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ARTICLE

Efficacy and safety of Low Dose Heparin infusion in intravenous fluids to prevent Peripherally Inserted Central Catheter (PICC) line occlusion among neonates: A Randomized Control Trial

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OBJECTIVES: To determine the efficacy of low-dose heparin in preventing central catheter occlusion and its safety among neonates.

MATERIALS AND METHODS: A randomized controlled trial was conducted among 42 neonates requiring peripherally inserted central catheter **(**PICC) lines. The neonates were divided into two groups: low dose heparin (0.5 units/kg/hr =0.2 units/ml) and control group (0.5 units/ml). The efficacy outcomes were duration of catheter patency, completion of catheter use, and the presence of catheter occlusion or thrombosis. The safety outcomes include heparin complications.

RESULTS: The study participants had a mean age of 17 days old at 35 weeks gestational age and mean weight of 1.97 kg. The participants given low dose heparin were 36% more likely to complete the use of central line and 12% less likely to develop catheter occlusion. Analyses showed non-statistically significant risk ratio of active bleeding, thrombocytopenia, and deranged prothrombin time in the low dose heparin group.

CONCLUSION: The use of low dose heparin (0.5 units/kg/hr = 0.2 units/ml) appears as effective as the control dose in completion of catheter use and prevention of catheter occlusion. There was also no significant difference in the adverse effects. Low dose heparin can be used as continuous infusion for preventing central line occlusion; however, it has no advantage in lowering the risk of complications.

KEYWORDS: *Peripherally Inserted Central Catheter (PICC), unfractionated heparin, occlusion, bleeding*

INTRODUCTION

Most neonates in the Intensive Care Unit require intravenous lines for the administration of antibiotics as well as for continuous fluids. Peripheral venous line insertion is an easy procedure however its major disadvantage is its limited dwelling time which would require frequent change in site after 3-5 days. . [10] In comparison to peripheral lines, central venous lines or central venous catheters serve as an access for high osmolar drugs and prolonged total parenteral nutrition. There are several central lines available but the most used in our institution are the umbilical vein catheter (UVC), tunneled catheter and peripherally inserted central catheter (PICC). The PICC lines are now frequently used because they serve as a stable, long-lasting access which may last for four weeks.

The presence of central venous catheters aids in providing optimal care among our neonates hence maintaining its patency is of utmost importance. There are several risk factors that may contribute to central line occlusion and lead to its early removal. Common complications include occlusion (15-48%), thrombosis (25%) and phlebitis (7.5%).[10] Newborns have increased risk for thromboembolic events among the pediatric group due to low levels of antithrombin III and may have a higher incidence of catheter occlusion. Heparin is a popular anti-coagulant with its action mediated through the activation of antithrombin III in the plasma. It is widely used for maintenance of intravascular access due to its rapid action and lower cost.[13]

Literature recommends the use of continuous heparin to prolong the use of central lines as documented in a systematic review on prophylactic use of heparin in central lines as studied by Bin-Nun et al. Most studies on continuous heparin infusion compared its efficacy in maintaining central line patency with a placebo or saline solution. In a study by Kamala et al., the use of continuous heparin infusion prolongs catheter patency by three days in comparison to no heparin. A meta-analysis of randomized controlled trials was done locally by Ilagan et al., which showed that continuous heparin infusion in PICC prolongs duration of catheter patency by two days. In these studies, varying heparin doses were used from 0.5 units/kg/hr (0.2units/ml) to as high as 1unit/ml. In the 9th American College of Chest Physicians consensus conference, they recommended the use of unfractionated heparin at 0.5units/kg/hr as continuous infusion in central lines. Recent studies by Birch et. al (2010) and Tang et al. (2011) showed that the use of heparin at a higher dose (0.5units/ml) decreases catheter occlusions hence prolongs catheter patency duration compared to no heparin administered. Locally, we have adopted the higher heparin dose at 0.5units/ml as continuous infusion in our neonatal intensive care unit (NICU) to maintain our PICC lines. Limited studies have been done comparing heparin doses in terms of efficacy and safety since most heparin studies has been compared to placebo or no heparin group. A comparison of two doses, like our study, was done by Barekatain et al. comparing a low dose heparin (1.5unit/kg/hr) and a higher dose heparin (0.5units/ml). The same outcome measures such as duration of catheter time and catheter occlusion were observed and revealed that a lower dose heparin is as effective as that of the higher dose in maintaining the patency of the PICC line.

Despite this, the benefits versus harm of heparin use in central lines are cautiously weighed. Considering the heparin doses that have been studied, it would be prudent to compare the lowest heparin dose (0.5 units/kg/ hr = 0.2units/ml) proven to prevent catheter occlusion with that of the current heparin dose (0.5 units/ml) being used. In line with this, the determination of a lower heparin dose may decrease the associated risk to the patient. This study aims to determine the efficacy of a low dose heparin in intravenous fluids to prevent central line occlusion. The specific objectives of the study are as follows: (a) To compare the

efficacy of heparin concentrations (0.5 units/kg/hr=0.2units/ml and 0.5 units/ml) in mean central line patency duration, proportion of completed use of central line and catheter occlusion; (b) To compare incidence of adverse effects such as significant thrombocytopenia (less than 100,000), deranged prothrombin time, intraventricular hemorrhage or any form of bleeding among two different doses.

Materials and Methodology

A randomized controlled trial was done to study the efficacy of a lower dose unfractionated heparin (0.5 units/kg/hr = 0.2units/ml) compared to conventional dose in preventing catheter occlusion of peripherally inserted central catheters (PICC). Single blinding and allocation concealment were done.

The study included all neonates with peripherally inserted central catheters (PICC) used for administration of intravenous fluids and antibiotics. Neonates who required reinsertion of PICC line were included as a separate group. Neonates with clinical evidence of bleeding, thrombocytopenia (less than 100,000), IVH grade 3 or 4, and prolonged PT, PTT were excluded.

The sample size was initially computed at 70 study participants using independent *t*-test for two sample proportion. In the last three months of the study, there was an unexpected closure of the Neonatal Intensive Care Unit (NICU) due to an increasing rate of infection. This caused a decrease in number of admissions and affected data collection. A post-hoc power analysis for One-Way Multivariate Analysis of Variance (MANOVA) was conducted using GPower version 3.1.9.4 to compute for the adequacy of sample size reached within seven months of the study. With three outcomes, two group categories, and an accumulated sample size of 42 participants, multivariate analysis estimated a partial eta squared (η^2) of 0.090 which can be utilized to compute for effect size f of 0.3145. With these estimates from the collected data, the acquired sample of 42 participants was sufficient to achieve a power of 93.11%.

The study included all neonates of a tertiary government hospital who required peripherally inserted central catheters (PICC) line for intravenous fluids including total parenteral nutrition (TPN) and antibiotics. Neonates who required re-insertion of a PICC line were included as well. A PICC line was inserted by a physician at the NICU following a sterile technique. The catheter size and insertion site were determined by the attending physician. The catheters used were Vygon French size 1 and French size 2.

The proper placement of the central line was evaluated with a radiograph. An informed consent was provided, and the study was explained to the parents of the participants. Once informed consent was secured, baseline workups such as complete blood count and prothrombin time were done prior to heparin and after 24 hours from heparin administration. A cranial ultrasound was done for those high risk for intraventricular hemorrhage. Neonates

with clinical evidence of bleeding, thrombocytopenia (less than 100,000), prolonged prothrombin time, and intracranial hemorrhage grade 3-4 were excluded.

The primary investigator prepared a randomization list. The group assignments were placed in sealed envelopes which were sequentially arranged. Once an eligible patient was encountered, the envelope was opened, and the group assignment of the participant was read. The participants were divided into two groups. The first group was the Control Group where heparin dose given to maintain central line patency is at 0.5units/ml (see Figure). The second group was the Intervention Group where heparin dose was at 0.5units/kg/hr (=0.2 units/ml). Both groups used unfractionated heparin (preparation 1000 units/ml, 5ml per vial) mixed with intravenous fluids and given via continuous infusion.

The primary investigator gathered the data of the study participants which includes the demographics, clinical data, and laboratories. Baseline demographics included were age, sex, gestational age, weight, type of catheter used, type of vein used, type of intravenous fluid (IVF), antibiotics being given and underlying medical conditions.

We computed for the heparin to be incorporated in the intravenous fluid including total parenteral nutrition and it was ordered in the chart. The chart order of the requested intravenous fluids was prepared by the pharmacist who is not part of the research group and does not do bedside rounds. Standard PICC line care was observed by the NICU staff for all study participants at all times: (a) the PICC lines were secured properly; (b) only 10ml syringes were used in administration of fluids and medications using the PICC lines and will be given via continuous infusion or via push-pause method; (c) extractions and insertions on the PICC line area were prohibited; (d) blood transfusion via PICC line was not allowed. The study participants and the duration of the PICC line patency was observed for one week to one month. The observation was set to a maximum of one month due to the recommended duration of PICC line use.

The primary outcomes included measured variables such as: (a) number or proportion of catheter occlusion; (b) number or proportion of completed use of central lines; and (c) mean duration of catheter use. Catheter occlusion is defined as the presence of any of the following (a) decrease or absence of flow through the central line, (b) erythema or swelling on the catheter site requiring prompt removal of the catheter or © presence of blood clot after removal of the catheter. The presence or absence of a blood clot or thrombus formation was documented by pushing 5ml of PNSS into the catheter after the central line has been removed. The number of completed use of central line is defined as the number of days from PICC line insertion to the day of completion of antibiotics and discontinuation of intravenous fluids. The duration of catheter use is defined as the number of days from the central line insertion to the removal of the catheter. The principal investigator made daily rounds in the morning and used a monitoring

sheet to observe for any sign of occlusion. The monitoring sheet was used to check for the PICC line status and if its removal is warranted. The PICC line was removed once noted with any signs of catheter occlusion. The presence of occlusion was confirmed by the principal investigator, co-investigator and one neonatology fellow. Secondary outcomes in the study are development of thrombocytopenia (less than 100,000), deranged prothrombin time, and any form of bleeding.

Heparin as a medication has its side effects which commonly presents with bleeding. Heparin was discontinued immediately among study participants with any sign of bleeding and derangement in the bleeding parameters however they were still included as part of the study for monitoring. The data of these participants were used to analyze the safety outcome of the study. The cranial ultrasound used for monitoring intraventricular hemorrhage was shouldered by the research funds among participants with high risk for bleeding. The study was approved by the Institutional Review Board – Independent Ethics Committee.

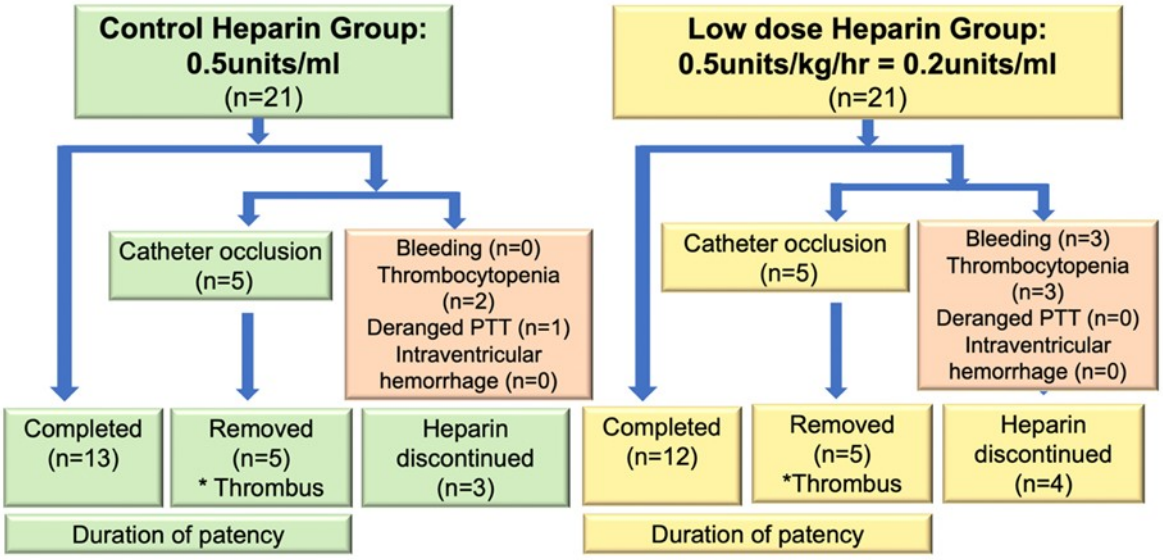

Figure. Study flow of neonates with PICC lines and outcomes on two different heparin doses given via continuous infusion

Statistical analyses were conducted using STATA Statistical Software, Version 13, College Station, TX: StataCorp LP. A *p*-value of 0.05 or less was considered statistically significant. Descriptive statistics included mean and standard deviation for continuous-level data, median and interquartile range for ordinal data, and frequency and proportion for nominal data. Comparative analyses of the demographic and clinical characteristics according to group allocation were conducted using Chi-Square Test of Homogeneity for nominal data or Fisher's Exact Test, if the expected frequency per cell is less than 5; Mann-Whitney U Test, for ordinal or non-normally distributed, continuous data; and, independent t-test for normally-distributed, continuous data. [17]

Between-group comparison of the duration of central line catheter patency was conducted using analysis of covariance, and the mean duration of patency was adjusted to significant confounders. [17] On the other hand, log-binomial regression using generalized linear model approach was performed to determine the relative risk of the outcomes (completed use of central line catheter, central line occlusion or thrombosis, active bleeding, thrombocytopenia, and deranged bleeding parameters) according to group assignment. Crude risk ratio (cRR) was initially estimated. Afterwards, significant confounders were screened, analyzed, and controlled using a 10% change-in-estimate criterion to estimate the adjusted risk ratio (aRR).[18]

RESULTS

The study had a total of 42 participants who met the inclusion criteria. There were 21 participants in the control group (0.5 units/ml) and 21 participants in the low heparin group (0.5 units/ kg/hr =0.2units/ml). Seven were withdrawn due to complications such as bleeding and deranged laboratory results hence the discontinuation of heparin infusion. There were 2 deaths from those patients withdrawn from the study. Intention To Treat analysis was done to preserve the sample size and randomization of the study. No participant was lost to follow-up.

Table 1 illustrates the demographic and clinical characteristics of the participants. The mean age of the participants was 17.76 days old (SD=11.80). The mean gestational age and the corrected gestational age upon entry to the study were 35.62 weeks and 37.86 weeks respectively. Most of the participants were male (61.90%). The mean weight of the study in the low dose heparin group at 2.06 kilograms (SD 0.96) was higher compared to control group at 1.89kilograms (SD 0.90). French size 1 peripherally inserted central catheter (PICC) was commonly used and was frequently inserted in the cephalic vein for both groups. The PICC line was primarily used for total parenteral nutrition with lipid emulsion as well as administration of medications which were mostly antibiotics. The top three medications in the control group were meropenem (42.86%), fluconazole (33.33%) and vancomycin (28.57%). The top three medications in the low dose heparin group were meropenem (42.86%), amikacin (23.57%), vancomycin (19.05%) and fluconazole (19.05%). Table 1 also shows that the most common underlying medical condition for both groups was infection (80.95%). The other medical conditions common in the low heparin group are surgical cases (47.62%) followed by respiratory diseases (23.81%). In the control group, gastro-intestinal cases (52.38%) ranked as the second common condition followed by surgical cases (23.81%) and respiratory diseases (23.81%). Comparative analyses of the different demographic and clinical characteristics according to group allocation indicated that none of the demographic and clinical characteristics were significantly different between the two dosages of heparin.

