlation of ultrasound measurement of inferior vena cava (IVC) to aorta (Ao) diameter ratio with hematocrit levels and severity of shock among children with dengue fever.

METHODOLOGY: This is a prospective study design conducted at the Emergency Room of Philippine Children's Medical Center. Clinical data and hematocrit of the children with dengue fever aged 1 month to 17 years and 364 days old were documented. The Inferior vena cava diameter (IVC)and the Aorta (Ao) diameter ratio was determined using bedside ultrasound.

RESULTS: The IVC/Ao diameter ratio correlates with high hematocrit and dengue shock in children. There is a significantly higher proportion of subjects with a hematocrit of normal range of age among those with a ratio $\geq$1.0. A ratio of <0.8 is significantly associated with high hematocrit level for age. Overall, IVC/Ao diameter ratio was significantly associated with severity of Dengue illness. Sensitivity of IVC/Ao diameter ratio of <1.00 in predicting dengue with warning signs and severe dengue was 87.7%. Specificity was higher at 97.1%. Measurement of IVC/Ao diameter ratio has high interrater and intrarater reliability.

CONCLUSION AND RECOMMENDATION: IVC/Ao diameter ratio was significantly associated with severity of dengue illness. It should be used to aid decision-making and monitor response to treatments in dengue fever.

KEYWORDS: ultrasound, inferior vena cava, Inferior Vena Cava to Aorta Diameter ratio, Hematocrit, Dengue Shock Syndrome

INTRODUCTION

The global incidence of dengue has grown dramatically in recent decades. About half of the world's population is now at risk.[1]One study on the prevalence of dengue estimates that 3.9 billion people, in 128 countries, are at risk with dengue infection. Severe dengue is a leading cause of serious illness and death, most especially in Asia, particularly in the Philippines.[2]It is epidemic in the Philippines and considered one of its eight pervasive infectious diseases.[3]

The three stages of clinical presentations are classified as febrile, critical, and convalescent. The critical stage, which lasts 24–48 hours, is the most critical period, with rapid plasma leakage leading to circulatory disturbance. Patients without significant plasma leak would gradually convalesce, but those who would develop major plasma leak may deteriorate in the face of critical loss of volume.[4]Serial estimation of hematocrit is a guide to volume resuscitation during the critical phase of dengue fever, and the rise of hematocrit indicates plasma leakage.[4] However, this needs frequent blood extractions. The turnaround time for establishing the hematocrit depends on several factors and may not be available in the initial phase of resuscitation.[4]

Many of the complications such profound shock, severe bleeding with severe disseminated intravascular coagulopathy, respiratory distress, and failure, multi-organ dysfunction of liver, kidneys and the neurological system and irreversible shock and death are preventable. Some degree of fluid overload is inevitable in patients with severe plasma leakage. The most important skill is giving patients enough intravenous fluid to maintain adequate perfusion to maintain normal vital signs, while waiting it out until plasma leakage process spontaneously reverses, at the same time avoiding excessive fluid overload.

Before fluid resuscitation, a baseline hematocrit is obtained, and frequent monitoring of the complete blood count is needed depending on the case of the patient. Aside from obtaining the hematocrit, the IVC/Aodiameter ratio can be a promising tool in objectively guiding the clinicians during the fluid resuscitation in real-time.[5]Several studies have shown the correlation of intravascular volume status with the Inferior Vena Cava (IVC) diameter in children. IVC diameter is low in children with hypovolemia.

This study aims to determine the correlation of ultrasound measurement of inferior vena cava (IVC) to aorta (Ao) diameter ratio with hematocrit levels and severity of shock among children with dengue fever seen at the emergency room of a tertiary government hospital.

Ultrasonography may be a noninvasive and objective way to assess intravascular volume, right heart function, and confirm a diagnosis of dehydration in children. Moreno noted that the IVC is a highly compliant vessel whose size varied with central venous pressure. They studied its size and dynamics in adult patients, finding that IVC diameter correlated well with its collapsibility index.[9]A study was

done in 2009 also showed that bedside ultrasonographic measurement of caval index greater than or equal to 50% is strongly associated with low central venous pressure. Hence bedside measurements of inferior vena cava using ultrasound could be a non-invasive tool to determine the central venous pressure during the initial evaluation in the emergency department.[10]

Recently, the use of IVC diameter and collapsibility has extended to more acutely ill patients, whether in emergency medicine or surgical patients in the intensive care unit (ICU). In a prospective observational study performed in an adult ED setting, both IVC diameter and IVC collapsibility index were correlated with volume status in adult trauma patients.[11]Yanagawa et al. reported an IVC diameter to correlate with hypovolemia in trauma patients.[12] There was also a higher mean IVC collapsibility index in the shock group.[13]Thanakitcharu et al. showed that the inferior vena cava diameter and collapsibility index is a practical non-invasive tool to evaluate the intravascular fluid volume in critically ill patients.[11]

This was also used in the study among diarrhea patients by Modi where they investigated the accuracy of the inferior vena cava for predicting dehydration in children with acute diarrhea in limited-resource settings. They found that point of care ultrasound of Inferior Vena Cava (IVC) to Aorta (Ao) diameter ratio was statistically associated with volume status.[14] Furthermore; it increases with the administration of IV boluses. Thusthe Inferior Vena Cava (IVC) to Aorta (Ao) diameter ratio, as determined by bedside ultrasound, is an objective and non-invasive method of evaluating fluid status in children.[15]

There were few studies done among dengue patients. A study by Thanacharwet showed that the dynamic measures to estimate changes in hemodynamic parameters and preload should be monitored to ensure adequate fluid therapy among patients with dengue, particularly patients with dengue shock.[17]

Raman studied the correlation of inferior vena cava ultrasound with packed red cell volume and clinical condition in children with dengue fever. The result showed that IVC collapsibility correlates with high hematocrit and dengue shock in children. Hence they concluded that the assessment of intravascular volume status by determining the IVC collapsibility using bedside ultrasound is a non-invasive tool in children with dengue fever.[18]

OBJECTIVES OF THE STUDY

General objective:

To determine the correlation of ultrasound measurement of inferior vena cava (IVC) to aorta (Ao) diameter ratio with hematocrit levels and severity of shock among children with dengue fever seen at the emergency room of a tertiary government hospital.

Specific objectives:

- To determine the Inferior Vena Cava to Aorta (IVC/Ao) diameter ratio of pediatric dengue patients as measured by bedside ultrasound.

- To correlate the IVC/Ao diameter ratio with the hematocrit of children with dengue fever using bedside ultrasonography.
- To correlate the IVC/Ao diameter ratio with the severity of children with dengue fever using bedside ultrasonography.
- To determine the diagnostic accuracy of the IVC/Ao diameter ratio using bedside ultrasonography, in predicting the severity of dengue illness in terms of:
    - Specificity
    - Sensitivity
    - Positive predictive value
    - Negative predictive value
    - Positive likelihood ratio
    - Negative likelihood ratio
    - Odds ratio

METHODOLOGY

This is a prospective observational study design conducted at the Emergency Room of Philippine Children's Medical Center, Agham Road, Quezon City. This study was approved by the Institutional Review Board.

- Informed consent was obtained from the parents or the guardian after the patient was selected to be part of the study. Assent was also obtained on patients >= 9 years old who were cognizant or conversant during the enrollment. If immediate stabilization was needed, the ER-resident obtained the informed consent for the study. Individual pertinent demographic, clinical data such as age, sex, weight, height, and body mass index were collected.

- Clinical assessment and observation were performed by the investigators and were documented at the time of the arrival at the Emergency Room. In the event that dengue was highly suspected, complete blood count and blood samples for dengue serology (NS1 antigen and or Dengue IgM) were taken. A total of 5 ml of blood were extracted from the patient. Anti-dengue IgM specific antibodies can be detected 3−6 days after fever onset. If the patient is on the first to the fourth day of illness, dengue NS1 was taken. If the patient is on 5th day of illness and onwards, dengue IgM was obtained. Ultrasound of Inferior Vena Cava and aorta was done thereafter. (Figure 1)

The equipment used in this study was the Sonosite portable ultrasound machine with a cardiac probe of 5-8 MHz frequency. Measurements were taken with the subjects in the supine position. The probe was placed at the subxiphoid region, just rostral or caudal to the insertion of the left renal vein into the IVC. In this view, the liver could be used as an acoustic window. No graded compression was used to displace the intestinal gas. In addition, care was taken not to compress the abdomen to avoid compressing the vessels being measured. A transverse view of the IVC and Ao was imaged. Images were recorded over several respiratory and cardiac cycles. The maximal anterior-posterior IVC diameter and descending Ao diameter were measured, placing calipers at the anterior and posterior midpoints of each vessel (Figure 2). The

IVC to aorta ratio was calculated for each child by dividing the maximal IVC diameter in centimeters by the maximal Ao diameter in centimeters.[15]

- Measurement was also taken in longitudinal position, and measurements on both views were recorded. The examination per patient was taken three times for the intraraterreliability. Toassess the inter-rater reliability, whenever possible, each measurement of IVC/Ao ratio was to be performed by the two investigators who were blinded to each other's measurements. In case of reading discrepancies, the measurements of IVC/Ao diameter ratio taken by the primary investigator was used in the statistical analysis. Clinical, laboratory, and ultrasonography data of each patient who are positive for NS1 antigen and or Dengue IgG and IgM was analyzed. IVC and Aorta ratio taken at the emergency room was compared with the baseline hematocrit and the severity of dengue.

FLOWCHART

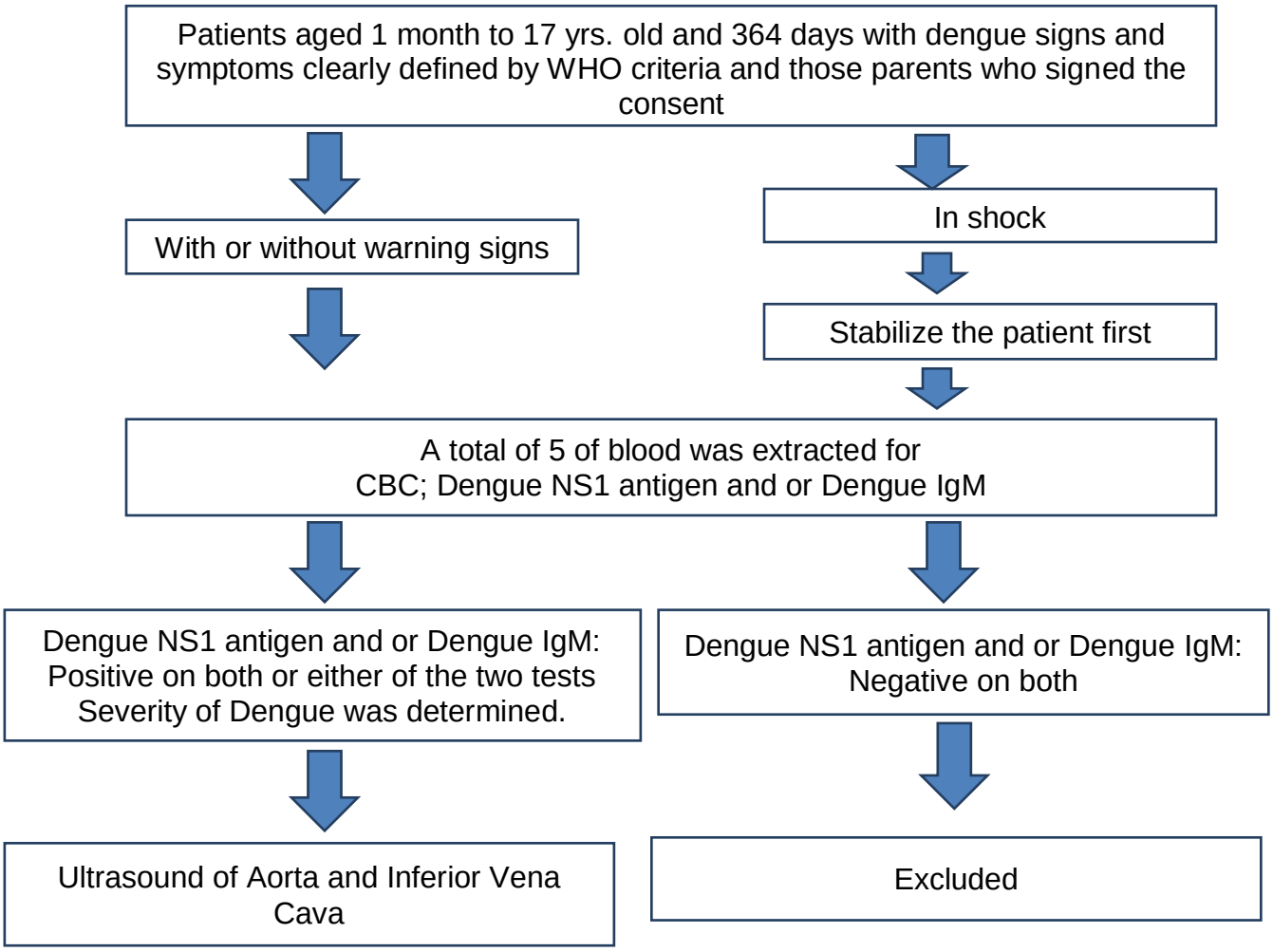
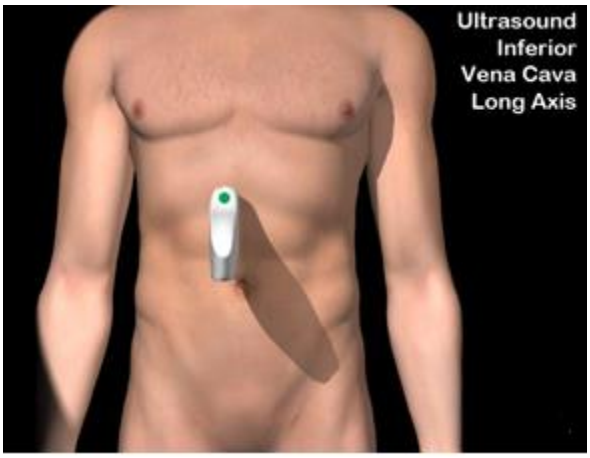


Figure 1. Selection of Participants

ULTRASOUND PROCESS

The patient was placed in a supine position.

The probe was placed at the subxiphoid region, just rostral or caudal to the insertion of the left renal vein into the IVC.



The aorta was identified above the vertebral shadow, and the IVC was identified toits screen left, closer to the probe marker.

A transverse and longitudinal views of the IVC and Ao were imaged. Images were recorded over several respiratory and cardiac cycles. The maximal anterior-posterior IVC diameter and descending Ao diameter were measured, placing calipers at the anterior and posterior midpoints of each vessel

IVC/Ao ratio calculation

Data Analysis

Figure 2. The Ultrasound Procedure

- The primary outcomes are the correlation coefficient of IVC to Ao diameter ratio with hematocrit and dengue severity and sensitivity, specificity, and predictive values of the ratio in predicting severe shock.

- Descriptive statistics were used to summarize the general and clinical characteristics of each participant. The clinical, laboratory and ultrasound data of children who were positive for dengue NS1 and or dengue IgG and IgM test were analyzed. Chi-square was done and Odd's ratio was computed whenever appropriate. Diagnostic accuracy parameters were determined using standard formulas. For all tests, a 95% confidence level was considered significant.Using Intraclass Correlation by2 waymixed effects model for K=2, the intrarater and interrater reliability was calculated to determine the consistency of measurements.

RESULTS

A total of 100 patients were included in the study from December 2018 to August 2019; 32 of which had Dengue Fever without warning signs, 31 with dengue fever with warning signs and 37 had dengue shock. There were more males (n=52) than females (n=48). The overall mean age of the subjects was 9.7 years. The mean age of children without warning signs, with warning signs and dengue severe are 14.7 yrs,10.3 yrs, and8.4 yrs old respectively. Of the study participants, 71 subjects presented between day 5 and day 7 after the onset of fever. Sixty-three subjects have normal BMI for age (63%). This was followed by children with severe wasting (12%) then by obese subjects (10%). (Table 1)

Table 1. Demographic and clinical characteristics of patients (n=100)

Characteristics	**Values**
Mean age ± SD, years. Age range	9.74 1 month-17 yrs old
Sex Male female	 52 48
Anthropometrics BMI (kg/m^2) Obese Overweight Normal Wasting Severe wasting	 10 7 63 8 12

IVC/Ao diameter ratio and Hematocrit levels

Table 2 shows the association of IVC/Ao diameter ratio with hematocrit levels. The ratio is significantly associated with hematocrit level. There is a significantly higher proportion of subjects with a hematocrit of normal range of age among those with anIVC/Ao diameter ratio ≥ 1.0. Odds ratio of 108.8 means that there is 108.8 times more likely to have a hematocrit of normal range of age given anIVC/Aoratio of ≥ 1.0. A level of 0.8-0.99 is not significantly associated with hematocrit level. On the other hand, anIVC/Ao diameter ratio of <0.8 is significantly associated with high hematocrit

level for age (p<0.0001). It is 24.7% less likely to find a normal hematocrit for age given an IVC/Ao diameter ratio of <0.8.

Table 2.IVC/Ao diameter ratio and Hematocrit

		Hematocrit (normal range for age)	Hematocrit (high for age)	Total	p-value
USG FINDING IVC/Ao ratio	≥1.0	40(81%)	2 (3.9%)	42	<0.0001 Odd's ratio 108.8 (22.24-552.9)
	0.80-0.99	6	12	18	0.141
	<0.8	3	37	40	<0.0001 Odd's ratio 0.0247 (0.006)
TOTAL		*49*	*51*	*100*	

IVC/Ao diameter ratio and Severity of Dengue Illness

Overall, IVC/Ao diameter ratio was significantly associated with severity of Dengue illness. 97% of those without warning signs had IVC/Ao diameter ratio of ≥1.00. For those with warning signs, 63.4% had anIVC/Ao diameter ratio of from 0.8-0.99, and 93% with severe dengue had anIVC/Ao diameter ratio of <0.80. (Table 3)

Table 3. IVC/Ao diameter ratio and Severity of Dengue Illness

		Dengue fever without warning signs	Dengue with Warning Signs	Severe Dengue	Total	p-value
USG FINDING IVC/Ao ratio	≥1.0	*34*	*8*	*0*	*42*	*<0.0001*
	0.80-0.99	*1*	*14*	*3*	*18*	*<0.0001*
	<0.8	*0*	*0*	*40*	*40*	*<0.0001*
TOTAL		*35*	*22*	*43*	*100*	

overall: p <0.0001

Diagnostic Accuracy Of US Measurement Of Aorta To IVC Diameter Ratio In Predicting Severe Dengue

Sensitivity or the probability of identifying those with true disease, of IVC/Ao diameter ratio of <1.00 in predicting dengue with warning signs and severe dengue (grouped) was 87.7%. Specificity or the probability of identifying those without the disease (without warning signs) was higher at 97.1%. Positive predictive value or diagnostic yield, or the probability of those with IVC/Ao diameter ratio of <1.00 having dengue with warning signs or severe dengue was 98.3% while negative predictive value was 80.9%

The Positive Likelihood Ratio (LR+) in our study was 30. 69, a strong evidence that those with a value of <1.00 very likely to have warning signs or severe dengue, and that we can rule in the disease. LR- was 0.127, strong evidence (near zero value) for those with ratio values of ≥1.00 not to have warning signs or severe dengue. (Table 4)

Table 4.Diagnostic accuracy of US measurement of IVC diameter to Aoratio in predicting severe dengue (With warning signs + Severe Dengue)

	Sensitivity	Specificity	Positive predictive value	Negative Predictive Value	Likelihood Ratio +	Likelihood Ratio (-)
Value (%)	87.7	97.1	98.3	80.9	30.69	0.127
95% confidence Interval	76.6-94.2	83.4-99.8	89.5-99.9	65.4-90.8	4.44-212.3	0.066-0.243

With an IVC/Ao diameter ratio value of <1.00 predicting severe dengue only, sensitivity was higher at 100%, specificity lower at 73.7%. , PPV lower at 74.1% and NPV higher at 100%. LR+ was lower than when the disease classification included dengue with warning signs. This means that with a narrower disease classification, we can identify all those with severe dengue, with a bigger false positive though, and with a value of ≥1.00, we can identify all those without severe dengue. (Table 5)

Table 5. Diagnostic accuracy of US measurement of IVC to Aodiameter ratio in predicting severe dengue (Severe Dengue)

	Sensitivity	Specificity	Positive predictive value	Negative Predictive Value	Likelihood Ratio +	Likelihood Ratio (-)
Value (%)	100	73.7	74.1	100	3.8	NA
95% confidence Interval	89.7-100	60.1-84.1	60.7-84.3	89.6-100	2.46-5.86	NA

Reliability

Sixty paired measurements of IVC/Ao diameter ratios were made to measure the interrater reliability. Intra-class correlation (ICC) using 2 way mixed effects model for K=2was done. The results show a consistency rating of 0.8804. This means that there is high interrater reliabilty. For the intrarater reliability in 100 subjects, the Intra-class correlation (ICC) consistency rating was 0.9137 which also being interprteted as high.

DISCUSSION

As measured by bedside ultrasound, the IVC/Ao ratio is lower in children with dengue fever with warning signs and severe dengue. Futhermore, IVC/Ao ratio (<1.0) is also low in patients with high hematocrit value. Thus, the IVC/Ao ratio as determined by bedside US, is an objective and non-invasive method of evaluating severity of dengue.

This study confirms some earlier pilot data showing that the inferior vena cava collapsibility estimated by qualitative method is significant in children with dengue shock and a high hematocrit value.[16] Furthermore, this is the first study to demonstrate the use of IVC/Ao ratio in establishing the severity of dengue shock as well as its correlation in hematocrit. In our study, results show that children with diagnosis of dengue with no warning signs have normal hemodynamic status and IVC/Ao ratio of ≥1.0 while children with severe dengue have IVC/Ao ratio of <0.8 and high hematocrit for age.

The low IVC/Ao ratio in patients with dengue is due to severe plama leakage and gastrointestinal losses such as vomiting, diarrhea and poor intake. Furthemore, bleeding could also contribute in some cases. Plasma leakage in dengue is associated with increased hematocrit and decrease in intravascular volume, leading to shock in children.[4]Hematocrit is a vital tool that guides fluid resuscitation in addition to clinical assessment of dengue fever in pediatric emergency setting. The turnaround time for estimating the hematocrit depends on a number of factors and may not be available in the initial phase of resuscitation. This study shows that IVC/Ao ratio of <0.8 cm is correlated with hemoconcentration, indicating intravascular volume depletion. Bedside US has been recommended for monitoring and assessment of plasma leakage and to predict disease severity in children with severe dengue illness.[20]

The pathogenesis of plama leakage in dengue has been extensively studied. Both innate immunity (NK cells and complement system) and adaptive immunity (humoral and cell-mediated immunity) play a role in the pathogenesis of DHF/DSS. Cytokines are implicated in the pathogenesis of vascular compromise and hemorrhage in dengue virus infection. Dengue viral infection causes the release of both inflammatory and inhibitory cytokines, and the net outcome will depend on the balance of cytokine actions. The levels of T-cell activation markers (soluble IL-2 receptor, soluble CD4 and CD8, IL-2, IFN- γ), monokines (TNF α, IFN- β), and granulocyte-macrophage colony-stimulating factor (GM-CSF) are increased with even higher levels present in patients who develop DHF/DSS. Elevated IL-6 levels are associated with a higher incidence of both shock and ascites. Similarly, high levels of IL-8 can be recovered from the serum and pleural fluid of patients with DSS .Complement activation mediated by nonstructural viral protein NS1 leads to local and systemic generation of anaphylatoxins and terminal complement complex (SC5b-9), which may contribute to the pathogenesis of the vascular leakage that occurs in patients with DHF/DSS (16).Endothelial cells also undergo apoptosis, which causes disruption of the endothelial cell barrier and the syndrome of generalized vascular leakage.[21]

Assessment of the size of the inferior vena cava (IVC) and its change in diameter in response to respiration have been investigated as a tool to screen for severe hypovolaemia, predict fluid responsiveness (FR) and assess potential intolerance to fluid loading. IVC size, collapsibility (IVCc) and distensibility (IVCd) have gained acceptance by emergency and intensive care unit (ICU) clinicians as fluid responsiveness predictors in patients with shock. The ease of acquisition, reproducibility of measurements and increasing availability of ultrasound devices have supported the expansion of its use.[22]

This study however was designed around a novel parameter: the ratio between the IVC and Ao diameters. The premise stems from the fact that the IVC and Ao diameter will be different in each child, possibly correlating with factors such as age, gender, weight, height and body surface

area.[23] However, the Ao diameter was predicted to be fairly stable within each child despite hydration because it is a vessel with low compliance, especially when compared to IVC. To address the question if Ao diameter could be affected by intravascular depletion and resultant tachycardia and activation of the sympathetic system, Sonneson et al found that the sympathetic stimulation did not alter the mechanical properties of the abdominal aorta.[24] Furthermore, Yanagawa et al reported a study of adults in hypovolemic shock in which the diameter of the abdominal aorta remained constant despite large volumes of blood loss.[12] Hence Ao diameter should not change much with the changes in the intravascular volume. In our study, the Ao diameter was found to remain stable in each subject. Thus, Ao diameter serves as an internal control for each child. The aorta is a no collapsible structure and maintains a relatively constant diameter irrespective of the fluid status. The aortic diameter correlates with BSA, age, and sex of the patient. Kosiak et al. research study states that IVC/Ao is more specific in the assessment of body fluid status. Thus measuring the IVC/Ao irrespective of the respiratory cycle has made the study simpler and patient specific, and does not necessitate looking at reference values for each age group.[25]

A study done by Sridhar et al shows that the mean IVC/Ao in euvolemic patients is 1.2 ± 0.12 SD, hypovolemic is 0.7 ± 0.09 SD, and volume overloaded is 1.6 ± 0.05 SD, respectively.[26] The utility of IVC/Ao in trauma patients by Son et al., quoted that non trauma patients had a mean IVC/Aorta index of 1.26 ± 0.17 SD and trauma patients had a mean index of 0.80 ± 0.33 SD.[27] Sonographic IVC/Ao for fluid status in young individuals from the American Journal of Emergency Medicine concluded that for the healthy young population, the IVC/Ao reference value is 1.2 ± 0.17 SD. The IVC/Aoratio seems to play a very important role in diagnosing fluid status in emergency patients.

In our study, it was observed that the IVC/Ao ratio ≥ 1.0 is observed in dengue without warning signs and those with normal hematoctritvalues for age while those with severe dengue and significant hemoconcentration had IVC/Ao diameter ratios of <0.8.

Our study showed that the IVC/Ao diameter ratio of <1.00 in predicting dengue with warning signs and severe dengue (grouped) was 87.7%. While the specificity or the probability of identifying those without the disease (without warning signs) was higher at 97.1%. Positive predictive value or diagnostic yield, or the probability of those with IVC/Ao diameter ratio of <1.00 having dengue with warning signs or severe dengue was 98.3% while negative predictive value was 80.9%. With a ratio value of <1.00 predicting severe dengue only, sensitivity was higher at 100%, specificity lower at 73.7%, PPV lower at 74.1% and NPV higher at 100%.

Intraobserver and interobserver reliabilities were measured. This study showed a high interrater and intrarater agreement. Previous researches demonstrated good interobserver agreement

in the measurement of IVC as performed by pediatric emergency physicians.[28] Measurements of IVC/Ao diameter taken by the emergency physicians has good interrater reliability.[29] Furthermore, bedside US and the measurement of IVC/Ao ratio can be ascertained in the first few minutes as assessment and initial steps of resuscitation are performed and can provide valuable supportive data regarding the need for fluids. The simplicity of the examination technique with quite constant measurement points can eliminate the examiner dependence. The IVC/Ao index seems to be more adequate and correlates more precisely with the clinical course.[25]

CONCLUSION

The IVC/Ao ratio correlates with the severity of dengue fever and with the hematocrit in the emergency setting. Overall, the IVC/Ao diameter ratio was significantly associated with the severity of dengue illness. Those without warning signs had IVC/Ao diameter ratio of ≥ 1.00. For those with warning signs, 63.4% had an IVC/Ao diameter ratio from 0.8-0.99, and 93% with severe dengue had an IVC/Ao diameter ratio of <0.80.Thus, the IVC/Aodiameter ratio is a helpful non-invasive bedside tool which supplements the clinical assessment of intravascular volume status in children with dengue shock.Knowing the IVC/Ao ratio would prompt the clinicians to be more aggressive in the management of severe dengue at the ER level.

RECOMMENDATIONS

Based on this study, the following are the recommendations:

1. The Emergency department should have dedicated ultrasound systems for bedside use. Bedside ultrasonography should be incorporated in the skills of consultants, residents and fellows. It should be used to aid decision-making and monitor response to treatments. The physician can utilize their history and physical examination findings and integrate these with their ultrasound findings into the patient's assessment.

2. Despite the increasing incorporation of handheld ultrasound and bedside ultrasonoraphy in multiple areas of medicine, formal evaluation in methods to generalize this technique is warranted.

3. Ultrasound of IVC and aorta should be done in suspected dengue cases. If the IVC/Ao ratio is <0.8 cm, a referral to critical care division should be done.

4. More data are needed to establish normal values in children with euvolemia and no normograms yet exist for the IVC/Ao ratio in either children or adults.

BIBLIOGRAPHY/REFERENCES

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The Global Distribution and Burden of Dengue. Nature. 2013 April 25; 496(7446) :504-507.

2. Brady OJ, Gething PW, Bhatt S, Messina JP, Brownstein JS, Hoen AG et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoSNegl Trop Dis. 2012 Aug; 1760.

3. Edillo F, Halasa Y, Largo F, Erasmo J, Amaoin N, Alera M, et al. Economic Cost and Burden of Dengue in the Philippines. The American Journal of Tropical Medicine and Hygiene. 2015 Feb 4; 92(2): 360–366.

4. World Health Organization. Handbook for Clinical Management of Dengue. July 2012. http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf.

5. Raman R, Lakshmi M. Correlation of inferior vena cava ultrasound with packed cell volume and clinical condition in children with dengue fever. Journal of Emergency Medicine, Trauma & Acute Care 2016:6 http://dx.doi.org/10.5339/jemtac.2016.6.

6. Chen L, Baker MD. Novel applications of ultrasound in pediatric emergency medicine. Pediatric Emergency Care. 2007; 23:115-123.

7. Yen K, Gorelick MH. Ultrasound applications for the pediatric emergency department: a review of the current literature. Pediatric Emergency Care. 2002; 18:226-234.

8. Chen L, Kim Y, Moore CL. Diagnosis and guided reduction of forearm fractures in children using bedside ultrasound. Pediatric Emergency Care. 2007; 23: 528-531.

9. Moreno F, Hagan A, Holmen J, Pryor T, Strickland R, Castle C. Evaluation of size and dynamics of the inferior vena cava as an index of right-sided cardiac function. American Journal of Cardiology. 2017 Dec 17; 53:579-585.

10. Nagdev A, Merchan R, Tirado-Gonzales A, Sisson C, Murphy M. Emergency department bedside ultrasonographic measurement of caval index for non-invasive determination of low central venous pressure. Annals of Emergency Medicine Volume 55 Number 3. 2010 March; 09(41): 290-295.

11. Thanakitcharu P, Charoenwut M, Siriwiwatankul N. Inferior vena cava and collapsibility index: a practical non-invasive evaluation of intravascular fluid volume in critically ill patients. J Med Assoc Thai. 2013 Mar; 96 Suppl 3: S14-122.

12. Yanagawa Y, Nishi K, Sakamoto T, Okada Y. Early diagnosis of hypovolemic shock by sonographic measurement of inferior vena cava in trauma patients. Journal of Trauma-Injury Infection & Critical Care. 2005 April;58:825-829.

13. Sefidbakht, S, Assadsangabi R, Abbasi, HR, Nabavizadeh A. Sonographic measurement of the inferior vena cava as a predictor of shock in trauma patients. Emergency Radiology. 2007; 14: 021181-185.

14. Modi P, Glavis J, Nasrin S, Guy A, Chowa EP, Dvor N, et al. Accuracy of inferior vena Cava ultrasound for predicting dehydration in children with acute diarrhea in resource-limited settings. Plos One. 2016 Jan 14; 11 (1): e0146859.

15. Kim Y, Santucci K, Chen L. Ultrasound measurement of the inferior vena cava diameter in the assessment of pediatric dehydration. Academic Emergency Medicine. 2007; 14:841-845.

16. Chen L, Hsiao A, Langhan M, Riera A, Santucci K. Use of bedside ultrasound to assess the degree of dehydration in children with gastroenteritis. AcadEmerg Med. 2010 October; 17(10):1042-1047.

17. Thanachartwet V, Wattanathum A, Sahassananda D, Wacharasint P, Chamnanchanunt S, Khine Kyaw E, et al. Dynamic measurement of hemodynamic parameters and cardiac preload in adults with dengue: A Prospective observational study. PLoS ONE 11(5). 2016 May 19: e0156135.

18. Raman R, Lakshmi M. Correlation of inferior vena cava ultrasound with packed cell volume and clinical condition in children with dengue fever. Journal of Emergency Medicine, Trauma & Acute Care 2016:6 http://dx.doi.org/10.5339/jemtac.2016.6.

19. American Heart Association: Pediatric Advance Life Support Manual Provider Manual, First American Heart Association Printing, October 2016.

20. Yacoub S, Mongkolsapaya J, Screaton G: The pathogenesis of dengue. CurrOpin Infect Dis 2013, 26:284–9.

21. Nichols D &Shaffner D. Roger's Textbook of Pediatric Intensive Care 5th edition. Wolters Kluwer. 2015:

22. Via G, Tavazzi G, Price S. Ten situations when IVC ultrasound may fail to accurately predict fluid responsiveness: a physiologically based point of view. Intesive Care Med;2016 February:134-016.

23. Munk A, Darge K, Wiesel M, and Troeger J. Diameter of infrarenal aorta and the iliac arteries in children: ultrasound measurements. Transplantation; 2002:73:631-635.

24. Sonneson B, Vernersson E, Hansen F, and Lanne T. Influence of sympathetic stimulation of mechanical properties of the aorta in humans. Acta Physiologica Scandinavia. 1997; 159:139-145.

25. Kosiak W, Sweiton D, Piskunowicz M. Sonographic inferior vena cava/aorta diameter index, a new approach to the body fluid status assessment in children and young adults in emergency ultrasound preliminary study. Acad J Emerg Med.2008;26:320-325.

26. Sridhar H, Mangalore P, Chandrasekaran V and Marikam R. Caval Aorta Index and CVP correlation in assessing fluid status: ultrasound bridging the gap. ISRN Emergency Medicine: 2012;828626.

27. Son K, Kim M, Kim Y, and Yoon Y. The utility of the IVC/Aorta diameter index in trauma patients. Journal of the Korean Society of Emergency Medicine: 2010;2:35–43.

28. Pershad J, Myers S, Plouman C, Rosson C, et al. Bedside limited echocardiography by the emergency physician is accurate during evaluation of the critically ill patient. Pediatrics 114: 2004; e66-671.

29. Hellman D, Whiting O, Joffe M, Lacalio R, and Shaw K. The rate at which residents learn to use hand-held echocardiography at bedside. American Journal of Medicine: 2005; 118:1010-1018.

30. Hughes H & Kahl L. The Johns Hopkins the Harriet Lane Handbook 21st edition.Elsevier. 2016: 365.

31. WHO Child Growth Standards. In Training Course on Child Growth Assessment. Geneva: WHO; 2008.

AWAKE P6 STIMULATION FOR POST-OPERATIVE NAUSEA AND VOMITING USING JAPANESE ACUPUNCTURE NEEDLE AMONG CHILDREN 5-18 YEARS OLD AT PHILIPPINE CHILDREN'S MEDICAL CENTER

MARY ESTHER R. MAALA, JANETTE T. FUSILERO-PASCUAL

ABSTRACT

OBJECTIVE: To compare the effectiveness of preoperative Japanese acupuncture for prevention of post-operative nausea and vomiting (PONV) in non-sedated children for surgery under general anesthesia**.**

METHODS: This is an RCT studying the effectiveness of press-tack Japanese needles in P6 prior to any sedatives in children age 5-18 years old for surgery under general anesthesia (n=66). Patients were randomized to receive either press-tack needle (n=33) or an identical press-tack without the metal component (n=33). Incidence of PONV was reported using BARF scale. Children, parents, anesthesiologists, and nurses were blinded to group assignment.

RESULTS: Eight of 33 (22%) in the intervention group while 17 of 33 (51.52%) in the placebo group experienced PONV (RR = 0.47, 95% CI [0.24-0.94], p-value 0.0224). One case reported an adverse event of worsening of nausea and vomiting.

CONCLUSIONS: Japanese acupuncture at P6 prior to sedation using press-tack needle significantly reduced the incidence of PONV in children after general anesthesia.

KEYWORDS: PONV, POV, P6, PC6, Japanese acupuncture, Acupuncture, RCT

INTRODUCTION

Over the past decades, acupuncture has gained acceptance as a complementary treatment in the practice of western medicine. But research in this area is limited with use of sham-needling as control. Recent reports criticize sham-needling in providing a reliable control setting. There is even greater paucity of data regarding use of acupuncture in pediatrics.

Among perioperative uses of acupuncture, treatment for post-operative nausea and vomiting (PONV) had been the most studied in the adult population. In children, only postoperative vomiting (POV) is usually described due to difficulty in assessing occurrence of nausea. Nausea is believed to be underreported. Current evidence supports the multimodal approach to lessen PONV in children, but most pediatric anesthesiologists are equipped with only pharmacologic options.

Currently, acupuncture is not being utilized in our institution as a complementary option to care for children. The perioperative applicability of acupuncture remains elusive in anesthetic

management even for the general population. More challenging would be the implementation of this alternative treatment in children undergoing surgical procedures. Significant amount of research for incorporation of pediatric acupuncture in perioperative period is lacking. No study on acupuncture had been done in children prior to induction of anesthesia mainly due to the fear of needles. [1] Previous studies in which acupuncture was started after the induction of anesthesia, revealed reduced efficacy, or a lack of efficacy, although the mechanism underlying this phenomenon is not known.[2]

The most studied use of perioperative acupuncture is prevention and treatment of PONV. In children, incidence of post-operative vomiting is twice as frequent as compared to adults. [3] Severe POV can result in wound dehiscence, dehydration, electrolyte imbalance and pulmonary aspiration. It is one of the leading causes of parental dissatisfaction after surgery and is the leading cause of unanticipated hospital admission following ambulatory surgery. Research in occurrence of perioperative nausea is also lacking since vomiting and retching are only the usual endpoints used. Occurrence of nausea and its impact in children recovering from surgery is thus underreported.