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PARTICIPANTS ACCORDING TO GROUP ALLOCATION

Characteristics	Group Allocation (N = 42)			*p*-value (Two-Tailed)
	Low Heparin (n = 21)	Control (n = 21)	Total (N = 42)	
Age (days old; x̄, SD)	20 (14.96)	15 (7.04)	17 (11.80)	0.194
Corrected Age (weeks; x̄, SD)	38 (3.66)	37(3.68)	37(3.65)	0.505
Gestational Age (weeks; x̄, SD)	35 (3.16)	35 (3.68)	35 (3.39)	0.789
Sex (*f*, %)				0.204
Male	11 (52.38%)	15 (71.43%)	26 (61.90%)	
Female	10 (47.62%)	6 (28.57%)	16 (38.10%)	
Weight (kilograms; x̄, SD)	2.06 (0.96)	1.89 (0.90)	1.97 (0.93)	0.568
Size of Catheter (French; *f*, %)				1.000
French Size 1	17 (80.95%)	17 (80.95%)	34 (80.95%)	
French Size 2	4 (19.05%)	4 (19.05%)	8 (19.05%	
Vein used for Catheter (*f*, %)				0.915
Cephalic	10 (47.62%)	12 (57.14%)	22 (52.38%)	
Basilic	4 (19.05%)	3 (14.29%)	7 (16.67%)	
Tibial	1 (4.76%)	0 (0.00%)	1 (2.38%)	
Saphenous	6 (28.57%)	6 (28.57%)	12 (28.57%)	
Intravenous Fluids (*f*, %)				1.000
TPN with Lipids	17 (80.95%)	17 (80.95%)	34 (80.95%)	
TPN without Lipids	1 (4.76%)	0 (0.00%)	1 (2.38%)	
Crystalloids	3 (14.29%)	4 (19.05%)	7 (16.67%)	
Medications (*f*, %)				
Antibiotics	19 (90.48%)	18 (85.71%)	37 (88.10%)	1.000
Anti-Fungal	5 (23.81%)	7 (33.33%)	12 (28.57%)	0.734

Underlying Medical Conditions (*f*, %)				
Infection	17 (80.95%)	17 (80.95%)	34 (80.95%)	1.000
Respiratory	5 (23.81%)	5 (23.81%)	10 (23.81%)	1.000
Cardiovascular	2 (9.52%)	2 (9.52%)	4 (9.52%)	1.000
Surgical	10 (47.62%)	5 (23.81%)	15 (35.71%)	0.197
Gastrointestinal	3 (14.29%)	11 (52.38%)	14 (33.33%)	0.009
Neurologic	3 (14.29%)	1 (4.76%)	4 (9.52%)	0.606

Significant at 0.05

†Significant at 0.01

The comparison of the efficacy outcomes between the two groups are presented in Table 2. Although the duration of central line patency was longer in the control group with higher heparin dose, this was not statistically significant. Results also indicated that the proportion of participants who had completed use of central line was slightly higher at 61.90% in the control group and 57.14% for the low dose heparin group, with an adjusted risk ratio of 1.36. Both groups had similar proportions of participants who had central line occlusion or thrombosis (23.81%), yielding an adjusted risk ratio of 0.78 (95% CI = 0.30 – 2.03), after adjusting for the confounding effect of duration of PICC use. The risk of central line occlusion or thrombosis was not statistically different between the two groups. Among the 23.81% of participants who had central occlusion, none of them had thrombosis upon catheter removal.

TABLE 2. BETWEEN-GROUP COMPARISONS OF EFFICACY OUTCOMES AMONG THE PARTICIPANTS ACCORDING TO GROUP ALLOCATION

Efficacy Outcomes	Group Allocation (N = 42)			Mean Difference (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)	*p*-value (Two-Tailed)
	Low Heparin (n = 21)	Control (n = 21)	Total (N = 42)				
Duration of Central Line Patency (Days; Adj. x̄, SD)	13.29 (6.19)	16.81 (8.55)	16.81 (7.58)	3.52 (–1.13 – 8.18)			0.112

Completed Use of Central Line (*f*, %)	12 (57.14%)	13 (61.90%)	25 (59.52%)	0.92 (0.56 – 1.52)	1.36 (0.86 – 2.15)	0.184
Central Line Occlusion (*f*, %)	5 (23.81%)	5 (23.81%)	10 (23.81%)	1.00 (0.34 – 2.95)	0.78 (0.30 – 2.03)	0.610

[a]Note: Summary statistic for duration of central line patency is presented in mean difference, while it is adjusted risk ratio for completed use of central line and central line occlusion or thrombosis. The mean duration of central line patency and the risk ratios for completed use of central line and central line thrombosis or occlusion were adjusted to significant confounders (duration of PICC).

[*]Significant at 0.05

[†]Significant at 0.01

Table 3 depicts the comparison of safety outcomes among the participants according to group allocation. Among the 42 participants, seven had their heparin discontinued due to complications such as bleeding and deranged laboratory findings. Less than a quarter of the participants had thrombocytopenia (11.90%), active bleeding (7.14%), or deranged prothrombin time (2.38%). Among participants in the low heparin dose group, 14.29% had active bleeding, 14.29% had thrombocytopenia and none had deranged prothrombin time. On the other hand, 9.52% had thrombocytopenia, 4.76% had deranged prothrombin time and none had bleeding among those who were in the control group. Cranial ultrasound was done to those with high risk for bleeding and showed no intracranial findings. Analyses after adjusting for confounding effects of age and sex indicated that the adjusted risk of active bleeding, thrombocytopenia, and deranged prothrombin time were not statistically significant between the groups.

TABLE 3. BETWEEN-GROUP COMPARISON OF SAFETY OUTCOMES AMONG PARTICIPANTS ACCORDING TO GROUP ALLOCATION

Safety Outcomes	Group Allocation (N = 42)			Crude RR (95% CI)	Adjusted RR (95% CI)	*p*-value (Two-Tailed)
	Low Heparin (n = 21)	Control (n = 21)	Total (N = 42)			
Active Bleeding (*f*, %)	3 (14.29%)	0 (0.00%)	3 (7.14%)	1.02 (0.98 – 1.01)	2.63 (0.45– 15.25)	0.280

Thrombocytopenia (*f*, %)	3 (14.29%)	2 (9.52%)	5 (11.90%)	1.50 (0.28 – 8.08)	1.38 (0.90 – 2.72)	0.752
Deranged Prothrombin Time (*f*, %)	0 (0.00%)	1 (4.76%)	1 (2.38%)	1.03 (0.96 – 1.09)	0.99 (0.98 – 1.01)	0.994

[a]Note: Risk ratios were adjusted for the participant's Age and Sex.

[*]Significant at 0.05

[†]Significant at 0.01

Discussion

In this study, 42 participants who underwent PICC line insertion were evaluated on the effectiveness and safety of low dose heparin (0.5units/kg/hr =0.2units/ml) in comparison to the control dose heparin (0.5units/ml). The mean gestational age and mean weight for both groups were 35 weeks and 1.94kg respectively. The PICC catheter frequently used was French size 1 due to its small diameter and smaller needle gauge introducer preferred for preterm and low birthweight patients. The size of the catheter would also depend on the visualized vein appropriate for PICC line insertion. The basilic vein is said to be a good site for its large diameter and less tortuosity, however, prior to insertion of the catheter all possible veins must be examined. In this study, the cephalic vein was the most common insertion site. The PICC line as a central access has been very helpful in providing adequate nutrition to our high-risk neonates in the form of Total Parenteral Nutrition (TPN) with accompanying lipid emulsion which is known for its high osmolality.

The most common underlying medical condition in the study was infection (80.95%) which is mostly sepsis or blood infection (54.76%) followed by pneumonia (30.95%). The organism commonly seen positive in the blood culture was *coagulase negative Staphylococcus* (CONS). These organisms are usually part of the normal skin flora however they can also become opportunistic organisms and frequently cause nosocomial infections among high-risk neonates.[25] PICC lines were of great importance to the completion of the medications, particularly the antibiotics (88.10%) for the treatment of infection in both

groups. It can be noted that the antibiotics frequently used for both groups were broad spectrum used for serious infections. The presence of sepsis is a significant risk factor affecting the efficacy and safety of heparin in the study. Presence of inflammation causes elevation of the acute phase reactants which may lead to increased blood viscosity and aggregation of erythrocytes. Blood viscosity promote fibrin and thrombus formation causing catheter occlusion. [21] On the other hand, sepsis may also lead to decreased platelet or thrombocytopenia.[22]

Thrombus formation is highly related to the Virchow's triad of endothelial damage, stasis and state of hypercoagulability which may occur in neonates with dehydration, asphyxia and polycythemia. [23] The presence of the other underlying medical conditions such as in surgical cases, gastrointestinal and cardiovascular diseases may increase risk for occlusion due to their hypercoagulable state. [23] Overall, the statistical analysis based on the demographics and clinical characteristics of both groups showed no significant difference hence they are comparable with each other.

Heparin is an anti-coagulant which inactivates factor Xa and thrombin. Higher doses of heparin prevent thrombus formation and fibrin conversion therefore helps in maintaining catheter patency.[1] The mean duration of central line patency in the study was not statistically significant but was noted to be three days longer in the control group with higher heparin dose (0.5units/ml). This difference in the duration of catheter patency of three days, however, may be considered of clinical importance particularly in the completion of fluids and medications.

This contrasts with the study by Barekatain et al., the mean duration of catheter patency in the low heparin dose (1.5units/kg/hr) and higher heparin dose (0.5units/ml) were 15.5 days and 14.6 days respectively which showed no significant difference in both groups.

More than half of the participants completed the use of the central line. Twelve participants from the low dose group (57.14%) and 13 (61.90%) from the control group completed use of the central line. Based on the adjusted risk ratio of 1.36, the study participants who received low dose heparin were 36% more likely to complete the use of central line. In terms of catheter occlusion, similar proportion of participants was noted with 5 (23.81%) participants each group. The adjusted risk ratio of 0.78 showed that study participants receiving the low dose heparin were 12% less likely to develop catheter occlusion. There was no thrombus formation noted after saline solution flushing of the catheter upon removal. The risk of completed use of central line, and the risk of central line occlusion or thrombosis were not statistically different between the two groups as well. This indicates that continuous infusion of low dose heparin (0.5units/kg/hr =0.2units/ml) may allow completion of catheter use and prevention of catheter occlusion.

Most studies on the use of continuous heparin infusion in maintaining catheter

patency and prevention on occlusion were done using different doses of unfractionated heparin and its effect was compared to placebo or no heparin group. In a study by Uslu et. al., a decrease in the PICC occlusion was noted in the heparin group at 0.5units/kg/hr (19.5%) as compared to no heparin group (45.5%). Another study with the same outcomes was done by Shah et. al. which also showed lower PICC line occlusion rate (6%) in the heparin group at 0.5units/kg/hr in comparison to the group without heparin (31%). Similar to the study by Barekatain et al., more than half of the study participants in both the high dose heparin at 0.5units/ml (58.5%) and low dose heparin at 1.5units/kg/hr (60.4%) completed treatment or central line use. The proportion of study participants with catheter occlusion presenting with lack of patency showed to be the same in both groups as well, 26.4% in the high dose heparin while 22.6% in the low dose heparin. The study by Barekatain et al. concluded that there was no significant difference in the efficacy of the two doses hence the use of low dose heparin (1.5units/kg/hr) in maintaining catheter patency and preventing catheter occlusion is as effective as the high dose heparin.

Newborns have increased hepatic clearance of heparin and a half-life of one to three hours hence the need for a higher heparin dose to achieve therapeutic level. [1] Heparin as a medication may cause adverse effects particularly of hematologic concerns. They may present with overt bleeding, significant thrombocytopenia (less than 100,000) or elevated activated prothrombin time (aPTT) based on age. It may be assumed that an increase in risk for complications may be expected with a higher heparin dose. In general, the most common complication noted in the study was thrombocytopenia (11.90%). In the low dose heparin group, bleeding and thrombocytopenia were frequently noted (14.29%). It is important to know that two study participants with active bleeding were also noted to have thrombocytopenia. There were two participants who had thrombocytopenia (9.52) and only one had a deranged prothrombin time in the control group. There was no case of intraventricular hemorrhage noted in the cranial ultrasound of the study participants. Study participants with low dose heparin (0.5units/kg/hr =0.2units/ml) had 263% higher risk for active bleeding and 36% higher risk for thrombocytopenia but these were not statistically significant. Similar to the findings in the study by Uslu et.al.,the use of low dose continuous heparin (0.5units/kg/hr) was not associated with complications such as thrombocytopenia, prolonged aPTT, septicemia and intracranial hemorrhage. Heparin incorporation has been discontinued upon recognition of any complication in the study participants. No participant was noted to have complications that was proven to be secondary to heparin alone because the presence of other risk factors such as infection is highly significant. In the presence of sepsis, bleeding may be observed secondary to thrombocytopenia. About 50% of patients with

sepsis would present with thrombocytopenia due to decreased platelet production or increased immune mediated platelet destruction. The activation of platelets occurs in response to coagulation and inflammatory cascades. [26] It is of great importance to note that the participants with complications particularly those with active bleeding also had concurrent sepsis with identified growth in their blood cultures. The two common blood culture isolates were coagulase negative *Staphylococcus* and *Acinetobacter baumanii.* Both gram positive and gram-negative organisms may have direct interaction and activation of the platelets which may affect its production and destruction. Platelets function by aggregating in the endothelial damage hence its depletion may lead to bleeding.[26] The complications in the use of low dose heparin (0.5units/kg/hr =0.2units/ml) were statistically non-significant. However, low dose heparin showed no significant decrease in the risk for complications in comparison to the control group.

Conclusions

The use of low dose heparin (0.5units/ kg/hr =0.2units/ml) appears as effective as the control dose (0.5units/ml) in completion of catheter use and prevention of catheter occlusion. There was also no significant decrease in the risk for complications in the low dose heparin. Low dose heparin can be used as continuous infusion for preventing central line occlusion however it has no advantage in lowering the risk for complications.

The sample size of the study was limited due to increased infection rate prompting sudden closure of the Neonatal Intensive Care Unit. The small sample size highly affected the confidence interval which showed a wide range and may indicate a less precise estimate.

Low dose heparin infusion may be considered as part of our NICU policy in maintaining PICC line patency. Further studies may be done comparing the efficacy and safety of several doses. Studies on relationship of heparin and sepsis may also be recommended since infection has been an important factor in this study.

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ARTICLE

Depression and anxiety among caregivers of children and adolescents with neurodevelopmental disorders in a government tertiary hospital during the Covid-19 pandemic

Erik Jan T. Estrada, Ermenilda L. Avendaño, Anna Lizza S. Mañalac

OBJECTIVES: To determine the burden of COVID-19 related mental health problems such as anxiety and/or depression among caregivers of children and adolescents with neurodevelopmental disorders in a government tertiary hospital.

MATERIALS AND METHODS: This is a cross-sectional study conducted at the Out-patient Department of PCMC. Caregiver data sheet and HADS-P forms were given to eligible caregivers.

RESULTS: A total of 102 caregivers were included. The prevalence of significant risk for anxiety disorder among caregivers of children and adolescents with neurodevelopmental disorders is 34.31% (n=35), 1.96% (n=2) for depression and 3.92% (n=4) for both anxiety and depression. Using logistic regression, marital status of common law partner and female sex have significant association with depression and anxiety; the number of household members has a direct association to significant risk for both anxiety and depression.

CONCLUSION: Female sex and common law partnership as marital status are associated with 2-3 times of having significant risk for anxiety or depression. The number of household members is correlated with an increased significant risk of having both anxiety and depression. Screening caregivers using appropriate tests would identify caregivers at significant risk for anxiety and depression and further create intervention programs.

KEYWORDS: *anxiety, depression, caregivers, neurodevelopmental disorders, COVID-19, mental health*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has greatly affected the lives of all people worldwide. The stress brought about by this pandemic continues to propagate and spread, stress not only from contacting the disease or the number of deaths reported but also the disruption of everyday lives and routine, the desire for survival, the isolation and consequently the different mental health problems that may arise[1]. The mental health of parents and caregivers is explored albeit given little

attention, yet it plays a major role in a child and even in family outcomes. The care of a child with neurodevelopmental disorder is a big challenge and these parents are at increased risk of suffering from mental health disorders like anxiety and depression[2]. Hence, with all the stress brought about by the COVID-19 pandemic and the demands of caring for a child with neurodevelopmental disorder, a timely investigation into the stress and mental health of parents is warranted. The study provides a timely screening of caregivers for depression and anxiety during the time of pandemic which can be included during clinic visits for a more holistic approach. Given the mental health problems identified, evidence-based parenting programs, training, and support can be formulated to address these mental health issues. The identified mental health problems and its consequences take time, hence long-term effective identification and intervention programs specifically for caregivers of children with neurodevelopmental disorder can be promoted during clinic visits.

Neurodevelopmental disorders are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning. Children with chronic conditions and special health care needs live at home under the direct care of their caregivers who have a direct effect and influence on the family's well-being and functioning[3]. These children need support in terms of their physical, social, and emotional needs and the majority rely on their parents and families[1].

Thus, caregivers play a central role among children with neurodevelopmental disorders particularly during the rehabilitation and education processes. Hence, their well-being and health are dependent also on the whole health condition of their family in terms of the support and services received, as well as participation in social life[8].

The different factors affecting family functioning include quality of life, treatment adherence and physical health. Alongside these factors are the key drivers of family functioning namely parents' emotional well-being and community/emotional support[3]. The mental health and wellness of caregivers are linked to family well-being. Bayer and colleagues explained in their study the association of child medical complexity with parent mental health and community support and found out that parents of children with medical complexity were at the highest risk for reporting poor or fair mental health. These parents had difficulty handling the demands of parenting and does not know where to find help in their community but on the other hand also receive emotional support from health care providers and advocacy groups[3].

A cross-sectional study done in 2019 by Fatima and colleagues in India assessed the burden of depression and anxiety among mothers of children with neurodevelopmental disorder.

It was found out that depression and anxiety were common among mothers of children with neurodevelopmental disorders. Among screened mothers, 38% had depression, 43% with anxiety and 30% both depression and anxiety[2].

In a systematic review and meta-analysis by Scherer in 2019, there is evidence for an association between parenting a child with intellectual and developmental disability and depression (95%) and anxiety (90%) symptoms, with almost all studies reporting a positive relationship and are consistent across disability type, setting, and sample size. Other factors associated with depression include household income, socio-economic which accounts elevated risk for poor maternal well-being among mothers. For parental depression, disability severity has been implicated, a higher severity means an array of behavioral problems and more care giver demands[5].

During the pandemic, a study by Chan and Fung in April 2021 where 129 parents participated found out that higher levels parenting stress, depressive symptoms and anxiety symptoms were seen during the pandemic among parents of children with developmental disorder compared to parents of children with typical development. One fourth of parents of children with neurodevelopmental disorders met the criteria for depression and 13.7% met the criteria for generalized anxiety disorder. Also, health worries and parenting stress contribute to poor mental health among parent subjects[1].

Pecor and colleagues investigated the effects of COVID-19 pandemic on quality of life, all caregivers reported lower scores compared to before and even during the pandemic but more dramatically for caregivers of children with neurodevelopmental disorder. By gender, mothers experienced higher levels of parental stress and mental problems as usually they are the primary caregivers[4]. This finding was consistent with a meta-analysis reporting higher depression in mothers compared with fathers which may result from higher responsibility in terms of caregiving among mothers or due to response bias as men tend to disclose depressive symptoms[5].

Looking into specific neurodevelopmental disorders, among parents of children with autism spectrum disorder, Wang and colleagues showed the relationship between COVID-19 pandemic and the increase in symptoms and anxiety and depression reaching 13.9% and 9.8% respectively. Compared to parents of neurotypically developing children, the parents of children with autism are more vulnerable. The psychological stress brought about by the pandemic played a key role in parental anxiety and depression scores[4]. Caregivers of children with attention-deficit/ hyperactivity disorder noted higher frequency of negative interactions with their children including increased irritability, verbal abuse

and punishment[6]. Currently there are no locally published studies.

Knowing that there is an increased prevalence of anxiety and depression among parents of children with special health care needs, how then can anxiety and depression be detected among caregivers? There are different validated tools to screen and detect depression and anxiety. Among them is the Hospital Anxiety and Depression Scale (HADS). The Hospital Anxiety and Depression Scale (HADS) was originally developed in 1983 by Zigmond and Snaith. This self-assessment scale is used reliably to detect states of depression and anxiety in the setting of hospital medical outpatient clinic[9]. This self-assessment scale is valid for screening purposes only and that diagnosis depends on clinical examination. The term hospital in the name of the tool, as explained by Snaith in 2003 suggests that it is valid in this setting however many studies have validated its use in community settings and primary care medical practice. The administration of HADS takes about 5 minutes. This can be answered by participants that are literate and able to read but in cases of illiteracy, poor vision, the tool may be read to the participants[10]. The HADS has undergone validation and translation in foreign languages. In a review by Bjelland and colleagues in 2002 it was found that HADS performed well in assessing severity of anxiety disorders and depression in both somatic and psychiatric cases, and in primary care patients and the general population. This tool was also validated for use in different populations such as the elderly and adolescents[10]. The HADS questionnaire was translated to Filipino and validated by Dr. Ma. Lourdes Rosanna E. De Guzman in 2014 and was labeled as Hospital Anxiety and Depression Scale – Pilipino (HADS-P). The cut-off score for Filipino is 11 with sensitivity of 75%, specificity of 70% and a positive predictive value of 75%[11].

OBJECTIVE OF THE STUDY

A. GENERAL OBJECTIVE

To determine the burden of COVID-19 related mental health problems among caregivers of children and adolescents with neurodevelopmental disorders in a government tertiary hospital.

B. SPECIFIC OBJECTIVES

1. To describe the demographics of caregivers of children and adolescents with neurodevelopmental disorders
2. To determine the prevalence of depression and anxiety among caregivers of children and adolescents with neurodevelopmental disorders
3. To determine the association of having anxiety and/or depression with sociodemographic factors, child characteristics and neurodevelopmental disabilities

METHODOLOGY

This was a cross-sectional study that was conducted as face-to-face session with the participants during the clinic visit and evaluation of their children with neurodevelopmental disorders at the Philippine Children's Medical Center, Quezon City.

The study's inclusion criteria are as follows:

1. Caregivers of children and adolescents with neurodevelopmental disorders who are seen at the Out-Patient Department of the Section of Neurodevelopmental Pediatrics
2. Caregivers of admitted children and adolescents with neurodevelopmental disorders
3. All caregivers in the family present during the time of consultation

The study's exclusion criteria are as follows:

1. Caregivers who are diagnosed with anxiety and depression, currently being managed by a health professional.

In a study by Fatima and colleagues**,** the assumption of proportion of anxiety and depression among mothers is 43.3% and 37.5% respectively and with relative precision of 20%, alpha error of 5% (95% confidence level)[2]. Using the Power Analysis and Sample Size (PASS) 2008 Output, the calculated sample size for depression is 98 and 102 for anxiety. Therefore, this study enrolled 102 eligible participants.

Permission from the author of HADS-P was obtained prior to using the questionnaire. A caregiver data sheet and HADS-P form was given to eligible caregivers by the principal investigator. An Adult Psychiatrist was on board for any crisis management.

Due to the on-going COVID-19 pandemic, standard health protocols were observed to prevent spread of the virus. The primary investigator secured informed consent and explained the objectives and methodology of the study. The administration of HADS-P was done on a face-to-face basis and took about 5-10 minutes. All participants were able to read and answer the questionnaire without any assistance from the investigator.

The participants were informed of HADS-P results immediately. Caregivers with remarkable screening test results were referred to Adult Psychiatry service in other government institutions with OPD services for adult patients for further evaluation and management.

During the data collection there was no need for crisis management and debriefing. The study was presented to the Institutional Research Ethics Committee of Philippine Children's Medical Center and commenced with the approval of the Ethics Committee.

Using statistical software (SPSS version 26), specific statistical analysis tools were employed in the analysis and interpretation of data. Descriptive statistics such as frequency count, percentage, mean, median and standard deviation were also used. Linear regression was done to predict the value of a variable based on the value of another variable while logistic regression was done for analyzing the relationship between one or more existing independent variables. Dummy coding was employed to incorporate categorical variables into regression analysis.

RESULTS

A total of 102 caregivers were included in this study. Table I shows the distribution of the caregivers according to demographic profile. Majority of the participants were from the age group of 31–40 years old (52.94%). Most participants were females (89.22%) and mothers (84.31%). As to civil status, 60.78% of the caregivers were married while 26.47% were common law partners. Almost half of the participants (44.12%) reached college levels and the majority of the caregivers were unemployed (63.73%).

Table I. *Demographic Profile of Caregivers of Children and Adolescents with Neurodevelopmental Disorders*

Demographic Profile Age	No./n=102	Percent
30 and below	17	16.67
31-40	54	52.94
41 and above	31	30.39
Mean	37.27 years (SD $\pm$ 0.68)	
Median	36 years old	
Range (min, max)	24, 60 years old	
Gender		
Male	11	10.78
Female	91	89.22
Marital Status		
Common law Partner	27	26.47
Married	62	60.78
Single Parent/Widow	13	12.75

Demographic Profile Age	No./n=102	Percent
Educational Attainment		
Elementary	6	5.88
High School	40	39.22
College	45	44.12
Vocational	11	10.78
Occupation		
Employed	29	28.43
Self-Employed	8	7.84
Unemployed	65	63.73
Relation to Child with Neurodevelopmental Disorder		
Father	11	10.78
Mother	86	84.31
Other Relative	5	4.90

In terms of family monthly income, majority of the participants have monthly income falling under the low-income class (Php 12,082-24,164) to lower middle-income class (Php 24,164 – Php 48,328) based on the Philippine Statistics Authority classification[13]. The majority of the caregivers have one child and 5 to 6 household members.

Table II. *Distribution of caregivers according to household information*

Household Information	No./n=102	Percent
Php 10,000 and below	41	40.20
Php 10,001 – Php 20,000	49	48.04
Above Php 20,000	12	11.76
Mean	Php 15,858.82 (SD $\pm$ Php 12,458.89)	
Median	Php 12,000.00	
Range (min, max)	Php 3,000, Php 70,000.00	
Number of Children		
1	33	32.35
2	27	26.47
3	23	22.55
More than 3	19	18.63
Median	2	
Range (min, max)	1, 6	

Number of Household Members		
4 and less	36	35.29
5 to 6	43	42.16
More than 6	23	22.55
Median	5	
Range (min, max)	2,17	

Looking into the demographic profile of children of caregivers in this study, majority were from the age group of 4–17 years old (44.12%) and first born (46.08%), As to neurodevelopmental diagnosis, majority have Autism Spectrum Disorder (34.31%), followed by those who have Intellectual Disability (21.57%), with Global Developmental Delay (20.59%), Cerebral Palsy (17.65%) and those with ADHD and down syndrome (both 1.96%). For intervention, most children have no intervention (therapies) yet and are not yet enrolled in schools (59.80%). A co-morbid diagnosis of Epilepsy was seen among 35.29% of these children and are maintained on anti-seizure medications.

Table III. *Demographic Profile of Caregivers' Children*

Demographic Profile	**No./n=102**	**Percent**
3 yrs old and below	26	25.49
4 – 7 years old	45	44.12
8 years old and above	31	30.39
Mean	6.40 years (SD $\pm$ 0.40)	
Median	6 years old	
Range (min, max)	0.42, 17 years old	
Birth Order		
1st	47	46.08
2nd	24	23.53
3rd	20	19.61
4th onwards	11	10.78
Diagnosis		
ADHD	2	1.96
Autism Spectrum Disorder	35	34.31
Cerebral Palsy	18	17.65
Down Syndrome	2	1.96
Global Developmental Delay	21	20.59
Infant at High Risk for Developmen-	2	1.96
Intellectual Disability	22	21.57

Intervention		
none	41	40.20
OT alone	12	11.76
PT alone	15	14.71
OT and PT	11	10.78
OT and ST	20	19.61
PT and ST	1	0.98
OT, PT, ST	2	1.96
Education		
none	61	59.80
SPED	24	23.53
Nursery – Grade 6	17	16.67
Maintenance Medication		
none	66	64.71
Taking medications	36	35.29

While majority of the caregivers did not display a significant risk for anxiety and depression, the prevalence of significant risk for anxiety disorder among caregivers and adolescents with neurodevelopmental disorders is 34.31% while significant risk of depression is seen in only 1.96%. Almost 4% (4 caregivers) showed a significant risk for having both anxiety and depression.

Table IV. *Prevalence of risk for depression and anxiety among caregivers of children and adolescents with neurodevelopmental disorders*

Risk for Depression and	No.	Percent
Normal	61	59.8
Anxiety	35	34.31
Depression	2	1.96
Depression and Anxiety	4	3.92
Total	102	100%

Caregivers of children with autism spectrum disorder showed higher risk of anxiety and depression than in the other neurodevelopmental diagnosis followed by caregivers of children with intellectual disability and global developmental delay.

Table V. *Cross tabulation of prevalence of significant risk for depression and anxiety according to neurodevelopmental disorders*

Diagnosis	Total		Normal		Depression		Anxiety		Depression and Anxiety	
	No.	%	No.	%	No.	%	No.	%	No.	%
Autism Spectrum Disorder Level 3	35	34.3	21	60	1	3	11	31	2	6
Intellectual Disability	22	21.6	13	59	-	-	9	41	-	-
Global Developmental Delay	21	20.6	12	57	1	5	7	33	1	5
Cerebral Palsy	18	17.6	13	72	-	-	5	28	-	-
ADHD moderate	2	2	-	-	-	-	1	50	1	50
Down Syndrome	2	2	2	100	-	-	-	-	-	-
Infant at High Risk for Developmental Delay	2	2	-	-	-	-	2	100	-	-

Logistic regression showed that caregivers with marital status of common law partner has 2.558 higher likelihood of anxiety disorder while 1.760 likelihood in depression than the other caregivers with different status. It may mean that caregivers with marital status of common law partner are more likely to have anxiety or depression disorder than caregivers with different status. As to sex, female caregivers have a higher score for anxiety disorder and depression than male caregivers. It may mean that female caregivers are more likely to have anxiety or depression disorder than male caregivers. In Table VI, using stepwise regression, there are two variables with a significant risk for anxiety and depression. The excluded variables have p-values greater than 0.05 level of significance which indicates that there is not enough evidence to conclude that these variables are associated with significant risk for anxiety and depression.