Japanese acupuncturists developed press-tack needles that are easy to use even by non-acupuncturist and is virtually painless upon application with its filiform tip (Figure 1).[4] These features might provide applicability among children in the perioperative period, especially prior to any drug administration, a period where acupuncture treatment had been shown to be more effective. [2]

Acupuncture has greater safety profile as compared to pharmacologic interventions for PONV. This study aims to address the feasibility of preventing post-operative nausea and vomiting in the pediatric population with preoperative use of innovative press-tack needles. With ease of applicability even for non-acupuncturist, this may provide a safer option in the practice of pediatric anesthesiology.

Consequently, by lessening the incidence of PONV, this may also be economically beneficial for shorter PACU stay and may provide evidence of use for ERAS program in pediatric surgery. Other subspecialties may benefit as well since this study may establish applicability of needling in unanesthetized pediatric patients with the use of finer Japanese acupuncture needles.

METHODOLOGY

This is a double-blinded, randomized controlled trial (RCT) among children 5-18 years old who underwent surgery using general inhalational anesthesia. Stimulation at P6 using Japanese press-tack acupuncture needles (*Pyonex*) prior to administration of any anesthetics. P6 was stimulated by tapping at least 10 times.

After Ethics Committee – Institutional Review Board (IRB) approval, recruitment of potential subjects was done during preoperative evaluation of patients at OPD every afternoon during weekdays. Upon

admission and after screening, informed consent from the parent/guardian was obtained; assent was secured for patients ages 7-17. Seventy (70) patients who underwent elective surgery under general inhalational anesthesia were included in this double-blinded randomized controlled trial.

The intervention, as well as the possible adverse events that may arise from the study, were explained to the parent/s or guardian. Actual acupuncture press-tack needle was shown to parents and guardian. They were oriented to use of BARF scale as well. All the questions or clarifications passed by the primary caregiver were addressed by the investigator. After the steps, only then was consent and assent obtained.

Patients were randomized using computer-generated random numbers. Randomization schedule was placed in sealed opaque envelopes which were opened only before the intervention. The patient, primary caregiver, anesthesia provider and PACU nurse were blinded to the type of intervention that the patient will receive. Only the investigator who performed the acupuncture was aware of the group assignment.

Vital signs at the ward were recorded immediately prior to transport to the OR complex. Patients were wheeled in to the OR complex 30 minutes prior to the contemplated procedure. Based on the randomization schedule, the intervention was performed by the investigator at the OR complex waiting area. Group A received acupuncture as follows: Left P6 point identified by the investigator, press-tack needle placed and then covered by a medical bandage.

Group B received placebo as follows: Left P6 identified by the investigator, identical press-tack without the needle tip placed and covered by an identical medical bandage.

Anesthesia provider is a PCMC pediatric anesthesiologist consultant/fellow-in-training other than the primary investigator or supervising investigator. After placing the intervention, anesthesia provider stimulated P6 acupressure point by gently tapping at least ten times.

Standard anesthetic induction proceeded in this order: (1) Fentanyl 1-2 ug/kg (2) Midazolam 0.2mg/kg (3) Atropine 0.02mg/kg (4) Propofol 2-3mg/kg. Airway was secured with either (1) endotracheal tube (2) laryngeal mask airway or (3) face mask with muscle relaxant of standard dose as necessary. Standard regional anesthesia was given as necessary.

After the surgical procedure, total anesthetic time was recorded. Total dose of opioid use was computed as well. Intervention was stimulated by the anesthesiologist-in-charge after inhalational gas has been turned off and prior to transfer to PACU. Initial BARF scale was recorded by the PACU nurse upon arrival at the recovery room; this was time 0.

Pain regimen was also administered during end of surgery using Paracetamol IV

15mg/kg and Ketorolac at an initial dose of 0.6mg/kg. Adjunct pain regimen was a standard rescue opioid dose as necessary for severe pain using age appropriate pain scale (FLACC age >5 to 7 years old, FACES scale 8-12 years old, NRS >12 years old).

For every 15 minutes for the first 3 hours, BARF scale was taken by the PACU nurse who was blinded from the type of intervention. For episodes of nausea, retching or vomiting (BARF ≥4/10) intervention was stimulated again by the anesthesiologist-in-charge. After five minutes without relief, a rescue dose of Ondansetron 0.1mg/kg IV (not exceeding 8mg/day) was given and recorded.

Intervention was removed by the investigator prior to discharge from PACU with Pediatric Post-Anesthesia Discharge Scoring System (Ped-PADSS) > 9/10 (*see Appendix*). Immediate adverse events were recorded.

Parent/s or guardian reoriented to the BARF scale were given monitoring sheet for scoring hourly during waking hours, from the 4^{th} to 24^{th} hour after withdrawal from anesthetic. Adverse events were also documented. Satisfaction rating using bipolar Likert scale of 1-5 was taken from the primary caregiver at the end of study period.

The investigator recorded the following data:

1. Demographics
2. PONV risk factors
3. BARF scale for the first 24 hours
4. Rescue acupuncture
5. Rescue anti-emetic
6. Adverse events
7. Satisfaction rating

The research team declares no conflict of interest. The study did not receive any support or funding from any company or institution. The clinical study underwent approval from the IRB of PCMC. A written consent and assent, if necessary, were obtained. Participation in the study was purely voluntary and without financial compensation.

Adverse reactions that developed were reported accordingly. Patients were given appropriate treatment without delay. They were reminded that they can withdraw from the study at any time. The investigator shouldered the cost of medications given for an adverse event that occurred during the study.

All data were encoded using Microsoft Excel and checked for duplicates. Data was be analyzed using Stata14MP. Patient information was kept with anonymity by utilizing code numbers. Data was encoded by the supervising investigator. Only the primary and supervising investigators had access to the password protected file.

To describe the homogeneity of the population, categorical variables such as gender and history of PONV were summarized using actual counts and frequencies. Continuous variables (i.e. age,

weight, or height) were described in terms of mean and standard deviation. Comparison of numerical variables between the study groups was done using t-test. For categorical data, Chi square test or Fisher exact test was performed. Level of significance was set at 0.05.

Data were processed using a per protocol analysis. For the primary outcome (occurrence of PONV), Chi-square test was used to compare the difference in the two groups. Risk ratio was also computed. For secondary outcomes such as rescue antiemetic and adverse events, Chi-square test or Fisher exact test was used. The cut-off for statistical significance was also set at $P<0.05$ for all tests.

RESULTS

Seventy (70) patients were eligible in the study (Figure 2). Four patients were excluded from the study, two from each study group. For the acupuncture group, two had a change in anesthetic management. For the control group, one withdrew from the study before the intervention was given and the second was excluded due to breach in protocol (unable to give acupuncture stimulation at the conclusion of surgery).

As can be seen from Table 1, the two groups were comparable. There were no statistically significant differences in the history of motion sickness, previous PONV, time of exposure to anesthetic gas, nor to opioid use perioperatively.

The incidence of nausea and vomiting was lower in the acupuncture group immediately after surgery (Figure 3). Same result was obtained with the analysis of BARF scales collected from the ward (Figure4).

There was a significant difference between groups for the primary endpoint: experiencing post-operative nausea and vomiting over the 24-hour observation period. The incidence and severity of PONV was reduced in the P6 acupuncture group (11 of 33; P = 0.02; Table 2) as compared with controls (17 of 33). The risk of PONV was computed to be 53% less in the treatment group versus the control group. Among the study subjects, only one guardian, from the acupuncture group, reported an adverse event of worsening nausea and vomiting. This was treated with IV antiemetic as per protocol.

There was no significant difference in the number of patients needing rescue acupuncture between the two groups. Thirteen (13 of 33) in the acupuncture group while 8 of 33 in the control group required rescue acupuncture at the PACU. However, in the treatment group, out of the 13 patients who received rescue acupuncture, 10 had relief from PONV and did not require further pharmacologic rescue medication. Similarly, the use of rescue antiemetic was significantly higher in the placebo group. (10 of 33; P = 0.03) compared to the acupuncture group (3 of 33; p-value 0.030).

Using the bipolar Likert scale, the acceptability of Japanese acupuncture to unanesthetized children was computed to be 74%. (49 of 66 parent/guardian were

satisfied with the non-pharmacologic intervention).

DISCUSSION

The results of this study provide significant evidence that press tack Japanese acupuncture needle prior to anesthesia reduces incidence of PONV in pediatric patients. This contrasts with studies in acupuncture in children for PONV concluding this modality initially as ineffective.[5-8]

Majority of previous trials in adjunct acupuncture have focused on Chinese method of needling. Control groups in these studies either used "contact needling" or "shallow needling". However, these methods are actual treatment modalities in Japanese acupuncture.[9] This study therefore questions reliability of previous conclusions and provides a new option of setting a randomized controlled trial.[4] Through perspective of biophysics and neuroscience, Quiroz-Gonzales, et al. provided a mechanism why "sham needling" in the control group may provide the same effect as the standard TCM needling in the treatment group. They studied the relationship between acupuncture points and receptive fields. The sensory signals from the receptive fields near the standard acupuncture points can still activate the same central nervous pathways for the intended standard acupuncture points.[10] This phenomenon has led to confusing results with both the two arms of intervention having the same results.[11] To date, experimental and clinical studies have shown that minimal or "sham acupuncture", used as placebo, is not necessarily inert from a physiological perspective.[12]

Alizadeh et al. concluded that two acupuncture points versus a single acupuncture point is more effective in preventing PONV.[13] Interestingly, our single point modality offered clinical significance post-operatively. Congruent to the Japanese acupuncture theme of lesser point stimulation is the lesser intensity in stimulation.[14]The tapping technique used in this research is a gentler technique compared to standard stimulation in TCM acupuncture.[15] This deemphasizes the core concept of Chinese acupuncture which is to seek De-Qi sensation before achieving a therapeutic effect.[16]

In this trial, only one case reported an adverse event (worsening of symptoms). Current data on safety of acupuncture mainly rely on TCM method of stimulation. Identified common adverse events include pain, bruising, bleeding and worsening of symptoms. Computed incidence of these mild adverse events was 11.8% with the use of Chinese acupuncture needles. Serious adverse events such as site infection or joint fibrosis in TCM acupuncture were related to substandard practice and inadequate training.[17]

Another result was the decrease in use of ondansetron, a serotonin antagonist, in the treatment group after the rescue acupuncture was provided. This supports the study done by Somri et al. where acupuncture was a valid non-pharmacologic alternative

treatment for vomiting.[7] Different subtypes of serotonin (5-HT) receptors are believed to be involved in the antiemetic and prokinetic effects of acupuncture. The antiemetic effect involved 5-HT3 mechanism while the prokinetic effect was observed to downregulate 5-HT4 receptors.[18]

Acupuncture for children has gained wide acceptance in Western medicine. However, the limited evidence is based mainly on TCM approach. Ethical considerations exist in its use in children since this Chinese approach is inherently painful for adults. [19]There are no studies in children due to fear of pain both by the children and parents.[1]This study will be the first to provide data through its painless approach with the use of innovative filiform needles in sticker form.

RECOMMENDATIONS

Collaboration with Japanese acupuncturists will be beneficial to expanding knowledge in this treatment strategy.[15] In Japanese acupuncture, duration and intensity of stimulation will further vary per age group.[20] With the wide age range of this study, utilizing a narrower age group might reveal a more precise treatment method.Ease in application and non-specialized skill in stimulation may also empower non-acupuncturists in hospitals. However, point localization by these non-acupuncturists should also be explored to established actual applicability in clinical setting. Point localization can vary greatly even among acupuncturists.[22]

With high acceptability in non-sedated children, other possible uses for anxiety and pain in the perioperative period should be explored. As this is an introductory pediatric research to use of Japanese acupuncture in the Philippine setting, a separate study exhausting possible adverse events from press tack needles will be contributory to holistic approach to children.

CONCLUSION

This study provided a statistically significant data in using single point acupuncture to decrease the incidence of PONV. By preventing use of anti-emetic post-operatively, effectivity of P6 point stimulation to symptomatic patients was also concluded. This study also established Japanese acupuncture using press-tack needles as an acceptable treatment approach to children and their parents in a hospital setting. Thus, Japanese acupuncture for PONV may provide an alternative to the popular alternative TCM.

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I would like to thank my sensei, Toru Nakamura, for his continued support and expert advice that led to the successful completion of this clinical trial using Japanese Acupuncture in the pediatric population. He is a keystone to understanding the centuries-old Eastern art of healing and applying it to modern practice of Western medicine.

REFERENCES

(1) Chernyak GV, Sessler DI. Perioperative Acupuncture and Related Techniques. Anesthesiology. 2005 May; 102(5):1031-1078

(2) Lee A, Done MI. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting: a meta-analysis. Anesth Analg. 1999: 88: 1362-1369 [PubMed: 10357346]

(3) Martin S, Baines D, Holtby H, Carr AS. APA Guidelines on the Prevention of Post-operative Vomiting in Children. APA Guidelines. Autumn 2016

(4) Miyazaki S, Hagihara A, Kanda R, Mukaino Y, Nobutomo K. Applicability of Press Needles to a double-blind Trial. Clin J Pain. 2009; 25: 438-444

(5) Rusy LM, Hoffman GM, Weisman SJ. Electroacupuncture prophylaxis of postoperative nausea and vomiting following pediatric tonsillectomy with or without adenoidectomy. Anesthesiology2002; 96: 300-305 [PubMed: 11818760]

(6) Wang SM, Kain ZN. P6 acupoint injections are as effective as droperidol in controlling early postoperative nausea and vomiting in children. Anesthesiology2002; 97: 359-366 [PubMed: 12151925]

(7) Somri M, Vaida SJ, Sabo E, Yassain G, Gankin I, Gaitini LA. Acupuncture versus ondansetron in the prevention of postoperative vomiting. A study of children undergoing dental surgery. Anaesthesia 2001; 56: 927-932. [PubMed 11576093]

(8) Lee A, Done MI. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting: a meta-analysis. Anesth Analg. 1999: 88: 1362-1369 [PubMed: 10357346]

(9) Vlessides, M. (2016).Pediatric Post-Op Nausea Identified with BARF scale. Retrieved from www.anesthesiologynews.com/Article/PrintArticle?articleID=38416

(10) Quiroz-Gonzalez S, Torres-Castillo S, Lopez-Gomez R, Estrada I. Acupuncture Points and their relationship with Multireceptive Fields of Neurons. Journal of Acupunctureand Meridian Studies. 2017; 10(2):81-89

(11) Ernst E. Acupuncture--a critical analysis. J Intern Med.2006 Feb; 259(2):125-37

(12) Lund I, Naslund J, Lundeberg T. Minimal acupuncture is not a valid placebo control in randomised controlled trials of acupuncture: a physiologist's perspective. Chin Med.2009; 30, 4-1

(13) Alizadeh R, Sara E, Saeed S, Bagheri-Hariri B, Shoar N. Acupuncture in Preventing Post-operative nausea and vomiting: efficacy of two points versus single one. Journal of Acupuncture and Meridian Studies.2014;7(2):71-75

(14) Chant B, Madison J, Coop P, Dieberg G. Contact Tools in Japanese Acupuncture:

An Ethnography of Acupuncture Practitioners in Japan. J Acupunct Meridian Stud.2017;10(5):331-9

(15) Kivity O. Japanese acupuncture and moxibustion: What's so unique? European Journal of Oriental Medicine.2018

(16) Chant B, Madison J, Coop P, Dieberg G. Beliefs and values in Japanese Acupuncture: An Ethnography of Acupuncture Practitioners in Japan. Integrative Medicine Research.2017;6(3):260-8

(17) Adams D, Cheng F, Jou H, Aung S, Yasui Y, Vohra S. The safety of pediatric acupuncture: a systematic review. Pediatrics. 2011 dec; 128(6):e1575-87

(18) Zhang X, et al. Effects and mechanisms of transcutaneous electoacupuncture on chemotherapy-induced nausea nd vomiting. Evid Based Complement Alternat Med.2014:860631

(19) Skjeie H, Brekke M. Big needles, small bodies--the absence of acupuncture treatment for infants in contemporary Shanghai: a qualitative study. BMJ. 2015 Volume 5, Issue 11

(20) Birch S. Shonishin: Japanese Pediatric Acupuncture. Thieme.2016

(21) McCoy CE. Understanding the Intention-to-Treat principle in Randomized Controlled Trials. West J Emerg Med. 2017 Oct; 18(6):1075-1078

(22) Godson DR, Wardle JL. Accuracy and precision in acupuncture point location: A critical systematic review. J Acupunct Meridian Stud. 2019 Apr; 12(2):52-66

(23) Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016; 375:454-463

Table 1. Patient Demographics

	Acupuncture n=33	Sham n=33	p-value
Age (years)	9.63 ± 4.02	9.88 ± 4.29	0.8136
Weight (kg)	32.76 ± 15.51	32.30 ± 2.69	0.9053
Height (cm)	126.94 ± 20.86	126.06 ± 19.17	0.8591
BMI (kg/m^2)	19.30 ± 4.88	19.39 ± 5.00	0.9407
Gender Male Female	 20 (60.61%) 13 (39.39%)	 22 (66.67%) 11 (33.33%)	0.609
ASA PS I II	 23 (69.70%) 10 (30.30%)	 20 (60.61%) 13 (38.24%)	0.438
PONV history No Yes	 22 (66.67%) 11 (33.33%)	 24 (72.73%) 9 (27.27%)	0.592
Motion sickness history No Yes	 25 (75.76%) 8 (24.24%)	 28 (84.85%) 5 (15.15%)	0.353
Menarche (females) No Yes	 1 (14.29%) 6 (85.71%)	 2 (22.22%) 7 (77.78%)	0.687
Surgical procedure Head and neck Intraperitoneal Extraperitoneal	 12 (36.36%) 10 (30.30%) 11 (33.33%)	 17 (51.52%) 12 (36.36%) 4 (12.12%)	0.116
Airway used Mask LMA ETT	 6 (18.18%) 3 (9.09%) 24 (72.73%)	 6 (18.18%) 1 (3.03%) 26 (78.79%)	0.583
Adjunct regional anesthesia No Yes	 20 (60.61%) 13 (39.39%)	 21 (63.64%) 12 (36.36%)	0.800
Anesthetic duration (min)	147.27 ± 103.67	171.45 ± 113.72	0.3701
Fentanyl use (mcg/kg/hr)	1.20 ± 0.77	1.09 ± 0.83	0.5697
Opioid use post-op No Yes	 10 (30.30%) 23 (69.70%)	 10 (30.30%) 23 (69.70%)	1.000
Opioid used Nalbuphine Tramadol Morphine	 16 (69.57%) 2 (8.70%) 5 (21.74%)	 18 (78.26%) 1 (4.35%) 4 (17.39%)	0.755

Table 2. BARF scale score ≥4 (per protocol analysis)

BARF >4	Acupuncture n=33	Placebo n=33	p-value
No	25 (75.76%)	16 (48.48%)	0.022
Yes	8 (24.24%)	17 (51.52%)	