Table VI: *Linear Regression analysis of independent variables correlated to scores of significant risk for anxiety and depression*

	Anxiety		Depression	
Significant variables	**Coefficients**	**P-value**	**Coefficients Beta**	**P-value**
Caregivers Marital Status (Dummy coding: CLP=1)	2.558	.004	1.760	.023
Caregiver's Sex	3.642	.004	2.333	.034

Excluded Variables	Coefficients Beta	P-value	Coefficients Beta	P-value
Caregiver's Age	.052	.611	-.023	.832
Caregivers Marital Status (Dummy coding: M=1)	.214	.130	.009	.954
Caregivers Marital Status (Dummy coding: Others=1)	-.146	.130	-.006	.954
Family Monthly Income	-.017	.860	-.114	.253
Number of Children	.020	.831	.008	.935
Number of Household Members	-.126	.184	-.022	.825
Child's Age	-.105	.284	-.080	.431
Child Diagnosis	.089	.344	.063	.516
Child Diagnosis	-.080	.395	-.070	.469
Child Diagnosis	-.008	.936	.057	.560
Child Diagnosis	-.009	.920	-.087	.370
Child Diagnosis	-.022	.819	.041	.672
R square	.139		.085	

Among the four participants at risk for both anxiety and depression, the number of household members has a direct association with risk for both anxiety and depression. The more household members there are, the higher the tendency to have significant risk for both anxiety and depression.

Table VII. *Logistic Regression analysis of independent variables association of significant risk for both anxiety and depression*

	Anxiety and Depression	
Significant variables	**Coefficients Beta**	**P-value**
Number of Household Members	.220	.051
Excluded Variables	**Coefficients Beta**	**P-value**
Caregiver's Age	.003	.956
Caregiver's Sex	.399	.528
Caregivers Marital Status (Dummy coding: M=1)	.140	.709
Caregivers Marital Status (Dummy coding: CLP=1)	.005	.946
Caregivers Marital Status (Dummy coding: Others=1)	.179	.673
Family Monthly Income	.631	.427
Number of Children	.195	.659
Child's Age	.046	.830

Child Diagnosis	1.014	.314
Child Diagnosis (Dummy coding: CP=1)	.597	.440
Child Diagnosis (Dummy coding: GDD=1)	.025	.874
Child Diagnosis (Dummy coding: ID=1)	2.050	.152
Child Diagnosis (Dummy coding: Others=1)	1.539	.215
R square	.106	

DISCUSSIONS

The present study showed the burden of COVID-19 related mental health problems among 102 caregivers of children and adolescents with neurodevelopmental disorders. Using the HADS-P, 35 caregivers (34.31%) were identified to have significant risk for anxiety, two were identified to have significant risk for depression and four caregivers for both anxiety and depression. These caregivers were informed of the screening results and subsequently referred to Adult Psychiatry service in other government institutions for further evaluation and management.

Among those with significant risk for anxiety, 31% have children with autism spectrum disorder. This finding is consistent with the study of Ersoy and colleagues in 2020 showing a higher level of anxiety on chronic diseases in mothers of children with autism compared to mothers with normal children during the time of pandemic[14]. A study by Purpura in 2021 showed that higher levels of stress are evident in caregivers of children with a primary diagnosis of autism spectrum disorder and intellectual disability than caregivers of children with other neurodevelopmental disorders. This was attributed to the intrinsic and pervasive characteristics of these two disorders[8]. Given the present situation, parents of children with autism may experience more stress aggravated by new or increased behavioral problems[15].

Before the pandemic, a study by Fatima and colleagues showed that depression and anxiety were common among mothers of children with neurodevelopmental disorders. It screened positive for 91 mothers and diagnosed 52 with generalized anxiety disorder which was consistent with the screening results of the present study[2]. During the pandemic it is expected that there would be higher prevalence of anxiety and depression, corollary to a study by Chan and Fung showing higher levels parenting stress,

depressive symptoms and anxiety symptoms among parents of children with developmental disorder compared to parents of children with typical development[1]. Hence, there is an increased risk of having anxiety and/ or depression among caregivers of children with neurodevelopmental disorders with or without the pandemic compared to their counterparts.

One of the objectives is to determine the association of having significant risk for anxiety and/or depression with sociodemographic factors, child characteristics and neurodevelopmental disabilities. Interestingly, female sex and marital status of common law partnership are associated to 2-3 times of having significant risk for anxiety or depression. This may be due to the fact the most participants are mothers (84%), mostly unemployed and the ones assigned as primary caregivers who are with their children for most of the day. Often, they must care for their children on top of other household chores and family responsibilities. Looking at the gender per se, a study by Amendola and colleagues in 2021 found that females reported higher symptoms of depression, anxiety, and circadian rhythm dysregulation than males. However, one important note is that lockdowns are a new type of situation and that the mental health of men and women may be affected both in similar and differing ways[17].

In terms of marital status, a study by Grundstrom investigated associations between relationship status and mental well-being. It revealed that cohabiting tended not to differ from marriage in terms of having better mental well-being. The risk factors for depressive symptoms and lower self-esteem are being single or being divorced[18]. This contradicts the findings of the present study. Another interesting finding in this study worth pursuing in the future is the finding that the number of household members correlated with having an increased significant risk for having both anxiety and depression. We can only surmise that more household members mean more responsibilities.

The nature of the study limits the researcher to use causal inferences to determine the association of having anxiety and/or depression with different factors; longitudinal research may be used for this one.

Conclusion

This study focused on the mental health of caregivers of children and adolescents with neurodevelopmental disorders. Thirty-five caregivers (34.31%) were identified to have significant risk for anxiety, two were identified to have significant risk for depression and four caregivers for both anxiety and depression. Female sex and marital status of common law partnership are associated to 2-3 times of having significant risk for anxiety or depression. Further, the number of household members is correlated with having increased significant risk of

having both anxiety and depression. The caregiver's age and sex, family income, number of children, child's neurodevelopmental diagnosis had no enough evidence to conclude that these variables have significant association to significant risk for both anxiety and depression. Screening of caregivers in clinical settings using appropriate tests would yield to identifying caregivers at significant risk for anxiety and depression and further create intervention programs both preventive and rehabilitative.

Screening for anxiety and depression of caregivers using appropriate tests should be part of the holistic care of children with neurodevelopmental disabilities since caregivers have a significant role in the success of these interventions. Timely checks on the mental health status of the caregivers are of paramount importance. Once identified, prompt referrals to appropriate services need to be made. Parent training and parental education as well as psychosocial support groups for parents can promote positive parenting and help address the mental health issues of parents especially during the time of COVID-19 pandemic.

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ARTICLE

Maternal and newborn impact of epidural dexamethasone as an adjuvant for labor analgesia: a meta-analysis

Crista Mae F. Fontanilla, Joy Ann R. Lim

BACKGROUND: Dexamethasone, an anti-inflammatory drug, has an assumed analgesic effect when given epidurally, with less side effects[5,7]. Although numerous studies have evaluated dexamethasone, there is a paucity of studies assessing its intrapartum use[6]

OBJECTIVES*:* To determine the effectiveness of epidural dexamethasone when used as an adjuvant for labor analgesia.

MATERIALS AND METHODS: A meta-analysis guided by the Cochrane handbook was performed. Articles were searched through PubMed, MEDLINE, CENTRAL, Google Scholar and ClinicalTrials.gov using search strategies such as keywords and MeSH terms. Cochrane version 2 risk-of-bias tool for randomized trials (RoB 2) was used to assess for quality. Quantitative data were pooled and analyzed using Review Manager 5.4.1.

RESULTS: A total of five trials involving 309 women in labor were analyzed. The pooled mean difference showed prolonged duration of epidural analgesia on patients who received epidural dexamethasone; pooled risk ratio between the experimental and control group demonstrated no significant maternal adverse events such as nausea and vomiting, shivering, hypotension, and fever. Pooled risk ratio and mean difference also showed that epidural dexamethasone had no significant effect on the neonatal APGAR and neonatal umbilical pH.

CONCLUSION: : Present data demonstrated the potential role of dexamethasone as an adjuvant to epidural solution during labor analgesia on providing local anesthetic dose sparing effect through prolongation of the duration of epidural analgesia, with limited maternal and neonatal adverse events. These results should be interpreted with caution before adopting this technique in routine clinical practice.

KEYWORDS: *Dexamethasone; Epidural; Labor analgesia; Meta-analysis*

INTRODUCTION

Labor is seen as one of the most intense and painful events in a woman's life. Pain causes a neuroendocrine stress response with effects on multiple maternal and fetal organ systems. The cardiopulmonary physiologic responses to pain are usually well tolerated by healthy parturients with normal pregnancies but may be of more concern in parturients with cardiopulmonary disease and at-risk fetuses[1]. The provision of labor analgesia reduces the plasma concentration of epinephrine. By reducing the maternal secretion of catecholamines, epidural analgesia may shift a previously dysfunctional labor pattern to a normal one[2,3]. Local anesthetic (LA) agents such as bupivacaine, levobupivacaine and ropivacaine are routinely used for producing analgesia. Current drugs used are short acting relative to the duration of labor, thus, use of an adjuvant is desirable. The addition of an analgesic adjuvant to regional anesthetic techniques is widely practiced with the aim of not only improving both quality and duration of anesthesia and prolonging postoperative analgesia, but also limiting dose related LA side effects[4]. Several adjuvants such as opioids, alpha-adrenergic agonists, neostigmine, midazolam, ketamine have been examined along with LA, but none showed an ideal analgesic property[5]. The optimal mixture for epidural analgesia does not exist yet. Clinically safe epidural usage of drugs should be pursued to enhance quality of pain relief while not compromising the safety of both the mother and the fetus. If there is no added benefit of administering an adjuvant, this should be omitted, or use of another agent should be preferred. Some newer adjuvants such as clonidine and neostigmine have been used for labor analgesia but are associated with side effects like hypotension, bradycardia and sedation[6].

Dexamethasone, a well-known anti-inflammatory drug, has also been investigated for its analgesic efficacy as an adjunct. It is under the class of corticosteroids, known to inhibit phospholipase A2 and expression of cyclooxygenase2, reducing prostaglandin synthesis. It is also known to block nociceptive C-fiber transmission and suppress neurologic ectopic discharge which represses hyperalgesia associated with acute nociception. The rationale for using dexamethasone epidurally was an assumed analgesic effect that was at least like other adjuvants but with less side effects than the others[5,7]. Researchers have deemed epidural dexamethasone safe. Thomas et al. showed that epidural dexamethasone reduced postoperative pain and analgesic requirements in patients undergoing laparoscopic cholecystectomy. Khafagy et al. demonstrated efficacy of epidural dexamethasone on postoperative analgesia in patients undergoing

lower abdominal surgeries. Research regarding new epidural drugs and drug combination is ever increasing. Prior meta-analyses evaluating the analgesic properties of dexamethasone did not identify studies performed in labor analgesia[8]. Although numerous studies have evaluated dexamethasone, there is a paucity of studies assessing its intrapartum use[6].

We aimed to determine the effectiveness and safety of epidural dexamethasone when used as an adjuvant for labor analgesia. Specific objectives were to determine the maternal effect of epidural dexamethasone with regards to the duration of epidural analgesia, total LA consumed, visual analog scale (VAS), onset of sensory block and maternal adverse event; and to determine if there was a difference in the neonatal outcome with regards to the APGAR score and umbilical pH of the newborn.

METHODOLOGY

This meta-analysis was guided by the Cochrane Handbook[11,] and reporting was accomplished in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Guidelines[12].

We performed a systematic literature search from various publicly accessible scientific journal databases such as PubMed, MEDLINE, Cochrane Central Registry of Controlled Trials, Google Scholar and database of unpublished trials in https:// clinicaltrials.gov was checked. Keywords and MeSH terms used in the literature search were "*dexamethasone*" [MeSH] or "*steroid*" or "*corticosteroid*" and "*epidural*" or "*epidural analgesia*" [MeSH] or "*epidural anesthesia*" [MeSH] or "*labor analgesia*" [MeSH] or "*obstetric analgesia*" [MeSH] OR "*obstetric anesthesia*" [MeSH].

No language or date restriction was applied. A manual search was done in the reference lists of the resulting list of publications for any relevant trials. Duplicate studies were removed, and screening of titles and abstracts were done. Studies were excluded using the inclusion and exclusion criteria and remaining studies were screened using their full text. Two review authors (primary investigator and co-investigator) independently screened the abstracts and titles of studies with reference to the specified eligibility criteria.

Prospective, randomized controlled trials comparing the effectiveness of epidural dexamethasone when used as an adjuvant to labor analgesia were included in this meta-analysis. Language restriction was not imposed. Prospective observational studies, retrospective analysis, trials conducted in pediatric populations, case reports, case series, animal studies, and studies not reporting on any of the predefined outcome

were excluded from the analysis. Studies that were included were parturients for labor analgesia, belonging to the American Society of Anesthesiologist (ASA) physical status II-III, 18 years of age or more, regardless of gravidity and cervical dilatation at the time of epidural insertion. Studies whose participants refused to undergo regional anesthesia, had deranged coagulation profile, with local infection, spine deformity, history of allergy to any medications to be used and with other contraindications to regional anesthesia were excluded from the study. Patients who were classified as ASA IV or more, with preexisting or gestational diabetes mellitus, already receiving steroids and with history of immunosuppression were also omitted.

The primary intervention was any dose of epidural dexamethasone used as an adjuvant to LA (such as bupivacaine, levobupivacaine, ropivacaine). The comparator was normal saline. Studies where dexamethasone was administered intrathecally were excluded.

The primary outcome was the duration of epidural analgesia and the total LA consumed for the whole course of labor. Secondary outcomes were other maternal and neonatal effects such as pain assessment, onset of sensory block, maternal adverse events and hemodynamics, neonate's APGAR, and umbilical pH.

All studies identified using the above search strategy were screened by two reviewers for relevance based on their titles and abstract that met the criteria. Studies which were deemed irrelevant were removed from the pool of studies. After the initial screening, the full texts of each identified article were retrieved for in-depth screening using the eligibility criteria. The decision to include or exclude were cross-checked by each reviewer. Duplicate studies were identified and screened for completeness. The two reviewers then compared their list of included studies and discrepancies were discussed until an agreement was made. Reasons for exclusion of the ineligible studies were identified and recorded. PRISMA flow diagram[12] was used to show the screening process of the study inclusion and exclusion.

Assessment for risk of bias was performed using the Review Manager program and version 2 of the Cochrane risk-of-bias tool for randomized trials tool (RoB 2.0). Each article included was appraised by the primary investigator and co-investigator based on 5 bias domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Within each domain, a series of signaling questions were answered with the aim to elicit information about features of the trial that were relevant to risk of bias. An algorithm based on answers to the signaling questions generated a proposed judgment about the risk of bias arising from each domain.

Judgment was either "Low" or "High" risk of bias or expressed as "Some concerns". Differences were resolved by reexamination of the original articles and through discussion.

A form to extract data was designed. For eligible studies, at least two review authors extracted the data using the agreed form. Discrepancies were resolved through discussion. The list of potential abstracts and citations of final studies included were saved and managed in a Microsoft Excel spreadsheet. Full text copies of studies included were saved in a Google drive accessible to the investigators. Risk of bias scorings and extracted data from the studies were managed using Review Manager software. The main data extracted from the included studies were:

Methods: study design, study setting, withdrawals, date of study

Participants: number, age, gender, inclusion criteria, exclusion criteria, other relevant characteristics

Interventions: intervention components, comparison, fidelity assessment

Outcomes: main and other outcomes specified and collected

The meta-analysis was performed using the Reviewer Manager Software, version 5.4.1[14]. All data were analyzed using a random-effects model due to clinical or methodological heterogeneity. The mean difference for the duration of analgesia, total LA consumed, VAS, onset of sensory block and neonatal umbilical pH between the groups were used. Relative risk for nausea and vomiting, shivering, hypotension, fever, APGAR were estimated. Forest plots of the outcomes of interest were generated to display effect estimates and confidence intervals for both individual studies and meta-analysis. The level of statistical significance was set at $p<0.05$ values with a 95% confidence interval. To assess heterogeneity between studies for the outcome, chi-square test was used as included in the forest plot of RevMan program, with $P<0.10$ indicating significant heterogeneity, and I^2 with suggested thresholds for low (24-49%), moderate (50-74%) and high (>75%) values. Heterogeneity was explored by performing a sensitivity analysis excluding outlier studies if they were methodologically different from other studies. Risk of publication bias was detected with the use of funnel plot.

Results

The initial search through databases and other sources yielded 850 references. Most articles were excluded due to duplicate records, different study designs, population, interventions, and outcomes used. Eighteen full text articles were reviewed for eligibility. Out of the eighteen, thirteen full text articles were excluded due to different patient population and intervention used. A total of five studies were then included in the analysis.

No local study was found during the systematic search. An article not in English language was translated by the American Journal of Translation Research. A flowchart of study selection was summarized in Figure I below.

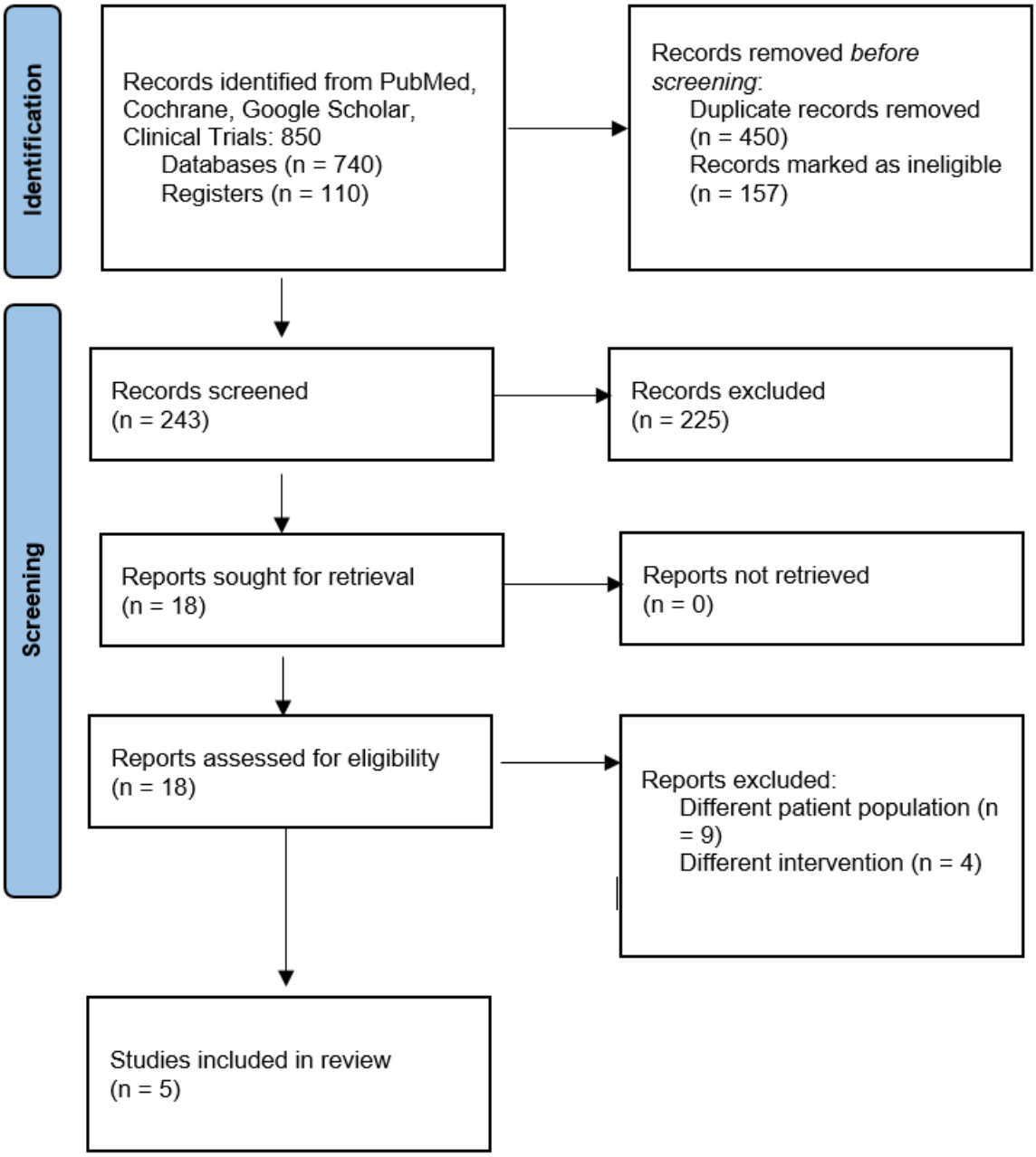


Figure 1: *PRISMA Flow Chart of Literature Search*[12]

Table 1: Characteristics of Included Studies[15]

Study ID, Author, Year, Location	Study Title	Population	Method/ Design	Anesthetic Technique	Comparator, LA Used, Sample Size	Intervention, LA Used, Sample Size	Study Outcomes
A Wu et al. 2021 China (Department of Anesthesiology, Yichun People's Hospital)	Feasibility of epidural injection of ropivacaine and dexamethasone for labor analgesia in women with preeclampsia	Inclusion: met the diagnostic criteria for preeclampsia and presented with typical symptoms; conscious and cooperated with the study; clinical data of the subjects were complete; ASA I-III; subjects agreed and signed the informed consent; vaginal delivery Exclusion: concurrent psychiatric disorders; multiple births; in active labor; allergic to the investigational drugs; severe cardiopulmonary disorders; placenta abruptio or placenta previa; <28 weeks of gestation; intermediate cesarean delivery	Randomized controlled trial	CLEA	Epidural ropivacaine 0.125% 39	Epidural ropivacaine 0.125% with dexamethasone 2mg 41	Maternal adverse events such as nausea/vomiting, hypotension, fever, bradycardia, motor block; APGAR in 1 & 5min

Study ID, Author, Year, Location	Study Title	Population	Method / Design	Anesthetic Technique	Comparator, LA Used, Sample Size	Intervention, LA Used, Sample Size	Study Outcomes
B Wahdan et al. 2019 Egypt (Department of Anesthesiology, Surgical ICU and Pain Management, Cairo University)	Epidural levobupivacaine versus a combination of levobupivacaine and dexamethasone in patients receiving epidural analgesia	Inclusion: 18 - 35 years of age; for normal vaginal delivery; ASA class I-II; no contraindication to regional anesthesia; with informed consent Exclusion: patient refusal; with failed epidurals; fetal distress; conversion to CS	Prospective double-blind trial	CLEA	Epidural levobupivacaine 0.125% 30	Epidural levobupivacaine 0.125% with dexamethasone 4mg 30	Duration of analgesia; Total amount of LA used; Pain score before after the block; Onset of sensory block; Maternal adverse events such as nausea/ vomiting, shivering; Maternal satisfaction; Neonatal umbilical pH

Study ID, Author, Year, Location	Study Title	Population	Method / Design	Anesthetic Technique	Comparator, LA Used, Sample Size	Intervention, LA Used, Sample Size	Study Outcomes
C Dhal, et al. 2018 India (Department of Anaesthesia and Intensive Care, Government Medical College and Hospital)	Can Epidural Dexamethasone Reduce Patient-Controlled Epidural Consumption in Laboring Women? A Double-Blind, Randomized, Placebo- Controlled Trial	Inclusion: ASA I-II; > 18 years old; primigravida with single gestation and cephalic presentation; at >= 37 weeks of gestation; cervical dilation <= 5 cm; pain score >30; requesting epidural analgesia Exclusion: patient refusal; administration of oral or parenteral analgesics in last 4 h before the start of neuraxial block; gestational age <37 weeks; history of obstetric complication; fetus with non-reassuring non- stress test; congenital abnormality; allergy to study drugs; preexisting or gestational diabetes mellitus; receiving steroids; history of immunosuppression; with local infection; deranged coagulation profile	Prospective, double-blind, randomized, controlled trial	CSEA	Intrathecal bupivacaine hyperbaric 0.5%, 2.5mg Epidural levobupivacaine 0.1% 30	Intrathecal bupivacaine hyperbaric 0.5%, 2.5mg Epidural levobupivacaine 0.1% with dexamethasone 8mg 30	Hourly drug consumption; Pain score before and after the block; Onset of analgesia; Maternal adverse events such as nausea/vomiting, shivering, fever, motor block; Maternal satisfaction; APGAR in 1 and 5 min

Study ID, Author, Year, Location	Study Title	Population	Method / Design	Anesthetic Technique	Comparator, LA Used, Sample Size	Intervention, LA Used, Sample Size	Study Outcomes
D Ali, et al. 2018 Egypt (Department of Anesthesia, Faculty of Medicine, Cairo University)	Using dexamethasone as an adjuvant to levobupivacaine in epidural anesthesia to change the pain intensity and duration in painless labor	Inclusion: between 21 and 35 years of age; for normal vaginal delivery; with cervical dilatation 4 cm or more; ASA II Exclusion: patient refusal; history of allergy to any medications to be used; coagulopathy; ASA III or more; spine deformity; any contraindications to neuraxial blocks; failed epidural; fetal distress; shift to cesarean section	Prospective double-blinded controlled trial	CLEA	Epidural levobupivacaine 0.125% 26	Epidural levobupivacaine 0.125% with dexamethasone 8mg 23	Duration of analgesia; Total amount of LA used; Pain score before and after the block; Onset of sensory block; Maternal adverse events such as nausea/vomiting, shivering; BP; HR; Maternal satisfaction; APGAR in 5 min; Neonatal umbilical pH

Study ID, Author, Year, Location	Study Title	Population	Method / Design	Anesthetic Technique	Comparator, LA Used, Sample Size	Intervention, LA Used, Sample Size	Study Outcomes
E Wang, et al. 2010 China (Department of Anesthesiology, Jiaxing Maternity and Child Health Care Hospital)	Influence of epidural dexamethasone on maternal temperature and serum cytokine concentration after labor epidural analgesia	Inclusion: healthy nulliparas ; spontaneous labor; singleton cephalic presentation; term (more than 37 weeks of pregnancy); requested epidural analgesia Exclusion: baseline temperature of 37.5 °C or more; metabolic disease; pregnancy-related complication such as diabetes mellitus or preeclampsia; increased risk of cesarean delivery; contraindication to epidural analgesia	Randomized, controlled trial	CLEA	Epidural bupivacaine 0.125% 30	Epidural bupivacaine 0.125% with dexamethasone 5.8mg 30	Total amount of LA used; Pain assessment before the block; Intrapartum fever; APGAR in 1 and 5 min

Study Characteristics

This meta-analysis included 5 randomized controlled trials[15-19] to determine the effectiveness of epidural dexamethasone when used as an adjuvant for labor analgesia (Table 1). It encompassed data for 309 women, in which 154 of them were randomized to the treatment group who received dexamethasone to the epidural solution and the remaining 155 fell to the control group who received the usual epidural solution. The population of these trials range from 49 (Ali et al) to 80 (Wu et al) parturients for vaginal delivery. One study was done in 2021 (Wu et al), another in 2019 (Wahdan et al), two studies done in 2018 (Dhal et al and Ali, et al) and the last study in 2010 (Wang et al).

The anesthetic technique used for labor analgesia by four of the five studies (Wu et al, Wahdan et al, Ali et al and Wang et al) was epidural anesthesia, while one study (Dhal et al) made use of the CSEA. The LA used for the epidural solution by three of the five studies (Wahdan et al, Dhal et al and Ali et al) was levobupivacaine, while the study by Wu et al used ropivacaine and the study by Wang et al used bupivacaine. Out of the five studies, two studies (Dhal et al and Ali et al) used 8mg of dexamethasone, one study (Wu et al) used 2mg dexamethasone, another (Wahdan et al) with 4mg dexamethasone, while Wang et al used 5.8mg dexamethasone.

For the primary outcome, only two studies (Wahdan et al and Ali et al) analyzed the duration of epidural analgesia in minutes. Four studies determined the total LA used; however, the study by Dhal et al measured the drug consumption per hour, while the remaining three studies (Wahdan et al, Ali et al and Wang et al) measured the total drug consumed through the course of labor. The secondary outcome assessed other maternal and neonatal effects of epidural dexamethasone. Pain before and after the block and onset of sensory block was assessed by three studies (Wahdan et al, Dhal et al and Ali et al). These five studies reported different adverse events such as nausea and vomiting (Wu et al, Wahdan et al, Dhal et al, Ali et al), shivering (Wahdan et al, Dhal et al, Ali et al), hypotension (Wu et al, Dhal et al) and fever (Dhal et al, Wang et al). The incidence of bradycardia was noted by Wu et al while Ali et al measured this by beats per minute. Maternal satisfaction was assessed by incidence (Wahdan et al), through 1-100 scale (Dhal et al) and by 0-3 scale (Ali et al). APGAR was included in four studies (Wu et al, Dhal et al, Ali et al and Wang et al) while only two studies (Wahdan et al and Ali et al) measured the neonatal umbilical pH. Characteristics of included studies were tabulated in Table 2.

All studies had low risk for bias from the randomization process and measurement of the outcome. Four from the five studies

had low risk of bias due to deviations from intended intervention and in selection of reported result while only three studies had low risk of bias due to missing outcome data (Figure 2).

The risk of bias of the selected studies was judged based on Risk of bias tool (ROB 2)[20]. Three out of the five included studies in this paper had low risk of bias based on the five different domains as summarized in Figure 3 below.