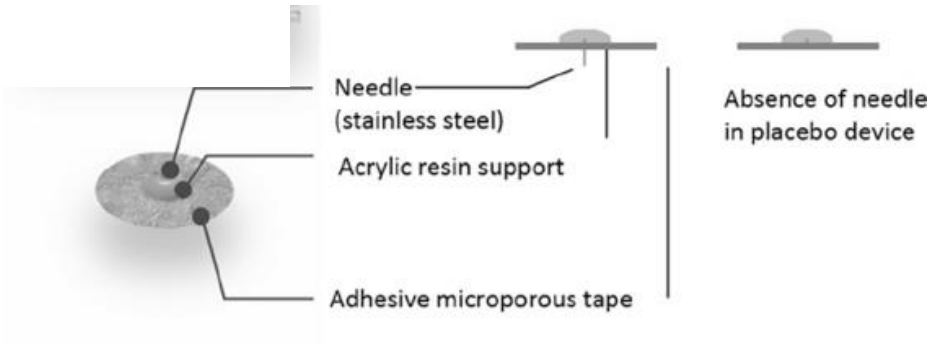

Figure 1. Press-tack needle and placebo device

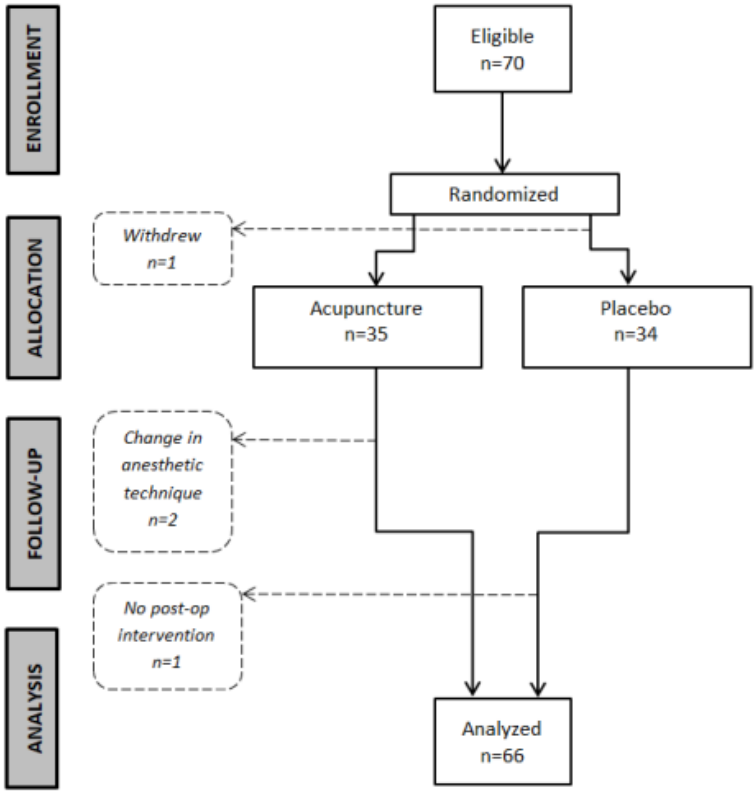

Figure 2. Flowchart for the clinical trial

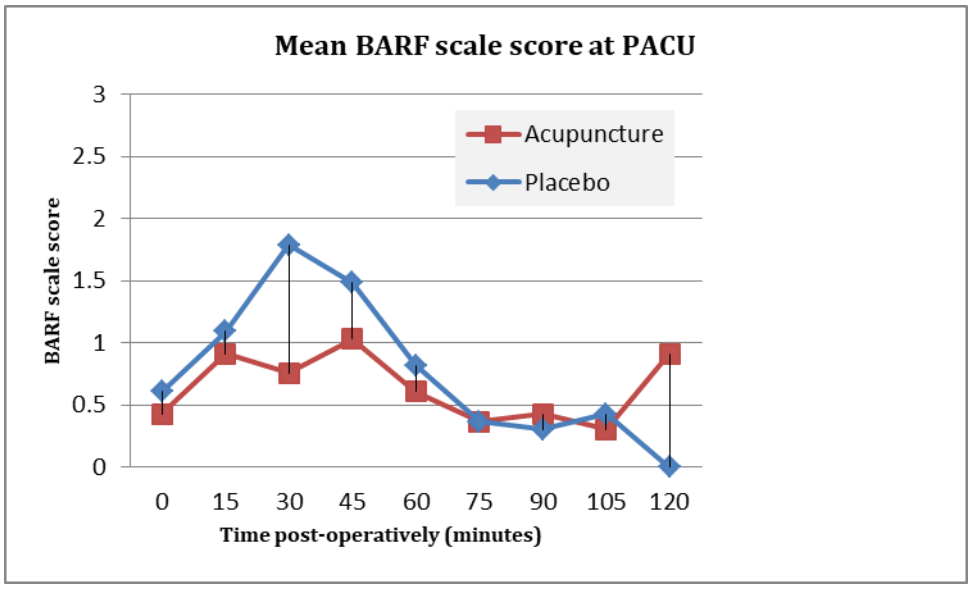

Figure 3. BARF scale score over time at the PACU

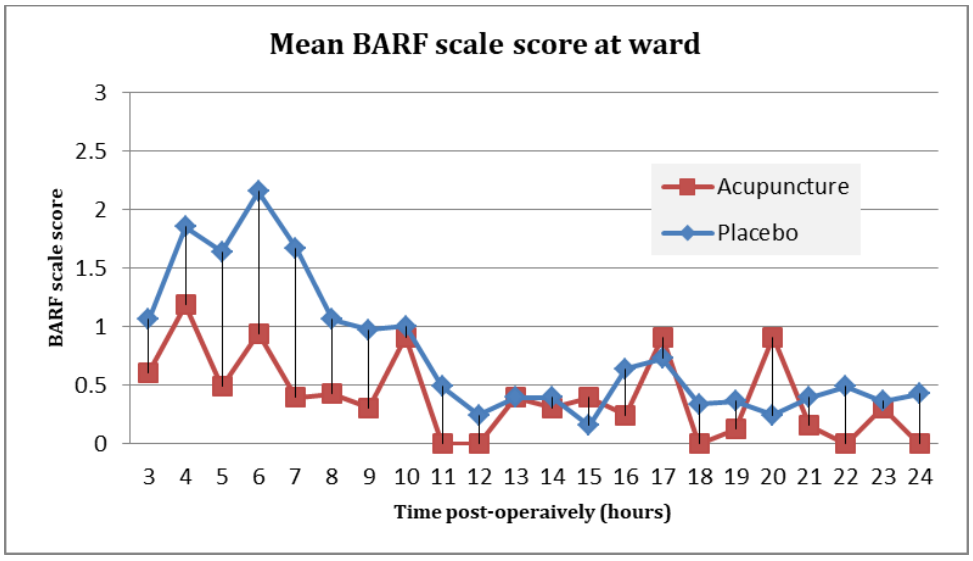

Figure 4. BARF scale score over time at the ward

PARENTAL PERCEPTION AND ATTITUDE ON CHILDHOOD IMMUNIZATION AND OTHER GOVERNMENT HEALTHCARE PROGRAMS AFTER THE DENGUE VACCINE CONTROVERSY: A HOSPITAL-BASED-CROSS-SECTIONAL STUDY

ELAINE DIANE G. SANTOS, MICHAEL M. RESURRECCION

ABSTRACT

BACKGROUND: The dengue vaccine controversy in the Philippines caused significant public anxiety affecting childhood vaccines, as well as other healthcare programs. An assessment of parental perception and attitude on childhood immunization and other government healthcare programs after the dengue vaccine controversy is lacking

OBJECTIVE: To determine the perception and attitude of parents on childhood immunization and other government health care programs after the dengue vaccine controversy at a tertiary pediatric hospital.

METHODOLOGY: A hospital-based cross-sectional survey was done at a tertiary pediatric hospital. A total of 96 subjects participated in the study. Parents with children ages 9 to 18 years old whose child was either vaccinated or non-vaccinated with dengue vaccine seen in the dengue clinic, outpatient department and private clinics were invited to answer the structured questionnaire. Proportional stratified sampling was employed. Mann Whitney U-test compared the perception and attitude scores between parents of children who were recipients and non-recipients of dengue vaccine. A p-value of <0.05 was considered as significant.

RESULTS: The overall perception and attitude of parents on childhood immunization, deworming and vitamin A supplementation did not differ significantly between parents of non-dengue vaccinated children and dengue-vaccinated children. Sociodemographic factors such as gender, marital status, educational attainment, employment, and economic status did not differ significantly in their perception and attitude in terms of childhood immunization, deworming and vitamin A supplementation.

CONCLUSIONS: The overall perception and attitude of parents in both groups showed no significant difference toward childhood immunization, deworming and vitamin A supplementation. There is no association with the overall perception and attitude of parents on childhood immunization, deworming and vitamin A supplementation and their sociodemographic factors.

RECOMMENDATIONS: Future similar studies may be conducted in other regions to determine parental perception and attitude towards the government's immunization program and other health care programs.

KEYWORDS: dengue vaccine, childhood immunization, deworming, vitamin A supplementation

INTRODUCTION

The World Health Organization (WHO) reported dengue fever as one of the most important mosquito-borne viral illnesses. It is a growing global threat that has rapidly spread to all tropical and subtropical regions in the recent decades, posing significant socioeconomic and disease burden. Severe dengue affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children and adults in these regions.[1,2]

Dengue fever is regarded as one of the major public health problems in the Philippines. It is endemic in all regions of the country. In the year 2010 to 2014, about 170,503 symptomatic dengue infections and 750 deaths were reported by the Philippines Department of Health (DoH). The annual incidence of dengue was reported to be at 178 symptomatic dengue episodes per 100,000 populations and a case fatality rate of approximately 0.44%. [3]

In the Philippines, the DoH implemented the National Dengue Prevention and Control Program. The strategies of this program include surveillance, case management and diagnosis, integrated vector management, outbreak response, health promotion, advocacy, and research. [5]

Despite the consistent effort of the international and local government to reduce dengue burden, there is still growing global epidemic of dengue hence the WHO Initiative for Vaccine Research (IVR) facilitated the development and introduction of dengue vaccines.[6]CYD-TDV (live attenuated dengue vaccine) was developed by Sanofi Pasteur (Lyon, France) for use in individuals aged 9 to 45 years, in five low or middle income countries: Brazil, Costa Rica, El Salvador, Mexico and Philippines. [7]

The DoH launched its school-based dengue immunization program last April 4, 2016 vaccinating grade 4 students from the National Capital Region, Calabarzon, and Central Luzon.[8]As of December 2017, approximately 800,000 children were administered with the dengue vaccine. The 800,000-plus figure is an increase from the 733,000 individuals, mostly children from Metro Manila, Region 3, and Region 4 whom the health department said were immunized with live attenuated dengue vaccine. [9]

However in November 2017 Sanofi made an official statement that the live attenuated dengue vaccine may pose severe dengue among those who had not contracted the disease. [10] This led to the temporary suspension of school-based dengue vaccination program which then ensued panic and confusion among parents and relatives of children vaccinated with dengue vaccine. The controversy has gained much attention affecting government-initiated health programs.

The series of events led the author to come up with a study which aims to determine parents' perception and attitude towards childhood immunization and other

government healthcare programs after the dengue vaccine controversy.

The widespread availability and use of vaccines have significantly reduced morbidity, mortality and health care costs associated with infectious diseases providing improved quality of life of patients worldwide. Several studies have identified factors underlying the lack of progress in developing countries, including weak health infrastructure, misconceptions and misperceptions about the efficacy and safety of vaccines, low health literacy, vaccine resistance and hesitancy, and cultural and religious factors. However, parental beliefs about vaccination are one of the major factors in achieving high vaccination rates. [12]

A review of literature indicated that parents' beliefs about the possibility of serious, distant adverse vaccine reactions (AVRs) belong to important factors strongly associated with vaccination hesitancy. The concerns of caregivers most often focus on the composition of vaccines as well as side effects, being usually related to their negative experiences with vaccination. Results of this study also demonstrated that factors such as place of residence, age of the respondents, economic status of families and the number of children in the family had no significant effect on the declared opinions about safety of vaccination.[13]

In any vaccination program, new vaccines such as the ones being developed and tested against dengue virus (DENV) infection have the potential to be accompanied by a variety of challenges. A crucial question from several points of view is whether the public is willing to accept and purchase the vaccine. A meta-analysis by Harapan etal. with1,151 participants stated that vaccine acceptance is an important predictor of the actual acceptance of a given group or society towards the vaccine in question. Vaccine acceptance has an important role in the initiation and continuation of a vaccination program. They identified socioeconomic status, knowledge, attitude, practice and personal experience of dengue fever as factors that were correlated with dengue vaccine acceptance.[15] This study reveals that poor attitude towards vaccination and low socioeconomic status are associated with low dengue vaccine acceptance.

In an effort to measure the impact of the fears and anxiety on broader vaccine confidence, the Philippines was re-surveyed by the Vaccine Confidence Project with their Vaccine Confidence Index, using the same representative sampling approach in the 2015 data. The 2018 study surveyed a further 1,500 participants to the 1,000 surveyed in 2015. The findings reflect a decrease in those who strongly agree that vaccines are important from 93% in 2015 to 32% in 2018. There was a decrease in those who strongly agree that vaccines are safe from 82% in 2015 to 21% in 2018; and the response on confidence in the effectiveness of vaccines decreased from 82% who strongly agree to 21% who agree.[16]

There has been no research that tackles on parental perception and attitude towards childhood immunization and other

government healthcare programs after the dengue vaccine controversy in the local setting hence the conceptualization of this study

OBJECTIVES OF THE STUDY

General Objective: To determine the perception and attitude of parents on childhood immunization and other government health care programs after the dengue vaccine controversy at a tertiary pediatric hospital.

Specific Objectives:

1. To determine the perception and attitude of parents towards government health care programs after the dengue vaccine controversy as to: Childhood Immunization, Deworming, Vitamin A supplementation.

2. To compare the perception and attitude of parents of recipients and non-recipients of dengue vaccine towards childhood immunization and other government healthcare programs.

3. To determine the associations of parental perception and attitude on childhood immunization, deworming and vitamin A supplementation and sociodemographic characteristics as to: Gender, Marital Status, Educational Attainment, Employment Status, Economic Status.

METHODOLOGY

This is a cross sectional study conducted in the Outpatient Department of a Tertiary Pediatric Hospital in Quezon City. The participants enrolled in this study are parents of children ages 9 to 18 years old consulting at the Outpatient Department of a Tertiary Pediatric Hospital regardless of vaccination status for dengue fever. They were invited to participate in the survey and were requested to sign a written informed consent before the questionnaire administration. The study protocol was reviewed and approved by PCMC Institutional Research Ethics Committee (IREC) prior to the conduct of the study. The principal investigator conducted a focused group discussion involving eight parents. There was equal number of male and female participants with age 20 years old and above, with children consulting at the outpatient department. The length of the focus group discussion (FGD) was 60 minutes. The FGD was held at a consultation room near the outpatient clinic. The participants answered ten open-ended questions after they have voluntarily signed a written informed consent. The principal investigator formulated a 13-item questionnaire from the data gathered from the focused group discussion

The questionnaire used in this study was formulated from the data gathered from the focused group discussion. This questionnaire was validated using both the English and Filipino languages. The internal consistency of the questionnaire was measured using Cronbach's alpha while

Interclass correlation coefficient was used to measure test-retest reliability.

The items were answered by each participant using a five-point Likert scale. The possible responses ranged from "strongly disagree" to "strongly agree". A score of zero to four could be received for each statement.

The internal consistency of the questionnaire showed a high Cronbach alpha of .756 which indicates good internal consistency among the items in the questionnaire. This means that the items consistently measure the parental perceptions and attitudes on childhood immunization and other government healthcare programs after the dengue vaccine controversy.

The test-retest reliability of the questionnaire which was measured by Interclass correlation showed a high test-retest correlation of 0.877 which indicates good reliability of the questionnaire. This means that individuals consistently report the same responses during different time periods.

New participants for the study were then recruited and oriented by the principal investigator. The investigator explained the study thoroughly and gave the participants adequate time and opportunity to raise questions. All inquiries from the participants were addressed. The participants were asked to sign a voluntary informed consent after the investigator made sure that all the subjects have fully understood the proceedings. Once qualified, the data from each participant were gathered using the General Information Sheet. Each subject answered a 13-itemquestionnaireformulated from the previously conducted focused group discussion.

The sociodemographic characteristics of the participant were described as categorical variables and summarized using frequencies and proportion. The perceptions and attitudes of parents, the distribution of parents who strongly agree, agree, neutral, disagree, and strongly disagree per question in the tool were summarized using frequencies and proportion. Mann Whitney U-test was used to compare the perception and attitude scores between parents of children who were recipients and non-recipients of dengue vaccine. SPSS 23 was used in all analysis. A p-value of <0.05 was considered as significant.

The answers to the 13-item questionnaire were grouped according to the following variables: 1. Parental perception towards childhood immunization, 2. Parental attitude towards childhood immunization, 3. Parental perception towards deworming and 4. Parental perceptions towards vitamin A supplementation; then the weighted means were computed using the five-point scale with the following interpretation:

Range	Verbal Interpretation
0.00 to 0.79	Generally, strongly disagree
0.80 to 1.59	Generally, disagree
1.60 to 2.39	Generally, not sure
2.40 to 3.19	Generally, agree
3.20 to 4.00	Generally, strongly agree

RESULTS

A total of 96 participants completed the questionnaire. Majority (51%) of the respondents were 30 to 41 years old with a mean age of 39. Eighty-six percent (86%) of the respondents were females. More than half (67%) were married and64% of the respondents were high school graduates. Seventy percent (70%) were unemployed. Majority (92%) of the participants belong to the lower income class. Thirty-four percent (34%) of the participants have at least 3 children. Thirty one percent (31%) of the participants have children who received the Dengue vaccine (Table 1).

Table 1.COMPARATIVE FREQUENCY AND PERCENTAGE DISTRIBUTION OF THE SOCIODEMOGRAPHIC CHARACTERISTICS OF PARENTS OF DENGUE VACCINE RECIPIENTS AND NON-DENGUE VACCINE RECIPIENTS

Characteristics (n=96)	**Dengue Vaccine Non-Recipients n=66, n (%)**	**Dengue Vaccine Recipients n=30,n (%)**
Age of Parents		
18-29	9 (13.6)	1 (3.3)
30-41	35 (53.0)	14 (46.7)
42-53	19 (28.8)	14 (46.7)
54 and above	3 (4.5)	1 (3.3)
Gender		
Male	7(10.6)	3 (10.0)
Female	57 (89.4)	27 (90.0)
Marital Status		
Single	20 (30.3)	6 (20.0)
Married	41 (62.1)	23 (76.7)
Separated	4 (6.1)	1 (3.3)
Widowed	1 (1.5)	0 (0.0)
Educational Attainment of Parents		
Primary	5 (7.6)	1 (3.3)
Secondary	40 (60.6)	21 (70.0)
College	13 (19.7)	4 (13.3)
Graduate Level	7 (10.6)	4 (13.3)
Vocational	1 (1.5)	0 (0.0)
Employment		
Employed	21 (31.8)	8 (26.6)
Unemployed	45 (68.2)	22 (73.3)

Continuation Table 1:		
Monthly income		
Upper Class (>/=80,000)	2 (3.0)	1 (3.3)
Middle Class (30, 000-79, 999)	3 (4.5)	2 (6.7)
Lower Class (</=29,000 pesos)	61 (92.4)	27 (90.0)
Number of Children		
1	8 (12.1)	4 (13.3)
2	14 (21.2)	9 (30.0)
3	23 (34.8)	10 (33.3)
>/=4	21 (31.8)	7 (23.3)
Number of Children given Dengue Vaccine		
1	0 (0.0)	22 (73.3)
2	0 (0.0)	8 (26.6)
3	0 (0.0)	0 (0.0)
>/=4	0 (0.0)	0 (0.0)

Parental Perception on Childhood Immunization

Eighty five percent (85%) of parents of dengue vaccine non-recipients and 83% of dengue vaccine recipients responded positively that vaccines strengthen their child's immunity (agree and strongly agree). The two groups perceived childhood immunization as safe and effective (dengue vaccine non-recipients 86.9%, dengue vaccine recipients 73.3%). Majority of the respondents (56.2%) are not sure if newer vaccines carry more risks and adverse effects. Parents from both groups perceived that doctors are still the most reliable source of information about childhood immunization (dengue vaccine non-recipients 90.8%, dengue vaccine recipients 96.6%). Thirty-three percent of dengue vaccine non-recipients and 43.4% of dengue vaccine recipients are not sure if childhood vaccines cause harmful adverse effects, illness and even death. Fifty-five percent (55%) of the respondents agreed and strongly agreed that information about benefits and side effects of childhood vaccines are readily available and accessible. (See Table 2)

The overall perception of parents towards childhood immunization after the dengue vaccine controversy averaged to 2.56 ± 0.51with a verbal interpretation of generally agree. The mean score on perception of non-dengue vaccinated children (2.56 ± 0.49) and dengue vaccinated children (2.54 ± 0.56) are not significantly different (P-value 0.629).

Table 2.PERCEPTION OF PARENTS ON CHILDHOOD IMMUNIZATION AFTER THE DENGUE VACCINE CONTROVERSY

Variables		(n=96), n (%)	Dengue vaccine Non-Recipients (n=66), n (%)	Dengue vaccine Recipients (n=30), n (%)	P-value
Childhood vaccines strengthen my child's immunity	Strongly disagree Disagree Not sure Agree Strongly Agree	3 (3.1) 1 (1.0) 11 (11.4) 36 (37.5) 45 (46.8)	1 (1.5) 1 (1.5) 8 (12.1) 21 (31.8) 35 (53)	2 (6.6) 0 (0.0) 3 (10) 15 (50) 10 (33.3)	0.1056
Childhood immunization is safe and effective.	Strongly disagree Disagree Not sure Agree Strongly Agree	4 (4.1) 2 (2.0) 10 (10.0) 43 (44.7) 37 (38.5)	2 (3.0) 1 (1.5) 5 (7.5) 31 (46.9) 27 (40.0)	2 (6.6) 1 (3.3) 5 (16.6) 12 (40.0) 10 (33.3)	0.1959
Newer vaccines carry more risks and adverse effects.	Strongly disagree Disagree Not sure Agree Strongly Agree	15 (15.6) 15 (15.6) 54 (56.2) 7 (7.2) 5 (5.2)	12 (7.9) 10 (15) 37 (56) 5 (7.5) 2 (3.0)	3 (10.0) 5 (16.6) 17 (56.6) 2 (6.6) 3 (10.0)	0.1813
Doctors are the most reliable sources of information about childhood immunization.	Strongly disagree Disagree Not sure Agree Strongly Agree	2 (2.0) 1 (1.0) 4 (4.1) 32 (33.3) 57 (59.3)	2 (3.0) 1 (1.5) 3 (4.5) 18 (27.2) 42 (63.6)	0 (0.0) 0 (0.0) 1 (3.3) 14 (46.6) 15 (50)	0.9891
Childhood vaccines cause many harmful adverse effects, illness and even death.	Strongly disagree Disagree Not sure Agree Strongly Agree	22 (22.9) 35 (36.4) 35 (36.4) 2 (2.0) 2 (2.0)	17 (25.7) 26 (39.3) 22 (33.3) 1 (1.5) 0 (0.0)	5 (3.3) 9 (30.0) 13 (43.4) 1 (3.3) 2 (6.6)	0.0996
Information about benefits and side effects of childhood vaccines are readily available.	Strongly disagree Disagree Not sure Agree Strongly Agree	3 (3.10) 7 (7.2) 33 (34.3) 41 (42.7) 12 (12.5)	2 (3.0) 5 (7.5) 20 (30) 30 (45.4) 2 (3.0)	1 (3.3) 2 (6.6) 13 (43.4) 11 (36.6) 3 (10.0)	0.1214
Overall perception	Mean SD	2.56 0.51	2.56 0.49	2.54 0.56	0.629

Parental Attitude on Childhood Immunization

Parents in both groups (dengue vaccine non-recipients 87.8%, dengue vaccine recipients 79.0%) agreed to vaccinate their children by a doctor or in the presence of a doctor. The two groups affirmed (87.4%) that a general consult must be done before vaccine administration. Majority, 72.8% of these parents (dengue vaccine non-recipients 77.2%, dengue vaccine recipients 63.2%) showed positive attitude towards childhood immunization if they were informed and understood the expected side effects before vaccine administration. (Table 3)

The overall attitude of parents towards childhood immunization after the dengue vaccine controversy averaged to 3.04 ± 0.77 with a verbal interpretation of generally agree. The mean score on attitude of parents of non-dengue vaccinated children (3.07 ± 0.73) and dengue vaccinated children (2.80 ± 1.08) towards childhood immunization after the dengue vaccine controversy did not differ significantly (P-value 0.778).

Table 3.ATTITUDE OF PARENTS ON CHILDHOOD IMMUNIZATION AFTER THEDENGUE VACCINE CONTROVERSY

Variables		(n=96), n (%)	Dengue vaccine Non-Recipients (n=66), n (%)	Dengue vaccine Recipients (n=30), n (%)	P-value
I will only allow my children to be vaccinated during their scheduled immunization if:					
It will be administered by a doctor or in a presence of a doctor.	Strongly disagree Disagree Not sure Agree Strongly Agree	3 (3.1) 1 (1.0) 10 (10.4) 50 (52.0) 32 (33.3)	2 (3.0) 0 (0.0) 6 (9.0) 36 (54.5) 22 (33.3)	1 (3.3) 1 (3.3) 4 (13.3) 14 (46.6) 10 (33.3)	0.9861
Check-up will be done before giving the vaccines.	Strongly disagree Disagree Not sure Agree Strongly Agree	3 (3.1) 2 (2.0) 7 (7.2) 47 (48.9) 37 (38.5)	2 (3.0) 2 (3.0) 5 (1.5) 31 (46.9) 26 (39.3)	1 (3.3) 0 (0.0) 2 (3.3) 16 (53.5) 11 (36.6)	0.8112
I have fully understood the expected side effects.	Strongly disagree Disagree Not sure Agree Strongly Agree	3 (3.1) 2 (2.0) 21 (21.8) 47 (48.9) 23 (23.9)	2 (3.0) 1 (1.5) 12 (18.1) 36 (54.5) 15 (22.7)	1 (3.3) 1 (3.3) 9 (30) 11 (36.6) 8 (26.6)	0.6389
Overall Attitude	Mean SD	3.04 0.77	3.07 0.73	2.80 1.08	0.778

Parental Perception on Government Healthcare Programs

This study determined the effect of dengue vaccine controversy on other government healthcare programs. The results showed that 73% of parents of dengue vaccine non-recipients and 70% of parents of dengue vaccine recipients perceived that deworming is safe and effective. The participants from both groups agreed (39.5%) and strongly agreed (32.3%) that parasitism can lead to malnutrition.However,35.4% of parents

from both groups (dengue vaccine non-recipients 33.3%, dengue vaccine recipients 40%) are uncertain of the adverse effects of deworming. (Table 4).

The overall mean perception scores of parents towards deworming is 2.65 ± 0.62 with verbal interpretation of generally agree. The mean score on perception of non-dengue vaccinated children (2.65 ± 0.65) and dengue vaccinated children (2.63 ± 0.33) on deworming are not significantly different (P-value 0.076).

Ninety percent of the respondents perceived that vitamin A supplementation is safe and effective. It has a mean score of 3.24 with a verbal interpretation of generally agree. The mean score on perception of non-dengue vaccinated children (3.28±0.82) and dengue vaccinated children (2.90±1.60) on vitamin A supplementation are not significantly different (P-value 0.938).

Table 4.PERCEPTION OF PARENTS ON OTHER GOVERNMENT HEALTH CARE PROGRAMS

Variables		(n=96), n (%)	Dengue vaccine Non-Recipients (n=66), n (%)	Dengue vaccine Recipients (n=30), n (%)	P-value
Government healthcare programs such as Deworming is safe and effective.	Strongly disagree Disagree Not sure Agree Strongly Agree	2 (2.0) 1 (1.0) 24 (25.0) 38 (39.5) 31 (32.3)	1 (1.5) 1 (1.5) 16 (24.2) 27 (40.9) 21 (31.8)	1 (3.3) 0 (0.0) 8 (26.6) 11 (36.6) 10 (33.3)	0.9069
Parasitic worms in children can lead to malnutrition.	Strongly disagree Disagree Not sure Agree Strongly Agree	2 (2.0) 1 (1.0) 6 (6.2) 44 (45.8) 43 (44.7)	1 (1.5) 0 (0.0) 3 (4.5) 31 (46.9) 31 (46.9)	1 (3.3) 1 (3.3) 3 (10) 13 (43.3) 12 (40)	0.3827
Deworming has harmful adverse effects to children and some even lead to deaths.	Strongly disagree Disagree Not sure Agree Strongly Agree	14 (14.5) 26 (27) 34 (35.4) 12 (12.5) 10 (10.4)	9 (13.6) 17 (25.7) 22 (33.3) 10 (15.1) 8 (12.1)	5 (3.3) 9 (30) 12 (40) 2 (6.6) 2 (6.6)	0.2224
Overall Perception	Mean SD	2.65 0.62	2.65 0.65	2.63 0.33	0.076
Government healthcare programs such as Vitamin A Supplementation is safe and effective.	Strongly disagree Disagree Not sure Agree Strongly Agree	2 (2.0) 1 (1.0) 7 (7.2) 41 (42.7) 45 (46.8)	1 (1.5) 1 (1.5) 2 (3.0) 32 (48.4) 30 (45.4)	1 (3.3) 0 (0.0) 5 (16.6) 9 (30) 15 (50)	0.9380
Overall Perception	Mean SD	3.24 0.93	3.28 0.82	2.90 1.60	0.938

Association of Sociodemographic Characteristics and Parental Perception and Attitude on Childhood Immunization, Deworming and Vitamin A supplementation

The overall mean perception on childhood immunization of female and male parents is 2.56. It has a verbal interpretation of generally agree. Analysis showed that there is no significant difference on the perception of female and male respondents on childhood immunization (P-value 0.400).

The overall mean attitude on childhood immunization of female and male parents is 3.04 with a verbal interpretation of generally agree. Analysis showed that there is no significant difference on the attitude of female and male respondents on childhood immunization (P-value 0.523).

The evaluation of the overall mean perception of female and male parents on deworming is 2.65. It has a verbal interpretation of generally agree. Analysis showed that there is no significant difference on the perception of female and male respondents on deworming (P-value 0.980).

Assessment of the overall mean perception of female and male parents on vitamin A supplementation is 3.24 with a verbal interpretation of generally strongly agree. This study showed that there is no significant difference on the gender of parents and their perception on vitamin A supplementation (P-value 0.901). (Table 5)

Table 5. ASSOCIATION OF GENDER AND PARENTAL PERCEPTIONAND ATTITUDE ONCHILDHOOD IMMUNIZATION, DEWORMING ANDVITAMIN ASUPPLEMENTATION

Variables		Overall Mean	Female n = 84 (87.5%)	Male n = 12 (12.5%)	P-value
Perception on immunization	**Mean**	2.56	2.57	2.47	0.400
	SD	0.51	0.49	0.66	
Attitude on immunization	**Mean**	3.04	3.07	2.80	0.523
	SD	0.77	0.73	1.08	
Perception on deworming	**Mean**	2.65	2.65	2.63	0.980
	SD	0.62	0.65	0.33	
Perception on Vitamin A supplementation	**Mean**	3.24	3.28	2.90	0.901
	SD	0.93	0.82	1.60	

The result of this study showed that the overall mean perception on childhood immunization of single and married parents is 2.56. It has a verbal interpretation of generally agree. The data in this study showed that there is no significant difference

on the marital status of parents and their perception on childhood immunization (P-value 0.533).

The outcome of this study demonstrates that the overall mean attitude on childhood immunization of single and married parents is 3.04. It is interpreted as generally agree. The result of the evaluation showed that there is no significant difference on the perception of single and married parents on childhood immunization (P-value 0.682).

The overall mean perception on deworming of single and married parents is 2.65. The mean is verbally interpreted as generally agree. Analysis showed that there is no significant difference on the marital status of parents and their perception on deworming (P-value 0.643).

The analysis of this study revealed that the overall mean perception of single and married parents on vitamin A supplementation is 3.24. This study showed that regardless of marital status, the respondents generally strongly agreed on vitamin A supplementation. There is no significant difference on the marital status of parents and their perception on vitamin A supplementation (P-value 0.997).

The overall mean perception on childhood immunization of parents with primary, secondary or vocational and college or graduate level of education is 2.56. It has a verbal interpretation of generally agree. The analysis of this study showed that there is no significant difference on the educational attainment of parents and their perception on childhood immunization (P-value 0.090).

The results of this study demonstrate that the overall mean attitude on childhood immunization of parents with primary, secondary, or vocational and college or graduate level of education is 3.04.This analysis showed that regardless of educational attainment, the respondents generally agree on childhood immunization. The evaluation of this report showed that there is no significant difference on the level of education of parents and their attitude on childhood immunization (P-value 0.304).

The analysis of this study showed that the overall mean perception on deworming of parents with primary, secondary, or vocational and college or graduate level of education is 2.65. This study shows that parents generally agree on deworming regardless of educational attainment. Further analysis showed that there is no significant difference on the educational attainment of parents and their perception on deworming (P-value 0.787).

The overall mean perception of parents of all level of education on vitamin A supplementation is 3.24. This data showed that regardless of parental level of education, the respondents generally strongly agreed on vitamin A supplementation. There is no significant difference on parents' educational attainment and their perception on vitamin A supplementation (P-value 0.827).

The overall mean perception (2.56) and attitude (3.04) regardless of employment status on childhood immunization showed that the parents generally agreed on childhood immunization. Statistics showed that there is no significant difference on the employment status of parents and their perception and attitude on childhood immunization.

The overall mean perception of parents on deworming regardless of employment status is 2.65. The employed and unemployed parents generally agreed on deworming. There is no significant difference regardless of employment status of parents and their perception on deworming (P-value 0.964).

This study showed that the overall mean perception on vitamin A supplementation of both unemployed and employed parents is 3.24. The parents generally strongly agreed on vitamin A supplementation regardless of employment status. Analysis showed that there is no significant difference on the perception of unemployed and employed parents on vitamin A supplementation (P-value 0.865).

The result of the study showed that the overall mean perception on childhood immunization and economic status is 2.56. The parents of different economic status generally agreed to have their child vaccinated. Analysis showed that there is no significant difference on the economic status of parents and their perception on childhood immunization (P-value 0.947).

The overall mean attitude on childhood immunization of lower class and middle- or upper-class parents is 3.04 with a verbal interpretation of generally agree. Analysis showed that there is no significant difference on the attitude of lower class and middle- or upper-class parents on childhood immunization (P-value 0.631).

This study demonstrates that the overall mean perception of parents of different economic status on deworming is 2.65. Parents with different economic status generally agreed on deworming. The parents' perception on deworming has no significant difference regardless of economic status (P-value 0.703).

The overall mean perception of lower class and middle- or upper-class parents on vitamin A supplementation is 3.24. These parents generally strongly agreed on vitamin A supplementation regardless of their economic status. Analysis showed that there is no significant difference on the perception of lower class and middle- or upper-class parents on vitamin A supplementation (P-value 0.425).

DISCUSSION

Vaccine safety scares are circumstances in which unwanted events are rightly or wrongly connected with vaccination and create feelings of anxiety and distrust in vaccines and health authorities.[26] Vaccination safety scares have the potential to damage public confidence in vaccines and lower immunization rates, resulting in disease outbreaks and deaths.[27]

In the Philippines, dengue vaccination was suspended in December 2017 when the vaccine manufacturer issued a warning against its own vaccine. Most vaccine memoranda reported on social media and on televisions were on vaccine related deaths. This led to significant public anxiety around dengue vaccine and other childhood vaccines, as well as other health interventions such as deworming in both public health programs and private clinics.[28]Parents became more conscious on their children's health and changed their health seeking behavior.[29]

Despite the dengue vaccine controversy, parents in this study (84.3%) perceived that childhood vaccines benefit their children by strengthening their immune system. This is line with the study by Alshammari et al. which showed that 60-90% of the respondents were knowledgeable regarding the health benefits of vaccinations in children even though 18.4% of their children had experienced vaccination-related minor adverse effects.[12]

In line with the safety and effectiveness of childhood immunization, 83.2% of parents from both groups responded positively (agree and strongly agree). However, four percent from both groups believed that childhood vaccines are harmful with majority are from parents with dengue vaccinated children (9.9%). Some of the respondents, 6.1% (dengue vaccine non-recipients 4.5%, dengue vaccine recipients 9.9%), perceived that childhood immunization is unsafe and not effective. This is also evident in the study conducted by Bults et,al. which showed that fear of side effects or harmful consequences is the most reported reason of parents in declining the H1N1 vaccination in Netherlands.[29]

Kara et al., reported that an increased frequency of vaccine-related adverse events may result in the global perception that vaccines are hazardous, despite continued improvements in vaccine safety.[31]This is also evident in the statement by the SAGE Vaccine Hesitancy Working Group that past negative or positive experience with a particular vaccination can influence hesitancy or willingness to vaccinate. Personal experience or knowledge of someone who experienced an adverse event following immunization (AEFI) can also influence hesitancy.[32] This negative experience by parents with either vaccinated or non-vaccinated children may have led to vaccine hesitancy. This is contrary to a previous study by King et al. which showed that the impact of influenza vaccine suspension in Australia is limited to the influenza vaccine alone. It did not affect their confidence in other established vaccination programs.[27]

Twelve percent of parents in this study (dengue vaccine non-recipients 10.5%, dengue vaccine recipients 7.6%) perceived that newer vaccines carry more risks and adverse effects. This is line with the study by Noakes et,al. which showed that respondents were more comfortable with old vaccines that they felt had been tried and tested. The respondents expressed more anxiety when discussing the introduction of new vaccines.[14]According to SAGE Vaccine Hesitancy Working Group, parents may

hesitate to accept a new vaccine when not proven to be effective.[32]

Despite the vaccine safety scare, majority of parents (92.6%) in this study agreed or strongly agreed that doctors are the most reliable source of information about childhood immunization. However, 10.3% of parents from both groups disagreed or strongly disagreed that this information is readily available or accessible. This is evident in the local study conducted by Valido et,al. which showed that trust in public health institutions has been criticized during the dengue vaccine controversy. Doctors are the most cited trustworthy sources of information. The lack of avenues and confidence in discussing what transpired in the implementation of the vaccination program has led to loss of trust in the dengue vaccination as well as other immunization public health programs.[30]

King et al. concluded that parents accorded great importance on information from a trustworthy and reputable source. General practitioners were acknowledged as a trusted source of information. However,information from physicians was not always a practical solution as they are not immediately accessible.[33]

This perception of inaccessibility of reliable information led parents to seek additional medical information from social media, television, or internet. Knowledge has been identified as an important factor which influences parents' decisions. A wider source of information has been related to a better level of knowledge in the frame of decision-making about vaccination.[34]The absence of clear messages from trusted heath authorities created information void for parents, inadvertently allowing the perpetuation and persistence of a negative association. [33]

Parents became more vigilant about their child's health after the dengue vaccine controversy. Majority of parents in this study are still willing to give the scheduled childhood vaccines to their children provided that it is administered by a doctor or at least in the presence of a primary physician during administration (85.3%), after a thorough general consult has been done (87.4%) and after they have fully understood the benefit and side effects of the vaccine (72.8%). This is evident in the local study by Valido et.al. where in there is a greater demand for more and specific information during the dengue vaccine controversy in the Philippines. After the dengue vaccine scare, these parents now preferred to consult from private health practitioners.[30]

A qualitative study conducted in the United Kingdom (UK) to examine parents' views of the Measles Mumps Rubella (MMR) vaccine controversy determined that health scares increase parental information needs, particularly in relation to future vaccination intent. However, it appears that for many study parents, in the circumstance of the suspension, vaccination was conditional on the provision of a clear safety message via authoritative sources. [33]

Despite the vaccine safety scare, majority of the parents in this study still believed that other government healthcare programs such as deworming, and vitamin A supplementation are safe, effective, and

beneficial. However, 22.9% of the respondents perceived deworming as harmful. This is in line with the study by Larson et al. which showed that dengue vaccine panic does not only undermined trust in the dengue vaccine, vaccines more broadly, but also other interventions provided by health clinics, such as deworming medication.[16]

The overall perception and attitude of parents towards childhood immunization in this study did not differ significantly in terms of gender, marital status, educational attainment, employment status and economic status. This is in line with the study by Braczkowska et al. which showed that economic status of families had no significant effect on the opinions about safety of vaccination.[13]This is however in contrast with the findings by Faleńczak et al. and Braczkowska et,al. which showed that parents with a higher level of education and past vaccine-related experience encountered more frequent negative opinions on vaccination.[13, 35] A study by Brown et,al. showed that lower vaccine uptake was associated to lower parental income and lower parental education which is in contrast with our study. [36]

CONCLUSION AND RECOMMENDATIONS

We interviewed a total of 96 parents with children 9 to 18 years old who were non-dengue vaccine recipients and dengue vaccine recipients using a self-administered questionnaire.