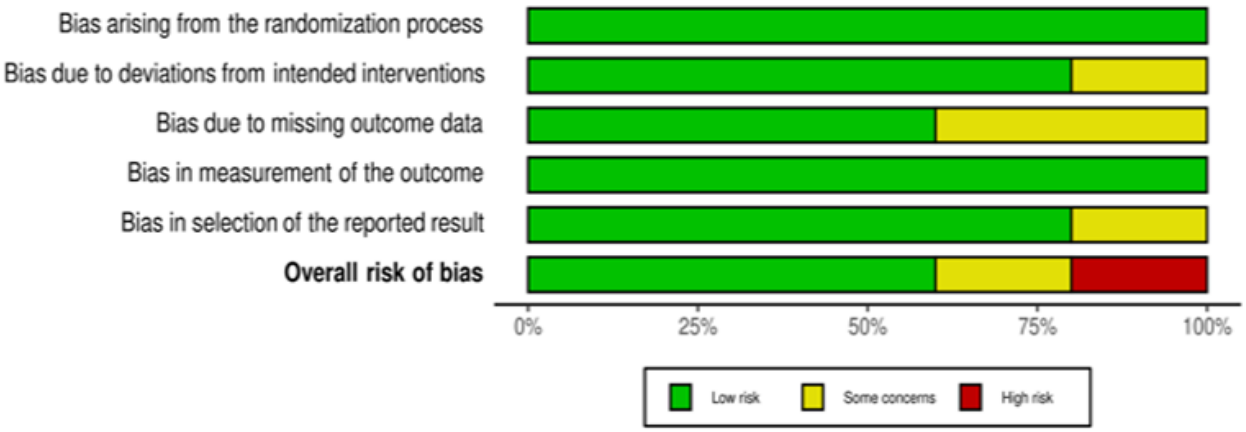


Figure 2: *Risk of bias graph of included studies*

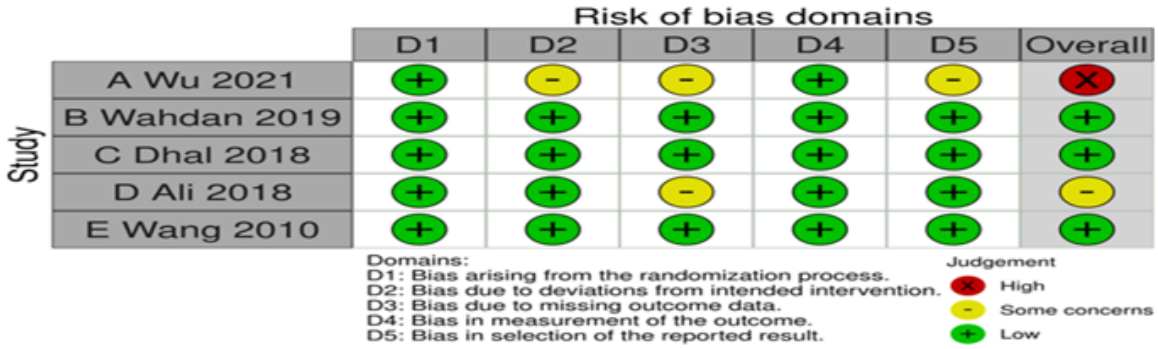


Figure 3: *Risk of bias summary of included studies*

Comparison of Outcomes

Mean duration of epidural analgesia (in minutes) for both the experimental and comparator group were primarily pooled in this study where the overall effect estimate was calculated as the mean difference with 95% confidence interval. . Pooled summary estimate was derived using the random effects model. Among the five included studies, only two reported the mean duration of epidural analgesia.

Figure 4 indicates that patients who had epidural dexamethasone as an adjuvant for labor analgesia had longer duration of analgesia by an average of 18.3 minutes compared to the group without dexamethasone. The level of heterogeneity using I^2 was 0% (low).

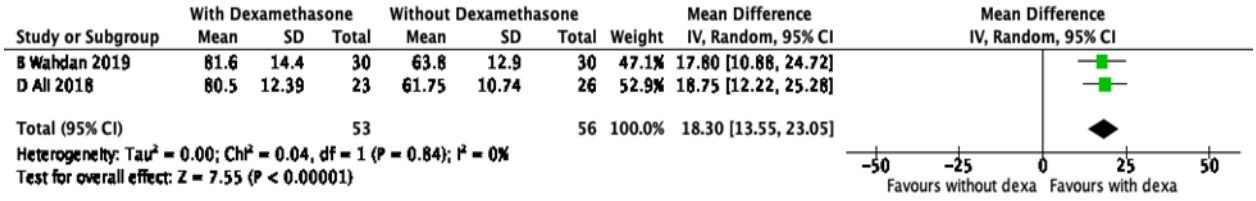


Figure 4: *Effect on the duration of epidural analgesia*

The total analgesic dose used for both experimental and comparator group were primarily pooled. The overall effect estimate was calculated as the mean difference with 95% confidence interval. Pooled summary estimate was derived using the random effects method. Three of the five included studies reported the total LA consumed through the course of labor (Figure 5). Overall, the pooled mean difference showed no significant difference between the two groups. The studies however, demonstrated high heterogeneity (I^2=87%).

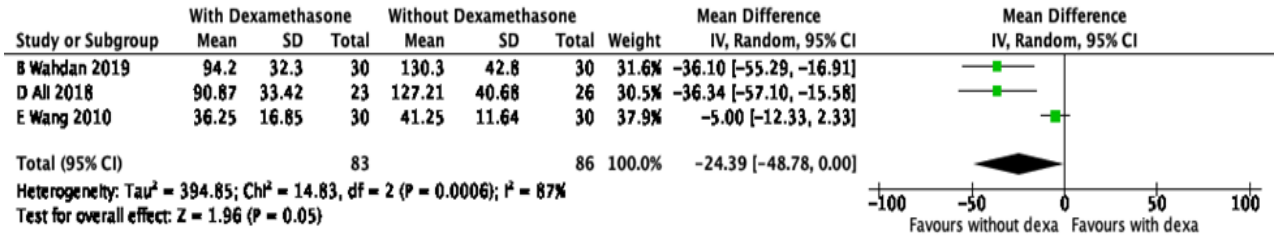
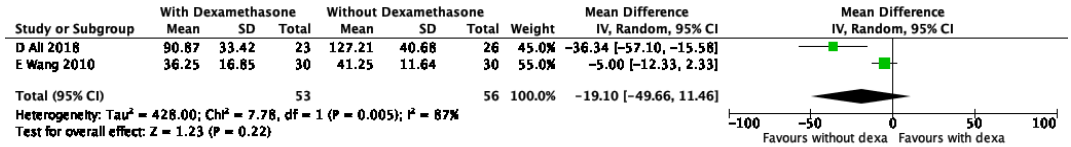


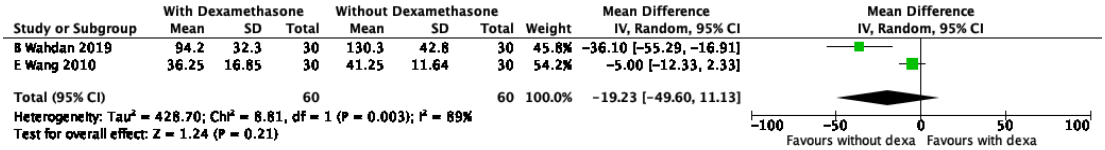
Figure 5: *Effect on the total LA consumed*

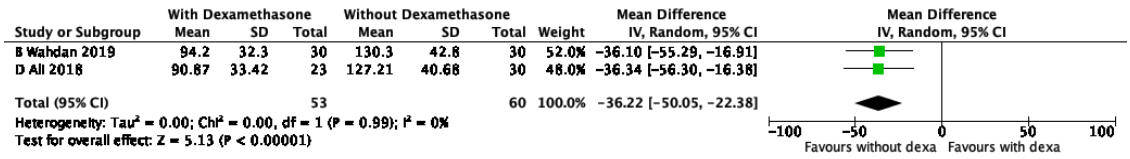
A sensitivity analysis omitting one study at a time was done to assess the robustness of the results as shown in Table 2. The three studies used different doses of dexamethasone 4mg (Wahdan et al), 8mg (Ali et al) and 5.8mg (Wang et al). Wang's trial also used Bupivacaine as its LA in the epidural solution while the other two studies used Levobupivacaine. Studies by Wahdan et al and Ali et al when removed, did not eliminate the large heterogeneity. When the study by Wang et al was removed, the heterogeneity on the total LA used between the two groups was eliminated (MD= -36.22mg; 95%CI=-50.05, -22.38; p-value=<0.00001; I^2=0%).

Table 2: Sensitivity analysis on the total LA consumed

Study removed	I^2	Pooled effect estimate
Wahdan 2019	87%	-19.10 (-49.66, 11.46); p=0.22
Ali 2018	89%	-19.23 (-49.60, 11.13); p=0.21
Wang 2019	0%	-36.22 (-50.05, -22.38); p<0.00001







Mean VAS before and after the block were primarily pooled in the study. The overall effect estimates were calculated as the mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects method. Three studies reported the pain scale before and 15 minutes after the performance of labor analgesia. The pooled mean differences in the parturients' VAS before (MD=0.19; 95%CI=-0.16, 0.54; p-value=0.28) and after (MD=0.00; 95% CI=-0.18, 0.19; p-value=0.97) the block showed no significant differences between the two groups. The studies showed low heterogeneity (I^2=37%; I^2=0%). (Figure 6 and 7)

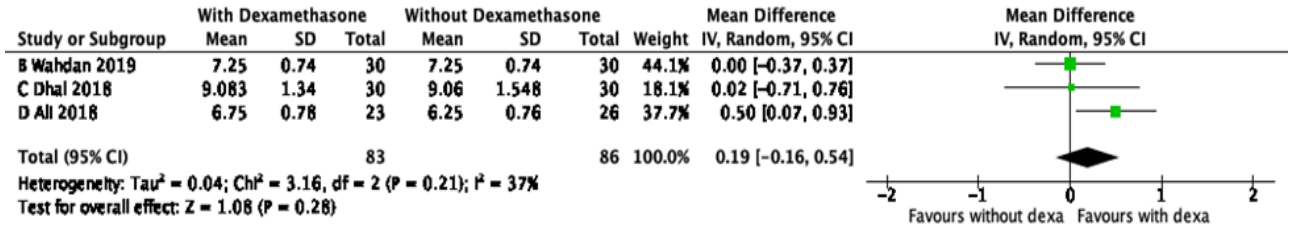


Figure 6: *Effect on the VAS before the block*

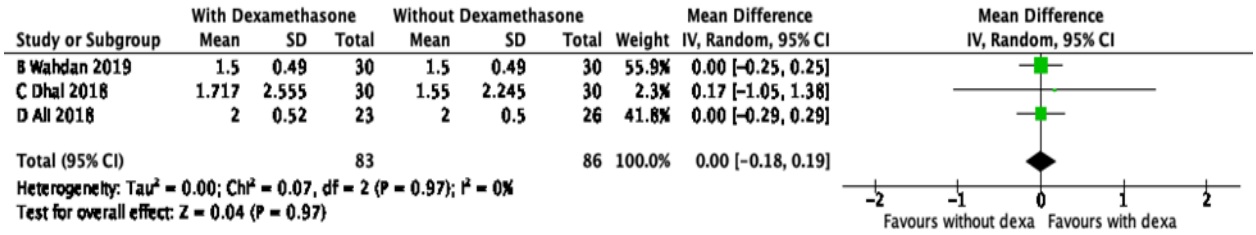


Figure 7: *Effect on the VAS after the block*

Mean onset of sensory block for both the experimental and control group were pooled. The overall effect estimate was calculated as the mean difference with 95% confidence interval. Pooled summary estimate was derived using the random effects method. Three studies reported the mean time for onset of sensory block among patients who received dexamethasone in the epidural solution and those who did not. As shown in Figure 8, the overall pooled mean difference between the two groups showed a statistical difference in the result (MD=1.81min; 95%CI=0.77, 2.85; p-value=0.0006). The level of heterogeneity using I^2 was 0% (low).

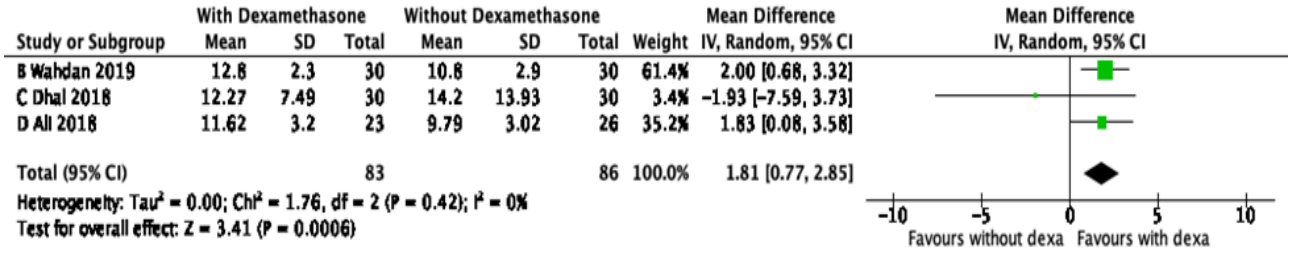


Figure 8: *Effect on the onset of sensory block*

Figures 9-12 show the risk of adverse events for both groups. The relative risk for the incidence of the observed complications and the random effects method were used to estimate the 95% confidence interval. A meta-analysis of clinical events such as nausea and vomiting (RR=1.15; 95%CI=0.68, 1.94; p-value=0.61; I^2=0%), shivering (RR=0.83; 95%CI=0.38, 1.81; p-value=0.65; I^2=19%), hypotension (RR=1.22; 95%CI=0.53, 2.85; p-value=0.64; I^2=0%) and fever (RR=1.16; 95%CI=0.02, 1.04; p-value=0.06; I^2=14%) showed no significant differences between the group who received dexamethasone and those who did not in their epidural solution. The studies demonstrated low heterogeneity.