The overall perception and attitude of parents in this study showed that they generally agree on childhood immunization, deworming and vitamin A supplementation despite the dengue vaccine controversy. There was no significant difference in the overall perception and attitude of parents whose children were or were not recipients of the dengue vaccine in terms of childhood immunization, deworming and vitamin A supplementation after the dengue vaccine controversy. This study showed that there is no association on the overall perception and attitude of parents on childhood immunization, deworming and vitamin A supplementation and their gender, marital status, educational attainment, employment, and economic status.

Future similar studies may be conducted in other provinces or regions to determine parental perception and attitude toward the government's immunization program and other health care programs.

BIBLIOGRAPHY

1. World Health Organization. (2018, September 13). Dengue and severe dengue

2. Wilder-Smith, A., Murray, & Quam, M. (2013). Epidemiology of dengue: past, present and future prospects. Clinical Epidemiology, 299.

3. Undurraga, E. A., Edillo, F. E., Erasmo, J. V., Alera, M. P., Yoon, I., Largo, F. M., & Shepard, D. S. (5, April). Disease Burden of Dengue in the Philippines: Adjusting for Underreporting by Comparing Active and Passive Dengue Surveillance in Punta Princesa, Cebu City

4. Gubler, D. J. (2015). The partnership for dengue control – A new global alliance for the prevention and control of dengue. Vaccine, 33(10), 1233.

5. Dengue Prevention and Control Program | Department of Health website. (n.d.)

6. World Health Organization. (2017, December 5). Dengue vaccine research.

7. Gatell, H., Alpuche-Aranda, C. M., Santos-Preciado, J. I., & Avila, M. H. (2016, November 1). Dengue vaccine: local decisions, global consequences.

8. Bonalos, P. (2016, April 4). DOH starts dengue vaccination program. CNN Philippines.

9. Lardizabal, C. (2017, December 8). DOH: More than 800,000 children vaccinated with Dengvaxia. CNN Philippines.

10. Drug firm warns of 'severe disease' from dengue vaccine for people with no prior infection. (2017, November 30). CNN Philippines.

11. Fatima, K., & Syed, N. I. (2018, October 31). Dengvaxia controversy: impact on vaccine hesitancy.

12. Alshammari, T. M., Subaiea, G. M., Hussain, T., Moin, A., & Yusuff, K. B. (2018). Parental perceptions, attitudes and acceptance of childhood immunization in Saudi Arabia: A cross sectional study. Vaccine, 36(1), 23-28.

13. Braczkowska, B., Kowalska, M., Barański, K., Gajda, M., Kurowski, T., & Zejda, J. (2018). Parental Opinions and Attitudes about Children's Vaccination Safety in Silesian Voivodeship, Poland

14. Noakes, K., Yarwood, J., & Salisbury, D. (2006). Parental Response to the Introduction of a Vaccine Against Human Papilloma Virus. Human Vaccines, 2(6), 243-248.

15. Harapan, H., Fajar, J. K., Sasmono, R. T., & Kuch, U. (2016). Dengue vaccine acceptance and willingness to pay. Human Vaccines & Immunotherapeutics, 13(4), 786-790

16. Larson, H. J., Go, K. H., & De Figueiredo, A. (2018, October 12). Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness.

17. Vaccine Confidence Project. (2018, November 11). Philippines: We are Turning Into a Nation of Anti-Vaxxers After the Dengvaxia Controversy: The Vaccine Confidence Project.

18. Altmann, T. K. (2008, August 03). Attitude: A Concept Analysis - Altmann - 2008 - Nursing Forum - Wiley Online Library.

19. McDonald, S. M. (2012, February). Perception: A concept analysis.

20. Immunization. (2018, February 23). Retrieved

fromhttps://www.who.int/topics/immunization/en/

21. UptoDate, Thomas, S. J., Rothman, A. L., Srikiatkhachorn, A., & Kalayanarooj, S. (2018, 24). Dengue virus infection: Clinical manifestations and diagnosis.

22. Kirstein, J., Douglas, W., Thakur, M., Boaz, M., Papa, T., Skipetrova, A., & Plennevaux, E. (2018). Immunogenicity of the CYD tetravalent dengue vaccine using an accelerated schedule: randomized phase II study in US adults. BMC Infectious Diseases, 18(1).

23. Leheny, S. (2017, February 21). 'Adverse Event,' Not the Same as 'Side Effect'.

24. National Statistics Office. 2012. 2012 Family income and expenditure survey. Retrieved from http://psa.gov.ph. Accessed 28July 2018.

25. Larson, H. J., Go, K. H., & De Figueiredo, A. (2018, October 12). Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness.

26. World Health Organization Regional Office for Europe. (2017). Vaccination and Trust: How Concerns arise and the Role of Communication in Mitigating crises. Copenhagen.

27. King, C., & Leask, J. (2017, January 23). The impact of a vaccine scare on Parental views, Trust and Information Needs: A Qualitative Study in Sydney, Australia.

28. Taylor. (n.d.). Vaccine Confidence Plummets in the Philippines Following Dengue Vaccine Scare: Why it Matters to Pandemic Preparedness.

29. Bults, M., Beaujean, D. J. M. A., Richardus, J. H., Steenbergen, J. E. van, & Voeten, H. A. C. M. (2011, July 5). Pandemic influenza A (H1N1) vaccination in The Netherlands: Parental reasoning underlying child vaccination choices.

30. Valido, E. M., Laksanawati, I. S., & Utarini, A. (2018, September 10). Acceptability of the Dengue Vaccination Among Parents in Urban Poor Communities of Quezon City, Philippines Before and After Vaccine Suspension.

31. Parental Vaccine Knowledge and Behaviours: a survey of ... (n.d.).

32. Vaccine acceptance: A model of determinants of vaccine ... (n.d.).

33. King, C. (2017, January 23). The impact of a vaccine scare on parental views, trust and information needs: a qualitative study in Sydney, Australia.

34. Damnjanović, K., Graeber, J., Ilić, S., Lam, W. Y., Lep, Ž., Morales, S., … Vingerhoets, L. (2018, June 13). Parental Decision-Making on Childhood Vaccination.

35. Braczkowska, B., Kowalska, M., Braczkowski, R., & Barański, K. (2017). Determinants of vaccine hesitancy.

36. Brown, K. F., Kroll, J. S., Hudson, M. J., Ramsay, M., Green, J., Long, S. J., … Sevdalis, N. (2010). Factors underlying parental decisions about combination childhood vaccinations including MMR: A systematic review. Vaccine, 28(26), 4235–4248. doi: 10.1016/j.vaccine.2010.04.052

ANXIETY AND DEPRESSION IN ADOLESCENTS WITH EPILEPSY AT PHILIPPINE CHILDREN'S MEDICAL CENTER

PEARL JOY L. SENDAYDIEGO, ELLAINE R. ROMANO, CRISTINA CRUZ-URBI, JOY P. MALINIT

ABSTRACT

OBJECTIVE: Epilepsy is a chronic neurologic disorder complicated by neurobehavioral comorbidities which adversely affect quality of life. The study determined the prevalence of anxiety and/or depression in adolescents with epilepsy and the association of these disorders with sociodemographic variables and seizure-related factors in the Philippines.

METHODOLOGY: Patients who fulfilled the inclusion and exclusion criteria were screened using the Hospital Anxiety and Depression Scale (HADS)/ Hospital Anxiety and Depression Scale-Pilipino (HADS-P).Epilepsy-related and sociodemographic variables in association with anxiety and depression were determined and analyzed.

RESULTS: A total of 145 adolescent patients were included in the study. There was a 17.4% prevalence of anxiety and 3.4% prevalence of depression according to the screening tool.There was no significant factor associated with occurrence of anxiety. Psychiatric illness in the first degree relative, frequent seizures at onset, no anti-epileptic drug use and monotherapy at the time of study were associated with depression. Presence of anxiety also increased the odds of having depression.

CONCLUSIONS: Affective disorders are common in adolescents with epilepsy and factors related to their occurrence must be anticipated. Hence, the need to screen the patients for psychiatric symptoms early and regularly.

KEYWORDS: epilepsy, adolescents, anxiety, depression

INTRODUCTION

Children with epilepsy are at high risk for behavioural and psychiatric disorders in population-based studies (1). Adolescence is a particularly vulnerable period marked by profound developmental changes and coping with these changes may be especially challenging for adolescents with epilepsy(2). Epilepsy impacts on both peer relationships and the development of independence and autonomy subsequently leading to low self esteem, depression, loneliness, anxiety and behavioral problems (3).Depression and anxiety in children and adolescents with epilepsy requires further attention because it

carries a risk of reduced quality of life and complications in life (4).

There is increasing prevalence of affective disorders in children with epilepsy compared with the general population and children with non-neurologic disorders (5). Depression is one of the most commonly occurring major psychiatric disorders, and it has become increasingly recognized that the disease often begins in adolescence (4).Point prevalence of depression in children is 1–2%, increasing to 3–8% in adolescents and by the end of adolescence approximately 1 in 5 adolescents will have experienced at least one depressive episode (1).

Prevalence of depression and anxiety in childhood epilepsy to be between 8 – 35% and 15 – 36%, respectively (6).This suggests that a comprehensive epilepsy service is needed to provide assessment and treatment of psychiatric problems and there should be regular monitoring of psychological adjustment of children with epilepsy (7, 8).These disorders are often either unrecognized or assessment are not available. Finding ways of improving the identification of the psychological morbidity such as using a locally validated screening tool would lead to early treatment and influence the course of the illness. Affective disorders in the general child population are also multifactorial, vulnerable to multi-etiologic risk factors including biological, social and seizure-related risk factors (2).

Hospital Anxiety and Depression Scale (HADS) developed by Zigmond and Snaithis designed to identify possible and probable cases of depression and anxiety disorders among the medically ill patients (9). It only includes psychological symptoms, while the somatic items which could be attributed to the physical illness have been omitted. It is a 14-item, self-assessment questionnaire, composed of 7-items for both the anxiety subscale and depression subscale sensitive to changes both during the course of the illness and in response to psychotherapeutic and psychopharmacological interventions (10). Sensitivity and specificity of the HADS were most often found to be in the range of 70% to 90% (11).

The HADS-Pilipino (HADS-P) recommended optimal cut-off score for Filipino is a HADS / HADS-P score of 11, with a sensitivity of 75% and a specificity of 70%, and a PPV of 75% (12). It has the advantage of being quick and easy to administer, with a high patient acceptability, and can discriminate to a certain extent between cases of depression and anxiety.

There is limited local data describing the profile of anxiety and or depression among adolescents with epilepsy and their association with seizure-related and sociodemographic variables. Identification of certain risk factors provided information on variables which may be modifiable to alter course of illness. The information was used for the establishment of a screening tool adaptable to our local setting.

General Objective

1. Determine the prevalence of anxiety and/or depression among adolescent patients with epilepsy at the Philippine Children's Medical Center and the relationship of these affective symptoms to seizure-related and sociodemographic variables.

Specific Objectives

1. Describe clinical characteristics of adolescent patients with epilepsy as to age, gender, education level, family history of psychiatric illness, medical comorbidities

2. Describe epilepsy characteristics as age of onset, seizure frequency, type of seizure/epilepsy syndrome, electroencephalogram findings, neuro imaging findings and drug treatment

3. Determine prevalence of anxiety and or depression rates among subjects using Hospital Anxiety and Depression Scale (HADS) or the locally translated and validated HADS-Pilipino (HADS-P)

4. Determine association of socio-demographic and epilepsy-related variables to occurrence of anxiety and depression

METHODOLOGY

Approval was obtained from the Philippine Children's Medical Center Institutional Review Board (IRB). This is an analytical cross-sectional study. Adolescent patients aged 10-19 years old with epilepsy were recruited at the Philippine Children's Medical Center Neurology Clinic (pay and charity service). For the Pay Clinic, a letter was given to the Attending Child Neurologist to ask permission to conduct of the study. During the clinic hours for both the Pay and Charity Service Clinics, adolescents with epilepsy were identified. Informed consent and assent were obtained. If the patient's attending physician is the primary investigator, co-investigator or senior investigator, any of the study members who are not in direct care of the patient obtained the consent/assent instead. Eligible participants under went further evaluation based on socio-demographic factors, epilepsy factors and HADS/HAPS-P tool. The study was conducted at the Neurology or Psychiatric Outpatient Clinic, in a single room, one subject at a time to maintain privacy.

From September 2018 to April 2019, demographic and clinical data from the patient via questionnaires (socio-demographic, seizure-related variables and HADS/HADS-P tool) and Outpatient Clinic charts were collected, reviewed, and analyzed. The study used the Filipino-translated and validated HADS questionnaire by De Guzman (12). Subjects screened positive under HADS/HADS-P were promptly referred to psychiatry service for further evaluation. For the Outpatient Pay Clinic, if the participant would warrant a psychiatric referral, the attending neurologist was informed of the investigator's findings and recommendation.

Descriptive statistics was used to summarize the socio-demographic and clinical characteristics of the participants.

Frequency and proportion were used for categorical variables, median and inter quartile range for non-normally distributed continuous variables and mean and SD for normally distributed continuous variables. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant predictors of HADS/HADS-P anxiety and/or depression on adolescent patients with epilepsy. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. STATA 13.1 was used for data analysis.

RESULTS

The socio-demographic characteristics and epilepsy-related clinical features of the adolescents with epilepsy are described in Table 1 and 2, respectively. Majority of participants had focal epilepsy, etiology unknown (49.7%) and structural/metabolic causes (23.4%). At the time of the study, most adolescents were seizure free for more than 12 months (47.4%) or were having 1 or more seizures during the past year but not more than once per month (45.6%). Most participants were on monotherapy (86.2%) with valproic acid as the most used anti-epileptic drug taken by 40 (27.6%) patients followed by phenobarbital in 34 (23.4%) and oxcarbazepine in 27 (18.6%).

The prevalence of anxiety and/or depression is presented in Table 3. Among adolescents with epilepsy, there was a higher prevalence of anxiety (17.4%) compared to depression (3.4%) in both males and females. There was also a 2.8% prevalence of occurrence of both anxiety and depression among the participants. Comparing the mean anxiety and depression score for males and females, were however, not significant. All patients who had anxiety and/or depressive symptoms were referred to psychiatry service, but some were lost to follow-up. Hence, confirmatory psychiatric diagnosis was provided for 23.5% of participants.

In the univariate analysis of socio-demographic and epilepsy-related clinical factors on hospital anxiety and depression scale, anxiety score ≥11, there was no significant factor associated with anxiety among adolescent patients with epilepsy (Table 4). Excluding 4 adolescents with coexisting HADS/HADS-P depression score of ≥11, the findings showed that adolescents on valproic acid were 2.90 times more likely to have anxiety (95% confidence interval = 1.19, 7.08, p = 0.019). Other factors were still noncontributory.

The results of the univariate analysis of socio-demographic and epilepsy-related clinical factors on hospital anxiety and depression scale, depression score ≥11 showed that 5 factors were significantly associated (Table 5). Adolescent patients with epilepsy that has a psychiatric illness in first degree relative were 12.7 times more likely to have depression (95% confidence interval = 1.81,88, p = 0.010). Patients who had seizure frequency (weekly or daily at onset) were 5.68 times more likely to experience depressive symptoms (95% confidence interval = 1.25,26, p = 0.025).

Patients not taking anti-epileptic drug at the time of study were associated with depression (odds ratio = 12.67, 95% confidence interval = 1.8,88.5, p = 0.010) and those on monotherapy were less likely to have depression compared to those not on anti-epileptic drug at the time of study (odds ratio = 0.09, 95% confidence interval = 0.01,0.62, p = 0.010). For every score increase in anxiety score based on HADS/HADS-P, the odds of having depression also increases by 25% (odds ratio = 1.25, 95% confidence interval = 1.04,1.51, p = 0.016). Other socio-demographic and epilepsy-related factors were not statistically significant.

Excluding four adolescents with coexisting HADS/HADS-P anxiety score of ≥11, there were 3 significant factors identified: more frequent seizures at onset (weekly or daily) (odds ratio= 7.68, 95% confidence interval = 1.14, 50, p = 0.036); no anti-epileptic drug at the time of the study (odds ratio= 29.56, 95% confidence interval = 3.5, 247, p = 0.002) and monotherapy use (odds ratio= 0.04, 95% confidence interval = 0.01, 0.32, p = 0.003).

DISCUSSION

Depression and anxiety in youth with epilepsy is often unrecognized despite the increasing number of affective disorders in pediatric patients with epilepsy. The prevalence in our study is comparable to the rates found in population-based studies. In contrast to the study of Kwong in which anxiety and depression are highly correlated with each other, we showed that presence of anxiety predisposes an adolescent to developing depression (2). Thus, regular evaluation is needed when a patient presents with anxiety symptoms. While there were no significant sociodemographic and epilepsy-related variables associated with anxiety, there were important factors to note which were relevant to depression.

Seizure frequency and severity was reported in most studies to be a contributory factor to affective disorders. A study among Asian population showed that frequent seizures at onset and high anxiety scores were highly correlated with depression, and this was demonstrated in the present study (2). But disparate to their findings, female gender, presence of medical comorbidities, younger age at onset and longer duration of epilepsy were not significantly associated. Like a local report by Manalac etal factors like gender, age at onset, duration of illness and type of epilepsy were observed not to be significantly associated with occurrence of neuropsychiatric disorders (13). The present study further showed that adolescent patients with epilepsy that has a psychiatric illness in first degree relative is linked to the occurrence of depression and was congruent to the one reported by Thome-Souza (14).

Although reported to be predictors of depression, the small number of subjects in the different syndromic epilepsy types as well as those using certain anti-epileptic drugs limits this interpretation. While one-fourth of the participants were on Phenobarbital, the current study found no link to depression. When participants with coexisting anxiety and depression were

excluded, valproic acid was noted to be highly associated with anxiety. Kinrys etal showed that valproic acid is efficacious in treatment of anxiety (15). However, the therapeutic level to attain clinical response was not examined. The participants in the present study may have reached therapeutic dosages for control of seizure but not for control of anxiety. Moreover, patients not taking anti-epileptic drug at the time of the study were associated with depression and those on monotherapy were 91 times less likely to have depression compared to those not on anti-epileptic drugs at the time of study. Certain antiepileptic drugs are used for their mood-stabilizing properties (16). Once withdrawn, symptoms of a mood disorder which was in remission can return. In this study's sample population, presence of a single drug use isa protective factor for depression. However, there were no subjects under the polytherapy group for comparison which precludes analysis.

Though the participants attended mainstream school, intellectual and cognitive function assessments were not performed. There could have been unrecognized presence of deficits which puts them at increased risk for depression and anxiety disorders (17).

All the eight participants seen by the psychiatry service were diagnosed to have an affective disorder according to the criteria under the Diagnostic and Statistical Manual for Mental Disorders, 5th edition. Patients were advised to beonclose monitoring to yield meaningful data on changes of severity of symptomatology.

CONCLUSION/ RECOMMENDATIONS

The current study shows that affective disorders are common in adolescent patients with epilepsy. There was a 17.4% prevalence of anxiety and 3.4% prevalence of depression in this study population according to the HADS/HADS-P tool. However, a confirmatory diagnosis was not done in some patients. The presence of psychiatric illness in the first degree relative, frequent seizures at onset, no anti-epileptic drug use, monotherapy and occurrence of anxiety are associated with depression that clinicians must be aware of. Influence of other risk factors is not demonstrated in this study. Collaboration with other Pediatric Neurology-Psychiatry institutions is recommended to increase and diversify the population. Performances of intellectual and cognitive assessments are likewise recommended. There were only less than one-fourth of participants seen by the psychiatry service, reflecting the unmet needs for timely screening of patients and under-recognition of these disorders among caregivers and health practioners, alike. A comprehensive assessment program is therefore required.

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REFERENCES

1. Reilly C, Agnew R, Neville BGR. Depression and anxiety in childhood epilepsy: a review. Seizure. 2011;20:589-597. [3]

2. Kwong KL, Lam D, Tsui S, et al. Anxiety and Depression in Adolescents With Epilepsy. *J Child Neurol*. 2016;31(2):203-210. [3, 4, 18]

3. McEwan MJ, Espie CA, Metcalfe J. A systematic review of the contribution of qualitative research to the study of quality of life in children and adolescents with epilepsy. *Seizure*. 2004;13(1):3-14. [3]

4. Ekinci O, Titus JB, Rodopman AA, Berkem M, Trevathan E. Depression and anxiety in children and adolescents with epilepsy: prevalence, risk factors, and treatment. Epilepsy & Behavior 2009;14(1):8–18. [3]

5. McDermott S, Mani S, Krishnaswami S. A population-based analysis of specific behavior problems associated with childhood seizures. Journal of Epilepsy 1995;8:110–8. [3]

6. Dunn DW, Besag F, Caplan R, Aldenkamp A, Gobbi G, Sillanpää M. Psychiatric and Behavioural Disorders in Children with Epilepsy (ILAE Task Force Report): Anxiety, depression and childhood epilepsy [published online ahead of print, 2016 May 16]. *Epileptic Disord*. 2016;doi:10.1684/epd.2016.0813. [3]

7. Dunn DW, Austin JK, Perkins SM. Prevalence of psychopathology in childhood epilepsy: categorical and dimensional measures. Developmental Medicine and Child Neurology 2009;51:364–72. [3]

8. Davies S, Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. *Dev Med Child Neurol*. 2003;45(5):292-295. [3]

9. Zigmond, A. S. and Snaith, R. P. The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica, 1983; 67: 361–370. [4]

10. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale – A review of validation data and clinical results. J Psychosom Res. 1997; 42(1):17-41. [4]

11. Goldberg DP, Cooper B, Eastwood MR, Kedward HB, Shepherd M. A standardized psychiatric interview for use in community surveys. Br J Prev Soc Med. 1970; 24(1):18-23. [4]

12. De Guzman, M. A Validation of the Hospital Anxiety and Depression Scale (HADS) in the Medically-Ill. Acta medica Philippina. 2014; 42(3): 53-62. [4]

13. Manalac A, Luspo P, Ortiz M. A Cross Sectional Study of the Neuropsychiatric Profile of Children with Epilepsy and their siblings using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) at the Philippine Children's Medical Center. 2013. Unpublished manuscript. [18]

14. Thome-Souza S, Kuczynski E, Assumpção F, et al. Which factors may play a pivotal role on determining the type of psychiatric disorder in children and adolescents with epilepsy? Epilepsy Behav 2004;5(6):988-94. [18]

15. Kinrys G, Pollack MH, Simon NM etal. Valproic acid for the treatment of social anxiety disorder. Int Clin Psychopharmacol. 2003; 18(3): 169-72. [19]

16. Kanner AM, Dunn DW. Diagnosis and management of depression and psychosis in children and adolescents with epilepsy. Journal of Child Neurology 2004;19:65–72. [19]

17. Whitney DG, Shapiro DN, etal. Factors associated with depression and anxiety in children with intellectual disabilities. J Intellect Disabil Res. 2019;63(5): 408-417. [19]

TABLE 1. SOCIAL AND DEMOGRAPHIC FEATURES OF PATIENTS (N=145)

	Frequency (%); Mean ± SD
Age, years	13.27 ± 2.60
Sex	
Male	88 (60.69)
Female	57 (39.31)
Educational level	
Grade 4	15 (10.42)
Grade 5	21 (14.58)
Grade 6	22 (15.28)
Grade 7	22 (15.28)
Grade 8	23 (15.97)
Grade 9	7 (4.87)
Grade 10	8 (5.56)
Grade 11	9 (6.25)
Grade 12	11 (7.64)
1st year college	6 (4.17)
Father Employment Status	
Unemployed	17 (11.72)
Employed	93 (64.14)
Self employed	29 (20)
Mother Employment Status	
Unemployed	84 (57.93)
Employed	39 (26.90)
Self employed	20 (13.79)
Psychiatric Illness in First Degree Relative	5 (3.45)
Concomitant Medical Illness	4 (2.76)

Abbreviation: SD, standard deviation

TABLE 2.EPILEPSY-RELATED CLINICAL FEATURES OF PATIENTS (N=145)

	Frequency (%); Median (IQR)
Age at Seizure Onset, years	7 (4 to 11)
Duration of Epilepsy, years	5 (2 to 9)
Epilepsy Type	
Focal Epilepsy, Structural-Metabolic	34 (23.45)
Focal Epilepsy, Post-infectious	2 (1.38)
Focal Epilepsy, Unknown	72 (49.66)
Generalized Epilepsy, Structural-Metabolic	1 (0.69)
Generalized Epilepsy, Post-infectious	2 (1.38)
Generalized Epilepsy, Unknown	27 (18.62)
Juvenile Myoclonic Epilepsy	1 (0.69)
Childhood Absence Epilepsy	4 (2.76)
Benign Childhood Epilepsy with Centrotemporal Spikes	2 (1.38)
EEG findings	
Normal	67 (46.53)
Abnormal	77 (53.47)
Neuroimaging findings	
Normal	87 (60)
Abnormal	42 (28.97)
Seizure Frequency (weekly or daily at onset)	14 (9.66)
Seizure Frequency	
seizure free ≥12 months	77 (53.10)
≥1 seizure for 12 months but <1 seizure per month	59 (40.69)
≥1 seizure per month	6 (4.14)
≥1 seizure per week	3 (2.07)
Anti-epileptic Drugs at Time of Study	
Topiramate	1 (0.69)
Clonazepam	1 (0.69)
Lamotrigine	7 (4.83)
Phenobarbital	34 (23.45)
Carbamazepine	1 (0.69)
Oxcarbazepine	27 (18.62)
Valproic acid	40 (27.59)
Levetiracetam	16 (11.03)
Perampanel	2 (1.38)
Zonisamide	2 (1.38)
None	5 (3.45)
Anti-epileptic Drug Use at Time of Study	
None	5 (3.45)
Monotherapy	125 (86.21)
Polytherapy	15 (10.34)

Abbreviation: IQR, inter-quartile range

TABLE 3. PREVALENCE OF ANXIETY AND DEPRESSION USING HADS/HADS-P (N=145)

	Total (n=145)	**Male (n=88)**	**Female (n=57)**	**P-value**
	Frequency (%); Mean ± SD			
Anxiety Score	7.65 ± 3.71	7.65 ± 3.63	7.65 ± 3.86	0.998
Depression Score	5.47 ± 3.24	5.41 ± 3.20	5.56 ± 3.33	0.783
Prevalence of Anxiety and/or Depression				0.657
Anxiety alone (Anxiety Score ≥11)	25 (17.24)	17 (19.32)	8 (14.04)	
Depression alone (Depression Score ≥11)	5 (3.45)	4 (4.55)	1 (1.75)	
Anxiety and Depression (Anxiety and Depression Score ≥11)	4 (2.76)	2 (2.27)	2 (3.51)	
Psychiatry Referral Status				
For scheduling	26 (76.47)	19 (82.61)	7 (63.64)	
Seen	8 (23.53)	4 (17.39)	4 (36.36)	
Major Depressive Disorder	2 (25.0)	0	2 (50)	
Bipolar II Disorder with Psychotic Features	1 (12.5)	0	1 (25)	
Persistent Depressive Disorder	1 (12.5)	0	1 (25)	
Other Specified Depressive Disorder	2 (25.0)	2 (50)	0	
Other Specified Anxiety Disorder	2 (25.0)	2 (50)	0	

Abbreviation: SD, standard deviation

TABLE 4. UNIVARIATE ANALYSIS OF SOCIO-DEMOGRAPHIC AND EPILEPSY-RELATED CLINICAL FACTORS ON HOSPITAL ANXIETY AND DEPRESSION SCALE, ANXIETY SCORE ≥11 (N=145)

	Cases (n=29)	**Control (n=116)**	**Odds ratio (95% CI)**	**P-value**
	Frequency (%); Mean ± SD; Median (IQR)			
Age	13.34 ± 2.68	13.25 ± 2.59	1.01 (0.87–1.19)	0.860
Sex				
Male	19 (65.52)	69 (59.48)	(reference)	-
Female	10 (34.48)	47 (40.52)	0.77 (0.33–1.81)	0.552
Educational level				
Grade 4	5 (17.24)	10 (8.70)		
Grade 5	6 (20.69)	15 (13.04)		
Grade 6	3 (10.34)	19 (16.52)		
Grade 7	2 (6.90)	20 (17.39)		
Grade 8	5 (17.24)	18 (15.65)	0.96 (0.81–1.12)	0.578
Grade 9	0	7 (6.09)		
Grade 10	3 (10.34)	5 (4.35)		
Grade 11	2 (6.90)	7 (6.09)		
Grade 12	1 (3.45)	10 (8.70)		
1st year college	2 (6.90)	4 (3.48)		
Father Employment Status				
Unemployed	5 (17.86)	12 (10.81)	(reference)	-
Employed	16 (57.14)	77 (69.37)	0.50 (0.15–1.61)	0.245
Self employed	7 (25)	22 (19.82)	0.76 (0.20–2.93)	0.407
Mother Employment Status				
Unemployed	15 (53.57)	69 (60)	(reference)	-
Employed	10 (35.71)	29 (25.22)	1.57 (0.64–3.94)	0.320
Self employed	3 (10.71)	17 (14.78)	0.81 (0.21–3.13)	0.762
Psychiatric Illness in First Degree Relative	2 (6.90)	3 (2.59)	2.79 (0.44–17.5)	0.274
Concomitant Medical Illness	1 (3.45)	3 (2.59)	1.34 (0.13–13.4)	0.801
Age at Seizure Onset	8 (4–11)	7 (4–11)	1.02 (0.93–1.11)	0.721
Duration of Epilepsy	6 (2–8)	5 (2–9)	0.99 (0.89–1.09)	0.779
Epilepsy Type				
Focal Epilepsy, Structural-Metabolic	8 (27.59)	26 (22.41)	1.32 (0.52–3.32)	0.557
Focal Epilepsy, Post-infectious				
Focal Epilepsy, Unknown	0	2 (1.72)	-	-
Generalized Epilepsy, Structural-Metabolic	11 (37.93)	61 (52.59)	0.55 (0.24–1.27)	0.161
Generalized Epilepsy, Post-	0	1 (0.86)	-	-

infectious				
Generalized Epilepsy, Unknown	0	2 (1.72)	-	-
Juvenile Myoclonic Epilepsy				
Childhood Absence Epilepsy	7 (24.14)	20 (17.24)	1.53 (0.57–4.06)	0.396
Benign Childhood Epilepsy with Centrotemporal Spikes	0	1 (0.86)	-	-
	2 (6.90)	2 (1.72)	4.22 (0.57–31.3)	0.159
	1 (3.45)	(0.86)	4.11 (0.25–67.7)	0.323
EEG findings				
Normal	14 (48.28)	53 (46.09)	(reference)	-
Abnormal	15 (51.72)	62 (53.91)	0.92 (0.41–2.07)	0.833
Neuroimaging findings				
Normal	17 (60.71)	70 (69.31)	(reference)	-
Abnormal	11 (39.29)	31 (30.69)	1.46 (0.61-3.48)	0.392
Seizure Frequency (weekly or daily at onset)	4 (13.79)	10 (8.62)	1.70 (0.49–5.85)	0.403
Seizure Frequency				
seizure free ≥12 months	12 (41.38)	65 (56.03)	(reference)	-
≥1 seizure for 12 months but <1 seizure per month	14 (48.28)	45 (38.79)	1.69 (0.71–3.98)	0.234
≥1 seizure per month	2 (6.90)	4 (3.45)	2.71 (0.44–16.5)	0.279
≥1 seizure per week	1 (3.45)	2 (1.72)	2.71 (0.23–32.3)	0.431
Anti-epileptic Drugs at Time of Study				
Topiramate	0	1 (0.86)	-	-
Clonazepam	0	1 (0.86)	-	-
Lamotrigine	3 (10.34)	4 (3.45)	3.23 (0.68–15.3)	0.140
Phenobarbital	5 (17.24)	29 (25)	0.63 (0.22–1.79)	0.381
Carbamazepine	5 (17.24)	22 (18.97)	0.89 (0.31–2.59)	0.831
Oxcarbazepine	4 (13.79)	23 (19.83)	0.65 (0.20–2.04)	0.458
Valproic acid	12 (41.38)	28 (24.14)	2.22 (0.95–5.20)	0.067
Levetiracetam	4 (13.79)	12 (10.34)	1.39 (0.41–4.66)	0.597
Perampanel	0	2 (1.72)	-	-
Zonisamide	2 (6.90)	0	-	-
None	0	5 (4.31)	-	-
Anti-epileptic Drug Use at Time of Study				
None	0	5 (4.31)	(reference)	-
Monotherapy	24 (82.76)	101 (90.99)	0.48 (0.15–1.52)	0.210
Polytherapy	5 (17.24)	10 (9.01)	-	-
Depression score	6.31 $\pm$ 3.19	5.26 $\pm$ 3.23	1.10 (0.97–1.25)	0.120

Abbreviations: SD, standard deviation; IQR, inter-quartile range

TABLE 5. UNIVARIATE ANALYSIS OF SOCIO-DEMOGRAPHIC AND EPILEPSY-RELATED CLINICAL FACTORS ON HOSPITAL ANXIETY AND DEPRESSION SCALE, DEPRESSION SCORE ≥11 (N=145)

	Cases (n=9)	**Control (n=136)**	**Odds ratio (95% CI)**	**P-value**
	Frequency (%); Mean ± SD; Median (IQR)			
Age	13.22 ± 2.11	13.27 ± 2.63	0.99 (0.76–1.29)	0.955
Sex				
Male	6 (66.67)	82 (60.29)	(reference)	-
Female	3 (33.33)	54 (39.71)	0.76 (0.18–3.17)	0.705
Educational level				
Grade 4	1 (11.11)	14 (10.37)		
Grade 5	1 (11.11)	20 (14.81)		
Grade 6	3 (33.33)	19 (14.07)		
Grade 7	0	22 (16.30)		
Grade 8	3 (33.33)	20 (14.81)	0.87 (0.65–1.17)	0.359
Grade 9	0	7 (5.19)		
Grade 10	1 (11.11)	7 (5.19)		
Grade 11	0	9 (6.67)		
Grade 12	0	11 (8.15)		
1st year college	0	6 (4.44)		
Father Employment Status				
Unemployed	0	17 (13.08)	(reference)	-
Employed	8 (88.89)	85 (65.38)	2.64 (0.32–22)	0.371
Self employed	1 (11.11)	28 (21.54)	-	-
Mother Employment Status				
Unemployed	8 (88.89)	76 (56.72)	(reference)	-
Employed	0	39 (29.10)	0.50 (0.06–4.24)	0.525
Self employed	1 (11.11)	19 (14.18)	-	-
Psychiatric Illness in First Degree Relative	2 (22.22)	3 (2.21)	12.7 (1.81–88)	**0.010**
Concomitant Medical Illness	1 (11.11)	3 (2.21)	5.54 (0.52–59)	0.157
Age at Seizure Onset	6 (5–9)	7 (4–11)	0.94 (0.81–1.10)	0.476
Duration of Epilepsy	6 (3–10)	5 (2–8.5)	1.07 (0.91–1.25)	0.422
Epilepsy Type				
Focal Epilepsy, Structural-Metabolic	3 (33.33)	31 (22.79)	1.69 (0.4–7.17)	0.474
Focal Epilepsy, Post-infectious	0	2 (1.47)	-	-
Focal Epilepsy, Unknown			0.8 (0.21–3.11)	0.747
Generalized Epilepsy, Structural-Metabolic	0	1 (0.74)	-	-

Generalized Epilepsy, Post-infectious	0	2 (1.47)	-	-
Generalized Epilepsy, Unknown	2 (22.22)	25 (18.38)	1.27 (0.25–6.48)	0.775
Juvenile Myoclonic Epilepsy	0	1 (0.74)	-	-
Childhood Absence Epilepsy	0	4 (2.94)	-	-
Benign Childhood Epilepsy with Centrotemporal Spikes	0	2 (1.47)	-	-
EEG findings				
Normal	4 (44.44)	63 (46.67)	(reference)	-
Abnormal	5 (55.56)	72 (53.33)	1.09 (0.28–4.25)	0.897
Neuroimaging findings				
Normal	4 (44.44)	83 (69.17)	(reference)	-
Abnormal	5 (55.56)	37 (30.83)	2.80 (0.71–11)	0.140
Seizure Frequency (weekly or daily at onset)	3 (33.33)	11 (8.09)	5.68 (1.25–26)	**0.025**
Seizure Frequency				
seizure free ≥12 months	4 (44.44)	73 (53.68)	(reference)	-
≥1 seizure for 12 months but <1 seizure per month	5 (55.56)	54 (39.71)	1.69 (0.43–6.59)	0.450
≥1 seizure per month	0	6 (4.41)	-	-
≥1 seizure per week	0	3 (2.21)	-	-
Anti-epileptic Drugs at Time of Study				
Topiramate	0	1 (0.74)	-	-
Clonazepam	0	1 (0.74)	-	-
Lamotrigine	1 (11.11)	6 (4.41)	-	-
Phenobarbital	0	34 (25)	2.71 (0.29–25.3)	0.382
Carbamazepine	3 (33.33)	24 (17.65)	2.33 (0.54–10)	0.254
Oxcarbazepine	0	27 (19.85)	-	-
Valproic acid	2 (22.22)	38 (27.94)	0.74 (0.15–3.71)	0.711
Levetiracetam	1 (11.11)	15 (11.03)	1.01 (0.12–8.63)	0.994
Perampanel	0	2 (1.47)	-	-
Zonisamide	0	2 (1.47)	-	-
None	2 (22.22)	3 (2.31)	12.67 (1.8–88.5)	**0.010**
Anti-epileptic Drug Use at Time of Study				-
None			(reference)	**0.015**
Monotherapy			0.09 (0.01–0.62)	-
Polytherapy	0	15 (11.03)	-	
Anxiety score	10.67 ± 4.66	7.45 ± 3.56	1.25 (1.04–1.51)	**0.016**

Abbreviations: SD, standard deviation; IQR, inter-quartile range

COMPARISON OF POSTOPERATIVE PAIN BETWEEN ULTRASOUND-GUIDED QUADRATUS LUMBO[illegible] ND-GUIDED CAUDAL EPIDURAL BLOCK IN C[illegible] RGOING UNILATERAL LOWER ABDOMINAL AND UROLOGICAL SURGERIES IN PHILIPPINE CHILDREN'S MEDICAL CENTER: A RANDOMIZED CONTROLLED TRIAL

AUBREY T. YUMANG, JANETTE T. FUSILERO-PASCUAL, MICHAEL SALVADOR D. CABATO

ABSTRACT

BACKGROUND: Ultrasound-guided quadratus lumborum block (QLB) is a regional anesthetic technique which can provide post op pain control for pediatric patients undergoing abdominal surgery. We hypothesized that the quadratus lumborum block would be as efficacious as a caudal block in providing pain control.