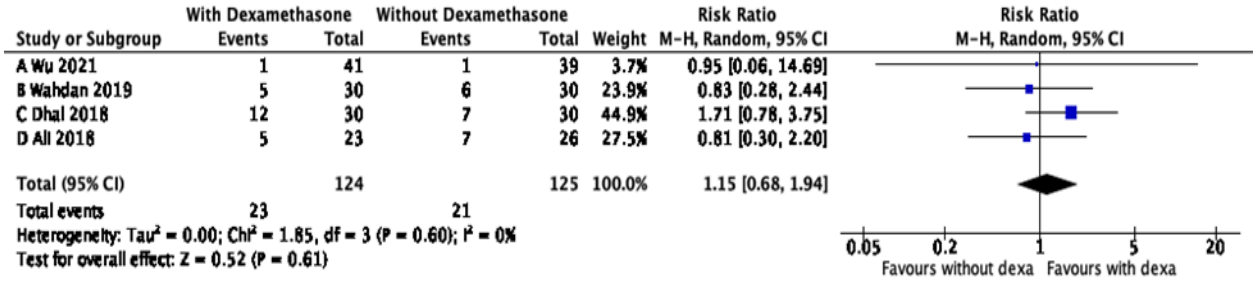


Figure 9: *Effect on the incidence of nausea and vomiting*

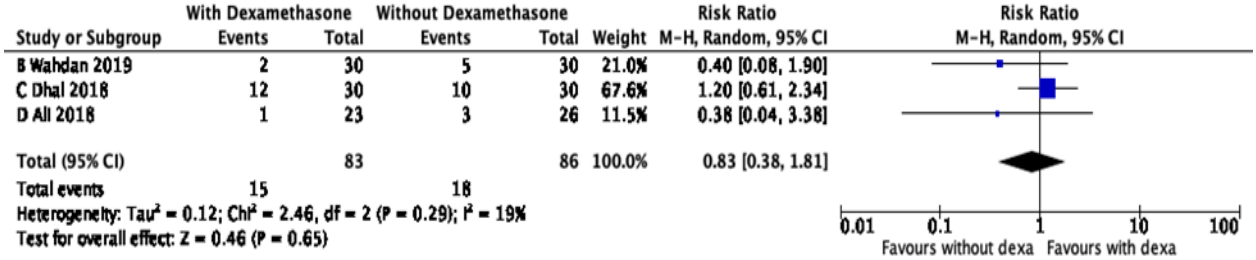


Figure 10: *Effect on the incidence of shivering*

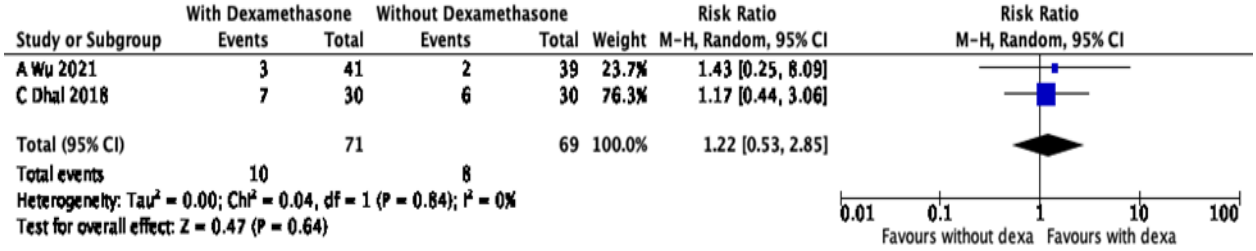


Figure 11: *Effect on the incidence of hypotension*

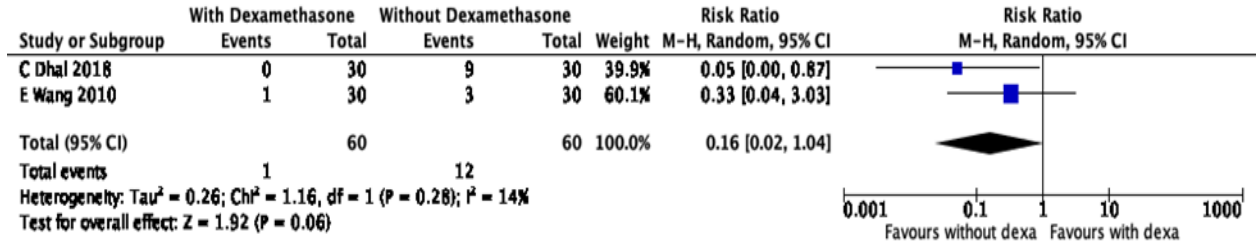


Figure 12: *Effect on the incidence of intrapartum fever*

Three studies reported the APGAR in 1 minute while four studies reported the APGAR in 5 minutes as their outcome. Relative risk for the incidence of APGAR score ≥7 in 1 and 5 minutes and random effects method were used to estimate the pooled effect with 95% confidence interval. Pooled risk ratio presented in Figures 13-14 showed no significant differences between the two groups in terms of APGAR score ≥7 in 1 and 5 minutes.

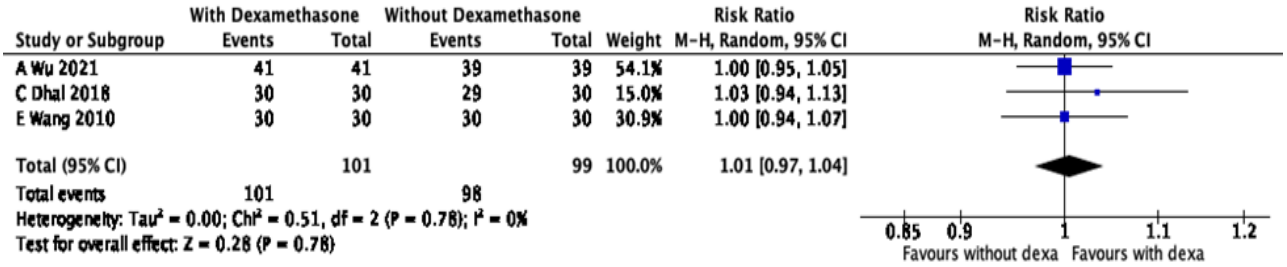


Figure 13: *APGAR score ≥7 in 1 minute*

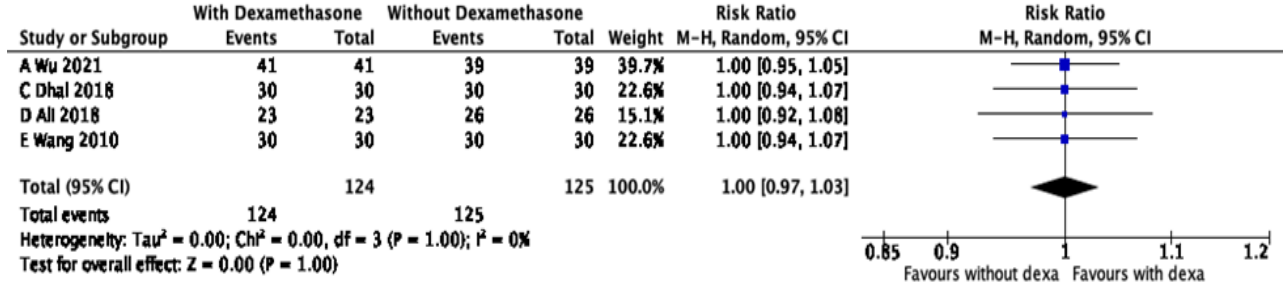


Figure 14: *APGAR score ≥7 in 5 minutes*

Only two studies reported the effect on the neonatal umbilical pH between the group with dexamethasone and the group without. The overall effect estimate was calculated as the mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects method. The pooled mean difference between the two groups was comparable as shown in Figure 15 (MD=-0.00; 95%CI=-0.04, 0.04; p-value=0.94). However, it showed moderate heterogeneity (I^2=68%). Ali's trial showed some concern on the overall risk of bias. The two studies also used different doses of dexamethasone, 4mg (Wahdan et al) and 8mg (Ali et al). Since this outcome only included two studies, sensitivity analysis omitting one study at a time to eliminate heterogeneity cannot be done.

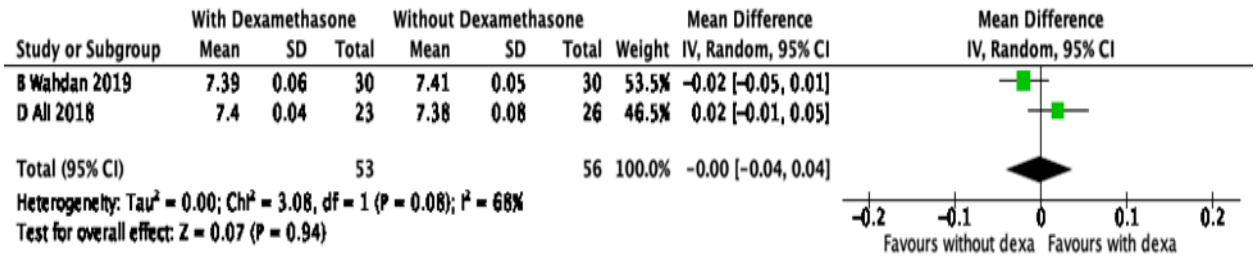


Figure 15: *Effect on the neonatal umbilical pH*

Funnel plot to address any publication bias was not done as there were <10 studies for each outcome.

DISCUSSION

In this study, we evaluated the effect of epidural dexamethasone on the maternal and newborn parameters during labor analgesia. Meta-analysis showed that parturients who were given epidural dexamethasone as an adjuvant for labor analgesia can have prolonged duration of analgesia by an average of 18.30 minutes (MD=18.30min; 95%CI=13.55, 23.05; p-value<0.00001; I^2 =0%). A longer duration of epidural analgesia limits additional administration of LA, limiting the possible dose related LA side effects. This reinforces the finding by Naghipour et al[21] on a randomized controlled trial that the duration of analgesia [with dexa (N=35) 372±58.1min vs without dexa (N=35) 234.6±24.3min; p-value=0.001] was significantly longer if dexamethasone was added to the epidural solution on patients undergoing abdominal or thoracic surgery.

In an RCT of dexamethasone via intrathecal route on parturients receiving combined spina-epidural analgesia, epidural consumption of LA [with dexa (N=40) 102.9±34.8mg vs without dexa (N=40) 120.1±41.9mg; p-value=0.049] was significantly lower in the group with intrathecal dexamethasone compared to the control group[22]. On the other hand, an RCT on dexamethasone via intravenous route demonstrated that the average hourly epidural drug consumption [with dexa (N=40) 10.34±1.79ml/h vs. without dexa (N=40) 11.34±1.83ml/h; p-value=0.015] was significantly lower in the dexamethasone group compared to the placebo group on patients undergoing labor analgesia[6]. In this meta-analysis, the pooled data on the effect on the total LA consumed through the course of labor initially showed that there was no difference between the group with epidural dexamethasone and the group without (MD=-24.39; 95%CI=-48.78, 0.00; p-value=0.05;

I^2=87%). When sensitivity analysis was conducted, significant heterogeneity was eliminated after excluding the study by Wang et al. This may be attributable to the use of a different LA. The resultant finding then revealed a statistical difference in the result (MD=-36.22mg; 95%CI=-50.05, -22.38; p-value=<0.00001; I^2=0%). The presence of heterogeneity involving this outcome reduced the robustness of the result and caution in dealing with the result is warranted.

A meta-analysis by Jebaraj et al[8] showed that epidural dexamethasone after abdominal surgery significantly decreased postoperative morphine consumption (MD=−7.89mg; 95%CI=−11.66, −3.71; p-value=0.0001) and number of patients requiring postoperative rescue analgesic boluses (RR=0.51; 95%CI=0.41, 0.63; p-value=0.00001). However, our present study on the analysis on pain assessment before (MD=0.19; 95%CI=-0.16, 0.54; p-value=0.28; I^2=37%) and after (MD=0.00; 95%CI=-0.18, 0.19; p-value=0.97; I^2=0%) labor analgesia showed no significant difference whether dexamethasone was administered in the epidural solution.

Pooled result on the effect on the onset of sensory block demonstrated that there is a statistical significance in the result of the two groups (MD=1.81min; 95%CI=0.77, 2.85; p-value=0.0006; I^2=0%). The group with epidural dexamethasone had a slightly longer onset by 1.81min. However, a difference of 1.81min is too short to have a significance in clinical practice on patients undergoing labor analgesia. Contradicting result was seen in a comparative study between intravenous and local dexamethasone as adjuvant to bupivacaine in perianal block demonstrating a rapid onset of blockade with administration of dexamethasone through either route compared to the group without dexamethasone at all [local dexa (N=18) 3.8$\pm$0.7min vs IV dexa (N=19) 3.8$\pm$0.9min vs without dexa (N=19) 5.5 +1.2min; p-value=<0.01][23].

In this study, pooled results study on the maternal adverse events such as nausea and vomiting (RR=1.15; 95%CI=0.68, 1.94; p-value=0.61; I^2=0%), shivering (RR=0.83; 95%CI=0.38, 1.81; p-value=0.65; I^2=19%), hypotension (RR=1.22; 95%CI=0.53, 2.85; p-value=0.64; I^2=0%) and fever (RR=1.16; 95%CI=0.02, 1.04; p-value=0.06; I^2=14%) demonstrated that the group with epidural dexamethasone was not statistically significant to the group with only plain epidural solution. Adverse effects with a single dose of dexamethasone are probably extremely rare and minor in nature, and previous studies have demonstrated that short term (<24 hours) use of dexamethasone was safe[21]. Side effects could be related conventionally to the neuraxial anesthesia and labor itself and not to the added medication[2,24,25].Neuraxial anesthesia-induced sympathetic block can cause unopposed vagal stimulation of the gastrointestinal system leading to increased secretions, relaxation of the sphincters and constriction of the bowels.

This reason, together with the delayed gastric emptying of laboring women, may predispose patients to nausea and vomiting[2]. Patients at increased risk to this may be given prophylactic anti-emetics. Regional anesthesia also inhibits central thermoregulatory control, preventing vasoconstriction and shivering to the blocked segments. Shivering arises in the unblocked segments to try and maintain the body temperature[24]. To prevent this, active warming through warm infusions, warm air and coverings are essential. Sympathetic blockade induced by neuraxial anesthesia may also lead to peripheral vasodilation[2]. The hypotension associated with this can be avoided through prevention of extensive block and the administration of additional intravenous crystalloid and vasopressors. Trials have noted a gradual rise in core temperature over several hours in laboring women receiving epidural analgesia that was not observed in women receiving no analgesia, which is incompletely understood[26]. When maternal fever occurs, efforts should be made to lower the maternal temperature and identify and treat the presumed maternal infection. Use of labor analgesia prevents the activation of the neuroendocrine stress response, affecting both the mother's and the fetus' organ systems. With the application of safe anesthesia practice to limit the adverse events of neuraxial analgesia, complications may be preventable and are rare, outweighing the risks involved[25].

This review also noted bradycardia as another complication but due to the inconsistency on how this outcome was reported, meta-analysis could not be performed. Wu et al compared the two groups by incidence [no. (%)] {with dexa (N=41) [2 (4.88%)]; without dexa (N=39) [2(5.13%)]} while Ali et al expressed the data as mean measurement in beats per minute in a graph but without numerical values.

Three studies assessed the maternal satisfaction between the two groups. Wahdan et al presented the data as incidence [no. (%)] of satisfied patients {with dexa (N=30) [24 (80%)]; without dexa (N=30) [25(83.3%)]; p-value=0.2}. Dhal et al assessed this by a scale of 0-100 [with dexa (N=30) 95.43$\pm$12.04; without dexa (N=30) 93$\pm$10.80; p-value=0.166]. The third study by Ali et al assessed the maternal satisfaction in a scale of 0-3 but no data was shown. Due to non-uniformity of how these data were presented, meta-analysis could not be performed.

The neonatal APGAR score and umbilical pH are determining factors of mortality and general well-being of the newborn. In this regard, it is important to consider the type of medications administered to the parturient which also has a minimal effect to the fetus. The result of the analysis between the two groups indicated that epidural dexamethasone as an adjuvant had no significant effect on the neonatal APGAR score [(1 minute: RR=1.01; 95%CI=0.97,

1.04; p-value=0.78; I^2=0%), (5 minutes: RR=1.00; 95%CI=0.97, 1.03; p-value=0.64; I^2=0%)] and on the neonatal umbilical pH (MD=-0.00; 95%CI=-0.04, 0.04; p-value=0.94). However, only two studies were included on assessing the effect on the neonatal umbilical cord blood gases which showed moderate heterogeneity (I^2=68%). The following factors may have contributed to the heterogeneity of this outcome: 1) some concern on the overall risk of bias in Ali's trial and 2) use of different doses of dexamethasone, 4mg (Wahdan et al) and 8mg (Ali et al). Similar to the neonatal outcome of this meta-analysis, a study that tested dexamethasone through the intrathecal route found that there was no significant difference between the group with dexamethasone in the intrathecal solution and the control group concerning the APGAR score {with dexa (N=40) [8(6-9)]; without dexa (N=40) [8(6-9)]; p-value=0.377} and the umbilical blood pH {with dexa (N=40) [7.39(±0.08)]; without dexa (N=40) [7.41(±5.0.05)]; p-value=0.232} [27].

Conclusion and Recommendation

The results of this meta-analysis showed that the use of dexamethasone as an adjuvant to epidural solution during labor analgesia appears to be effective in prolonging the duration of epidural analgesia, limiting the total LA consumed, with limited maternal and neonatal adverse events. However, due to the presence of heterogeneity, these results should be interpreted with caution and additional studies are needed before adopting this technique in routine clinical practice.