OBJECTIVE: To compare the postoperative analgesic effect of ultrasound-guided QLB versus ultrasound-guided caudal block among 1-6 years old children undergoing lower abdominal and urological surgeries in Philippine Children's Medical Center.

METHODS: This is a single blinded randomized control trial. 50 patients enrolled aged between 1 and 6 years. The patients were randomly classified into the caudal block group and quadratus lumborum block group. The primary outcome is the need for analgesia during the first 24 hours.

RESULTS: A significant difference in the proportion of patients who requested for rescue analgesia was observed with caudal block having more patients in need of analgesic (100% CB vs 48% QLB, $p<0.001$). No postoperative complication was observed.

CONCLUSIONS AND RECOMMENDATIONS: The quadratus lumborum block was more effective in reducing the postoperative pain management during the initial 48 hours. Quadratus lumborum block is recommended for future pediatric procedures requiring postoperative pain control, safety, practicality and economy.

KEYWORDS: Analgesia, Postoperative Pain, Qlb

INTRODUCTION

Postoperative pain is commonly experienced after surgery and children tend to rely on a parent or guardian to give medication to help relieve the pain. One study showed that the children in the 'around the clock' group took more medication, but they did not ha relief [1]. The purpose of this r is to find the best alternative to decrease post-operative pain in children undergoing lower abdominal surgeries. The investigator will perform ultrasound-guided quadratus lumborum block (QLB) and the more commonly used caudal epidural block but coupled with ultrasound guidance in an anesthetized children. The investigator plans to establish which technique is more advantageous in terms of postoperative pain control, safety, practicality and economy.

MATERIALS AND METHODOLOGY

The research design used was a single :ed control trial.Target ıtients aged 1-6years old scheduled for lower abdominal and urological surgeries in PCMC. Patient sampling was randomized using computer generated random numbers (Random.org), this created a list of number and each number referred to one of the two groups.

Block randomization was used to ensure equality of the groups.

Sample size was computed using G*Power 3.1.9.2 a statistical software [2] for computing sample size. Based on the result of the study of Dogra et al [3] and Oksus et al [4] on percentage needing rescue analgesia with Caudal epidural block is 61.5%, and quadratus lumborum block is 12%, with Power 0.9 alpha 0.05, two tailed , a sample size a sample size of 44 was computed. Accounting for 10% dropout rate, a total sample size of 50 is needed.

This study aimed to include a total of fifty patients who underwent elective unilateral low abdominal and urological surgeries under general anesthesia with Laryngeal Mask Airway using Igel LMA. The patients were aged 1 to 6years with American Society of Anesthesiologists (ASA) physical status of I an

Preoperatively, all patıents were evaluated, and parental consent was obtained. Exclusion criteria included known allergies to local anesthetics, infection or redness at the injection site, anatomic anomalies or coagulation disorders, severe obesity, liver, cardiac, renal, neurological/mental and upper or lower airway disease, or unwillingness to participate in the study.

Ultrasound guided quadratus lumborum block and ultrasound guided caudal block were done accordingly. The operation initiated 15 minutes after the block was applied, and all patients was operated on with a standardized technique and was monitored every five minutes. At the end of surgery, paracetamol 15 mg/kg IV was administered to all patients. Patientswas then extubated immediately after surgery and sent to PACU. Any complications occurring during the procedure was recorded and managed immediately. Complications such as hypersensitivity was immediately given anti-histamine medications such as diphenhydramine 1mg/kg and close monitoring afterwards. Hypotension and bradycardia were dealt with Atropine 0.02mg/kg and hydration. If postoperative vomiting occurs, Ondansetron 0.1mg/kg IV was given.

At the PACU, parent /guardian was instructed to assess the patient's pain using FLACC scoring. The researcher visited the patient at 24 hours and 48 hours if admitted, and was followed up by phone if outpatient lf-reported data. Pain levels sing a FLACC(Face, Legs, Activity, Cry, Consolability) scale [5] at one hour and at 2,6,12,24and 48 hours. Paracetamol 15mg/kg was administered to patientsif the FLACC score was 4 or greater. Parents was instructed on how to use the FLACC score pain scale. Parents were instructed to give paracetamol 15mg/kg every 6 hours when patient had greater than 4 FLACC score at home. The anesthesiologist recorded the data received from the parents over the phone. Parents were asked to rate satisfaction using PPPM-SF Parents' Postoperative Pain Measure – Short Form [6] as well as adverse events. Cases of adverse events were managed accordingly.

The primary outcome was whether there is a need for analgesia in the first 24 hours. Secondary outcomes were the time the first analgesia was required and measured using FLACC scores and parent satisfaction. Satisfaction levels of the parents were given verbally as a level from 1 to 10, with the lowest level of satisfaction at a value of 1 and the highest level at 10.Intent to treat analysis was used. Patients who dropped out after the randomization procedure were analyzed in the group he / she was randomized.

Data gathered from the data abstraction form was encoded using Microsoft Excel 2010. Stata v14 MP was used for data analysis. Numerical variables such as age was summarized using mean and standard deviation. Categorical variables such as sex and surgical procedures was summarized as number [illegible] FLACC score was summar[illegible] and interquartile range.Chi-square test was used to compare whether there is difference in the need for rescue dose medications and patient satisfaction in the two groups. Mann Whitney U test was used to compare the FLACC score among the two groups with a p-value of <0.05 was considered significant.

RESULTS

A total of 50 patients were included in the study and no case deviated from the protocol. The patients were composed of 33 males (66%) and 17 females (34%) and the mean age is about 3 years old. Body Mass Index of patients were within normal range as well. Majority of patients for caudal (96%) and quadratus lumborum (88%) blocks were categorized as ASA-PS I. Distribution of surgical procedure of patients are homogenous between the two groups.

Table 1. Demographic and clinical profile of patients (n=50)

	CB (n=25)	**QLB (n=25)**	***p-value***
Age, years	3.12 ± 1.76	2.72 ± 1.90	0.448*
Gender			0.765†
Male	17 (68)	16 (64)	
Female	8 (32)	9 (36)	
Weight, kilograms	15.17 ± 4.91	12.94 ± 4.11	0.087*
Height, centimeters	84.6 ± 11.04	78.72 ± 13.12	0.093*
BMI (normal)	25	25	-
ASA PS			0.297†
I	24 (96)	22 (88)	
II	1 (4)	3 (12)	
[illegible]			0.9235
Urological procedure	14(56)	17(68)	
Lower abdominal procedure	11(44)	8(32)	

All patients under the caudal block group asked for rescue analgesia. A significant difference in the proportion of patients who requested for Rescue Analgesia between caudal block and quadratus lumborum block was observed, with caudal block having more patients in need of analgesic (100% CB vs 48% QLB, p<0.001).

Table 2. Need for Rescue Analgesia of patients (n=50)

	CB (n=25)	QLB (n=25)	*p-value*
Yes	25(100)	12(48)	**<0.001**†
No	0	13(52)	**<0.001**†

The median frequency of anesthesia taken for patients in the caudal block was significantly higher than that of the quadratus lumborum block. The median time to first analgesic use was 6 hours with patients in the caudal block requiring analgesic earlier than those in the quadratus lumborum block (2 hours vs 6 hours, p<0.001). Analgesic use was observed more frequently in the caudal block than in the quadratus lumborum block from 2 to 24 hours post operation.

Table 3. Time to regional anesthesia and FLACC scores of children 1-6 years old undergoing unilateral lower abdominal and urological surgeries in Philippine Children's Medical Center (n=50)

	CB (n=25)	QLB (n=25)	p-value
	Median (Range); Frequency (%)		
Number of analgesia taken	(n=25)	(n=12)	**<0.001**‡
	4 (1-6)	1 (1-4)	

	CB (n=25)	QLB (n=25)	p-value
	Median (Range); Frequency (%)		
Time to first analgesic use, hours	(n=25)	(n=12)	**0.001**‡
	2 (2-6)	6 (2-24)	
Analgesic use due to FLACC score >4†			
1st hour	0	0	-
2nd hour	16 (64.00)	2 (8.00)	**<0.001**
6th hour	23 (92.00)	7 (28.00)	**<0.001**
12th hour	21 (84.00)	6 (24.00)	**<0.001**
24th hour	15 (60.00)	4 (16.00)	**0.003**
48th hour	1 (4.00)	0	1.000

Parents were asked to answer the Parent's Post-Operative Pain Measure – Short Form (PPPM-SF) after observing their children during the 48-hour post-operation period. Patients under caudal block had a higher median score (median score of 8, ranges from 2 to 10) compared to those in the quadratus lumborum block (median score of 1, ranges from 0 to 6). Children's appetite was the most reported change in behavior (80%). Generally, more patients in the caudal block were reported to have an obvious change in behavior than those in the quadratus lumborum block.

Table 4. Parent's Post-Operative Pain Measure – Short Form of children 1-6 years old undergoing unilateral lower abdominal and urological surgeries in Philippine Children's Medical Center (n=50)

	CB (n=25)	QLB (n=25)	p-value
	Median (Range); Frequency (%)		
PPPM-SF score	8 (2-10)	1 (0-6)	**<0.001**‡
PPPM-SF			

	CB (n=25)	QLB (n=25)	p-value
	Median (Range); Frequency (%)		
Questions†			
Whine or complain more than usual	19 (76)	5 (20)	<**0.001**
Play less than usual	17 (68)	2 (8)	<**0.001**
Not do the things s/he normally does	15 (60)	0	<**0.001**
Act more worried than usual	18 (72)	1 (4)	<**0.001**
Act more quiet than usual	13 (52)	3 (12)	**0.005**
Have less energy than usual	19 (76)	2 (8)	<**0.001**
Eat less than usual	25 (100)	15 (60)	**0.001**
Hold the sore part of his/her body	4 (16)	1 (4)	0.349
Groan or moan more than usual	20 (80)	5 (20)	<**0.001**
Want to be close to you more than usual	12 (48)	6 (24)	0.140

There were no reported cases of adverse outcomes within 48 hours post-operation of patients.

DISCUSSION

This is a pioneer study with a single-blind, randomized clinical trial comparing the quadratus lumborum block and caudal block for postoperative pain relief after lower abdominal surgery in children in the Philippines. The results of the study showed that the QLB block provided a safe and more effective pain relief compared with the caudal block in lower abdominal surgery in children, such as hernia repair and orchidopexy.

Several studies have explored the efficacy of plane nerve block versus truncal and central nerve blockade. In one study, Blanco et al [7] [8] compared the efficacy of the TAP and QL blocks for postoperative analgesia in cesarean delivery operations. It was reported that the QL block was superior to the TAP block with respect to the duration of the effect, pain relief, opioid consumption, and the success of the block.

Visoiu and Yakovleva [9] were the first to report on providing analgesia with a catheter using a QL block in a lateral ediatric colostomy repair. al [10] applied continuous QL block with a catheter after a nephrectomy for Wilm's tumor in pediatric patients while in a supine position, and they also reported successful postoperative analgesia with this technique. In pyeloplasty performed on 5 children in the lateral position, Baidya et al [11] used a QL-TM

block with the application of a single-dose injection transmuscularly, between the psoas major and the QL; postoperative analgesia was reported successful. Murouchi [12] [13] described the intramuscular approach in a pediatric patient undergoing laparoscopic appendectomy equally reporting successful analgesia after bilateral application of a QL-IM block.

In our study, all patients who underwent caudal block needed rescue analgesia while only 48% of patients in the QLB group warranted this adjunct treatment. This result was significant with a p value of <0.001. This supports the claim of QLB having better pain control since it has more central origin. Distribution of the nerve anesthetized provides broader coverage on both somatic and visceral nervous system that last for 24-48 hours.

Results show that the patients in the CB group had significantly shorter time to request 1st analgesic regimen. The mechanism of the QL block has not been fully clarified. However, Carline et al [14] provided a possible mechanism of prolonged analgesia from QL block w
on spread of local anesthetic

The QL block was determined to have a longer duration of effectiveness. These results were seen to be consistent with those of Blanco et al. [7][8] In this study, the QLB was observed to be statistically superior to the caudal block based on the FLACC scores at 1hour and at 2, 6, 12, 24 and 48 hours post-operatively.

Our results demonstrated better post-operative state based on PPPM-SF results 48-hour after surgery. PPPM-SF is inversely proportional to caregiver's level of satisfaction. Patients under caudal block had a higher median score of 8 (ranges from 2 to 10) compared to those in the quadratus lumborum block with a median score of 1 (ranges from 0 to 6). This indicates earlier return of patient to preoperative state. In the QLB group, patients are comfortable and calm consequently making the parents at ease.

In a case undergoing laparoscopic gynecological surgery, unilateral weakness was experienced in hip flexion and knee extension, which lasted for approximately 18 hours after the application of the QL block. However, this seems to be the only reported complication in literature. Blanco et al [8] reported that no complications were encountered in patients who had a cesarean delivery, particularly because the QL2 block is a superficial and safe block. In the current study, no complications developed in either group. However, there was not adequate power to show a difference in uncommon
No opioids were required,
ıld be discharged early; the
surgical team viewed these as positive aspects.

CONCLUSION AND RECOMMENDATION

Our results strongly support the use of quadratus lumborum block versus among children undergoing lower abdominal and urological surgeries due to its superior

postoperative analgesic effect as measured by: need for rescue analgesia, time to first rescue analgesic use, pain score using FLACC score and parent satisfaction using parent's PPMSF scores as compared to ultrasound-guided caudal block. Both techniques can be safely done in children. Limitation of this study is that we were unable to measure the dermatomal sensory block level of the QL block to the children aged 1 to 6 yearscompared with the caudal block.

Therefore, recommendation on the use of the different techniques of QLB, different anesthetic agents on different procedures should be done for future studies with comparison with patient's hemodynamic changes during intraoperative and postoperative monitoring in different age group. These aim to make clear criteria to assess the performance of each QL block in comprehensive aspects, which will contribute to the advancement of regional blocks.

REFERENCES:

[1] Hobson A, Wiffen PJ, Conlon JA. As required versus fixed schedule analgesic administration for postoperative pain in children. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD011404. DOI: 10.1002/14651858.CD011404.pub2

[2]Faul, F., Erdfelder, E., Lang, A.-G. & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods, 39, 175-191.

[3]Dogra,N.,et al A study to compare caudal levobupivacaine, tramadol and a combination of both in paediatric inguinal hernia surgeries, Indian Journal of Anesthesia May 2018, v62,I5, 359-365

[4]Öksüz, G., Bilal, B., Gürkan, Y., Urfalioğlu, A., Arslan, M., Gişi, G., &Öksüz, H. (2017). Quadratus Lumborum Block Versus Transversus Abdominis Plane Block in Children Undergoing Low Abdominal Surgery. Regional Anesthesia and Pain Medicine, 42(5), 674–679.

[5}S. Merkel et al,. The FLACC: A behavioral scale for scoring postoperative pain in young children, Pediatric Nurse 23, p. 293–297) 1997.

[6]Von Baeyer, C. L., Chambers, C. T., & Eakins, D. M. (2011). Development of a 10-Item Short Form of the Parents' Postoperative Pain Measure: The PPPM-SF. The Journal of Pain, 12(3), 401–406. doi:10.1016/j.jpain.2010.10.002

[AP block under ultrasound lescription of a 'non pops technique'," Regional Anesthesia and Pain Medicine, vol. 32, supplement 1, p. 130, 2007.

[8]R. Blanco, T. Ansari, and E. Girgis, "Quadratus lumborum block for postoperative pain after caesarean section: a randomised controlled trial," European

Journal of Anaesthesiology, vol. 32, no. 11, pp. 812–818, 2015.

[9]Visoiu M, Yakovleva N: Continuous postoperative analgesia via quadratus lumborum block—An alternative to transversus abdominis plane block. PaediatricAnaesthesia 2013;23:959–961.

[10]Chakraborty, J. Goswami, and V. Patro, "Ultrasound-guided continuous quadratus lumborum block for postoperative analgesia in a pediatric patient," A & A Case Reports, vol. 4, no. 3, pp. 34–36, 2015

[11]D. K. Baidya, S. Maitra, M. K. Arora, and A. Agarwal, "Quadratus lumborum block: an effective method of perioperative analgesia in children undergoing pyeloplasty," Journal of Clinical Anesthesia, vol. 27, no. 8, pp. 694–696, 2015.

[12]T. Murouchi, "Quadratus lumborum block intramuscular approach for pediatric surgery," Acta Anaesthesiologica Taiwanica, 2016.

[13]T. Murouchi, S. Iwasaki, and M. Yamakage, "Quadratus lumborum block: analgesic effects and chronological ropivacaine concentrations after laparoscopic surgery," Regi
and Pain Medicine, vol. 41,
150, 2016.

[14]L. Carline, G. A. McLeod, C. Lamb, and L. Colvin, "A cadaver study comparing spread of dye and nerve involvement after three different quadratus lumborum blocks," British Journal of Anaesthesia, vol.