This meta-analysis was not free from limitations. There were only 5 studies included in this analysis and the number of included trials on each outcome were limited. Hence, a single study has a large influence in the ultimate outcome, which may lead to biases. Heterogeneity was found in some of the outcomes. Heterogeneity may be due to difference in the dose of epidural dexamethasone, type of LA used and concerns on the risk of bias. Some of the outcomes have inconsistencies on how the data were presented, affecting the number of included trials on each outcome.

Because of the limitations mentioned on this study, application of these findings in the management of parturients in labor should be treated with caution. Future studies with rigorous design and larger sample size are needed to further identify the role of epidural dexamethasone as an adjuvant to labor analgesia. Better literature search through inclusion of quality studies and adherence on the methods used and uniformity on the reported outcome are critical to minimize bias and achieve findings that can be safely applied in clinical practice.

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ARTICLE

Caregiver satisfaction with the use of telemedicine in the neurodevelopmental evaluation of children at the Philippine Children's Medical Center

Aurora Aurea M. Reyes, Anna Dominique M. Aniag, Kathryn B. Braganza

OBJECTIVES*:* This study aims to assess caregiver satisfaction with the use of telemedicine in the evaluation of children referred for neurodevelopmental evaluation at the Philippine Children's Medical Center (PCMC) Neurodevelopmental Pediatrics Clinic.

MATERIALS AND METHODS: : A survey was conducted on caregivers of pediatric patients aged 3 months to 18 years and 11 months old for neurodevelopmental evaluation. A questionnaire to determine the demographic and clinical data and Parent/Caregiver-Reported Satisfaction Form were administered via email, Facebook messenger or phone call.

RESULTS: Seventy-three caregivers completed the questionnaire. Most (95.9%) were mothers, 47.9% were college graduates with one parent working and 43% have an income of 10,000-20,000. Almost half (47.9%) of the children they care for were ages 3-months to 2-year 11 -months, predominantly males, with 35.6% diagnosed with autism spectrum disorder, and 69.9% were new patients. Caregivers were very highly satisfied with telemedicine in all domains (technical functioning, comfort and perceived privacy, access to care and overall satisfaction) as it obtained a mean of 4.51 and median of 5.00. There was no significant difference in the responses based on the age of the child and type of visit.

CONCLUSION: Caregivers showed very high level of satisfaction with the use of telemedicine in the neurodevelopmental evaluation of children at PCMC and holds a significant promise for its use both within the context of the pandemic and beyond.

RECOMMENDATIONS: Further studies on caregivers' satisfaction with the use of telemedicine over a sustained period and comparing telemedicine and in-person assessment are recommended.

KEYWORDS: *Neurodevelopmental Pediatrics, Telemedicine, Satisfaction, Neurodevelopmental Evaluation*

INTRODUCTION

The coronavirus disease (COVID-19) in the Philippines is part of the worldwide pandemic caused by severe acute respiratory syndrome 2 (SARS-CoV-2).[1] To prevent exponential increase in the cases as well as the local transmission of the virus, on March 16, 2020, the government imposed an enhanced community quarantine (ECQ) in Luzon restricting the movement of population except for necessity, work, and health circumstances. Temporary closure of out-patient services of hospitals including the Philippine Children's Medical Center (PCMC) out-patient clinic, was done to prevent further spread of the diseases as well as to reallocate staffing resources to other critical care. The Department of Health (DOH) and the National Privacy Commission (NPC) developed a framework for using telemedicine services for doing medical consultations over the phone, chat, short messaging service (SMS), and other audio and visual-conferencing platforms to improve access to health services in the country. Telemedicine is defined as "the delivery of health care services, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers."[1] PCMC launched their telemedicine service for General OPD last June 22, 2020, and Neurodevelopmental Pediatrics soon followed. Neurodevelopmental Pediatrics involves assessing, evaluating, diagnosing, managing and monitoring children with developmental and behavioral concerns, as well as those with school problems and parent-child challenges. As there is an increase in the number of patients being seen thru telemedicine in our clinic, a better understanding of how satisfied the caregivers feel with its use, becomes increasingly important. Caregiver satisfaction data will provide preliminary evidence for the effectiveness of the use of telemedicine, enabling the section to ascertain whether their expectations are being met as well as exposing areas that require improvements towards set standards since this is an understudied area.

Telemedicine has been used in different areas of healthcare management for several years, and several studies have highlighted its advantages including: (1) reduced waiting time; (2) immediate feedback about diagnosis and course of action; (3) increased access to specialists; and (4) increased access to multiple medical services. . [5] Most parents expressed a high level of satisfaction and identified decreased stress to them and to their child as well as having a high likelihood of a successful medical examination due to greater cooperation by the child as benefits.[8]

Most studies showed high level of satisfaction with the use of telemedicine on both the provider and the patient's end. However, a study done by Masi et al. viewed otherwise. In this study, it pointed out that some telemedicine services were either unavailable, not feasible or ineffective for some children with neurodevelopmental disabilities.[24] Probable reasons identified include technological problems, the quality of the patient-provider relationship, the quality of the examination and care, safety, privacy, and accountability.[24] There are a number of limitations that should be taken into account in interpreting the findings of some studies mentioned. Some parents may have been unable to complete the questionnaire due to overwhelming care and work responsibilities and there is a risk of selection bias which would have an impact on the survey results. Of the few studies that have been reported on caregiver's satisfaction with telemedicine aimed at pediatric patients, none has reported in the neurodevelopmental evaluation of children with developmental disabilities in our country since it's not yet widely used in the practice prior to the pandemic.

In this study, we aimed to describe the demographic and clinical profile of caregivers and children for neurodevelopmental evaluation who utilized telemedicine, determine caregivers' satisfaction with telemedicine for neurodevelopmental evaluation in terms of the following domains: technical functioning, comfort (ease of use) and perceived privacy, access to care and overall satisfaction, and compare their responses based on the age of the child and the type of visit. We hypothesize that caregivers are generally satisfied with the use of telemedicine at our OPD.

Materials and Methodology

This is a survey conducted in PCMC from May 2022 to August 2022. The study was divided in 4 phases: development of questionnaire, translation and cross-cultural validation, validation and testing, and survey proper. Dr. Kathleen M. Myers, the principal author of the Parent-Reported Satisfaction with Telepsychiatry was contacted and consent for use in the study and translation of the form to Filipino by a linguist was requested and granted. This questionnaire was adapted for this study. The items in the form reflect 4 domains of satisfaction reported to be highly correlated with global satisfaction for pediatric telemedicine patients and these include 1) Technical functioning (items 2, 3, 5, 10); 2) Comfort of patient with the technology and perceived privacy items (items 1, 4, 6); 3) Timely, geographic access to care (items 7, 8, 9) and 4) Overall satisfaction with the telemedicine visit (Items 11 and 17.) Some items (items 12,13,14,15,16) specific for neurodevelopmental evaluation were added in the Parent/Caregiver-Reported Satisfaction Form.

The developed Parent/Caregiver-Reported Satisfaction Form was translated to Filipino by a linguist specialist. Seventeen satisfaction items were rated on a five-point Likert scale [e.g., Very Low (1) – Very High (5)] and each item is rated on how strongly he or she disagrees with the statement, with 1 representing very low satisfaction and 5 representing very high satisfaction. Another questionnaire was developed to assess the demographic and socioeconomic data and clinical characteristics of patients and their caregivers.

The developed Parent/Caregiver-Reported Satisfaction Form was tested for content validity. Four Neurodevelopmental Pediatricians reviewed the developed questionnaire for its validity. This was analyzed thru the item-level content validity index (I-CVI) which is the proportion of the experts who agreed that the item was relevant. All items showed higher than I-CVI 0.80 meaning all items were relevant thus were all included. A face validity testing was then done where each of the item was reviewed by a set of 13 caregivers of patients at the PCMC OPD. At 95% confidence level and 80% power of test, a minimum of 13 respondents was computed based on Bonett formula to have a valid Cronbach's alpha results. The Cronbach's Alpha computed at 0.7 implied that the reliability/internal consistency of the questionnaire was at an acceptable level. Also, removing any item does not increase the reliability to 0.8 or 0.9, hence all items were retained. The validated questionnaire was administered to another set of 13 caregivers from the PCMC OPD and a retest was done after 7 days to establish the test-retest reliability. Reliability was measured by internal consistency which measures how well each item correlates with other items in the scale. Internal consistency or the relatedness of items within a factor was assessed also using Cronbach's alpha where a value of >0.70 was considered an acceptable internal consistency and reliability. The resulting correlation coefficient obtained was 0.777 which falls on an acceptable level.

All patients 3 months to 18 years and 11 months referred to Neurodevelopmental Pediatrics and those previously seen and scheduled for follow-up were identified. Participants who have not been the child's primary caregiver for at least 6 months were excluded in the study. Target minimum sample of 41 participants was required based on the study of Morgan (2014)[12] where the estimated satisfaction level is around 88%. Additionally, 5% level of significance and 10% desired half-width of the confidence interval. Respondents who met the inclusion criteria were informed about the study. They were then asked if they were willing to participate in this study, and once they agreed the patient's caregiver was then asked to sign a consent form to signify their intention of joining the study. The informed consent was given through several methods, depending on the availability and means of the participants.

The participants were asked to write their consent, affix their signature, and send to an e-mail address that was specifically made for this study as a pdf file or a picture. For caregivers with limited technological capability, informed consent was obtained via a recorded phone call. Once the informed consent was signed and sent, the demographic and socio-economic questionnaire was sent either via e-mail or Facebook messenger or obtained through an interview. After the evaluation, the caregiver was asked to answer the Parent/Caregiver - Reported Satisfaction with Telemedicine Form through interview or via Facebook messenger and e-mail or phone call.

Descriptive statistics such as frequency and percentage were used to present categorical data, while mean and median was utilized for presenting the Likert scale items. In comparing the satisfaction according to the patient's profile, F test through One Way ANOVA was used. Level of significance is at 5%, and Medcalc Statistical software was used to carry out statistical calculations.

RESULTS

A total of 73 caregivers who have participated in telemedicine consults were included in the study. The children that they take care of were from 3 months to 2 years and 11 months (47.9%) while 30.1% were from 3 years to 5 years and 11 months. There were slightly more males (64.4%) and around 70% of them were new patients. Moreover, most of the caregivers were mothers (95.9%), being the primary caregiver themselves. Based on marital status, 60.3% of them were married while 31.5% were common-law. On educational attainment, almost half of them (47.9%) were able to finish their college education, while 26% were able to finish high school. Around 53% of the respondents were unemployed, while 37% were employed. Based on monthly income, most of the respondents earn around 10,000 to 20,000 (43.8%) while 21.9% of them earn less than 10,000. Furthermore, 63% of the patients only have one parent working, while 34.2% have both parents working.

Table 1. *Demographic and Clinical Profile of Caregivers and Children for Neurodevelopmental Evaluation Who Utilize Telemedicine*

Clinical Profile	Values Frequency (%); Mean ± SD
Age (years)	
3 month to 2 years and 11 months	35 (47.9)
3 to 5 years and 11 months	22 (30.1)
6 to 9 years and 11 months	11 (15.1)
10 years old and above	5 (6.8)
Gender, n, %	
Male	47 (64.4)
Female	26 (35.6)

Classification, n, %	51 (69.9)
New	22 (30.1)
Follow up	
Diagnosis	
Autism Spectrum Disorder	26 (35.6)
Global Developmental Delay	19 (26.0)
Infant at Risk for Development Delay	15 (20.5)
Others	13 (17.8)
Relationship to Child	
Father	1 (1.4)
Maternal Aunt	1 (1.4)
Mother	70 (95.9)
Others: Grandmother	1 (1.4)
Primary caregiver	
Father	3 (4.1)
Helper	1 (1.4)
Myself	46 (63.0)
Myself and Partner	6 (8.2)
Others	17 (23.3)
Marital Status	
Common-law	23 (31.5)
Married	44 (60.3)
Others: Boyfriend	1 (1.4)
Separated	5 (6.8)
Educational Attainment	
College Graduate	35 (47.9)
College Undergraduate	11 (15.1)
High School Graduate	19 (26.0)
Vocational Graduate	6 (8.2)
Vocational Undergraduate	2 (2.7)
Employment status	
Employed	27 (37.0)
Self employed	7 (9.6)
Unemployed	39 (53.4)
Monthly income	
< 10,000	16 (21.9)
10,000 - 20,000	32 (43.8)
20,000 - 30,000	12 (16.4)
30,000 - 40, 000	8 (10.9)
40,000 - 50,000	2 (2.7)
50,000 - 60,000	1 (1.4)
Number of parents working	
One	46 (63.0)
Both	25 (34.2)
None	2 (2.7)

Table 2 reveals that the caregivers were very highly satisfied overall with their telemedicine visit as it obtained a mean of 4.51 and median of 5.00. All of the items show mean overall scores above 4.0 on a 5-point Likert across all domains. Similarly, they are also very highly satisfied with their telemedicine visit in terms of its technical functioning as it obtained a median of 5.0 and mean of 4.62. Furthermore, with resulting median of 5.0 and mean of 4.75, parents/caregivers are also very highly satisfied in terms of the comfort of patient and provider with technology, and perceived privacy. On timely, geographic access to care, it also resulted to a median of 5.0 and mean of 4.79 also implying very high level of satisfaction. Among all the items, the highest obtained mean is 4.89 which is being able to understand the specialist's recommendation and sufficiency information about their child's diagnosis given by the clinician. On the other hand, the item having the lowest obtained mean of 4.42 is about telemedicine visit being as good as the regular in-person visit. However, this item remained to have very high satisfaction rating.

Table 2. *Caregivers' Satisfaction With Telemedicine For Neurodevelopmental Evaluation*

	Median	Mean	Interpretation
Technical Functioning	5.00	4.62	Very High
Nakikita ko nang mabuti ang espesyalista	5.00	4.68	Very High
Naririnig ko nang mabuti ang espesyalista	5.00	4.49	Very High
Naiintindihan ko ang rekomendasyon ng espesyalista	5.00	4.89	Very High
Kasing buti ng karaniwang personal na pagbisita ang pagbisita sa telemedicine	5.00	4.42	Very High
Comfort of Patient and Provider with Technology and perceived privacy	5.00	4.75	Very High
Komportable akong nakapagtatanong sa espesyalista	5.00	4.81	Very High
Tiwala akong hindi naririnig ng ibang nasa kuwarto ang impormasyon ukol sa aking anak	5.00	4.67	Very High
Naramdaman kong komportable ang espesyalista na makita ang aking anak sa harapan ng screen	5.00	4.78	Very High
Timely, Geographic access to care	5.00	4.79	Very High
Dahil sa Telemedicine, nagawang makipagkita kaagad sa isang espesyalista ang aking anak	5.00	4.84	Very High
Kung wala ang telemedicine, hindi makatatanggap ng serbisyo ng isang espesyalista ang aking anak	5.00	4.74	Very High
Makatatanggap ng tulong na kinakailangan ang aking anak dahil sa aming pagbisita sa tele-medicine sa isang espesyalista	5.00	4.79	Very High
Overall Satisfaction with Telemedicine Visit	5.00	4.77	Very High
Sa hinaharap, payag akong makita muli ng isang espesyalista ang aking anak gamit ang telemedicine	5.00	4.51	Very High
Nagawang maipaliwanag ng espesyalista kung paano isasagawa ang pagsusuring neurode-velopmental	5.00	4.79	Very High
Isinagawa sa isang maayos na pamamaraan ang pagsusuring neurodevelopmental	5.00	4.68	Very High
Malinaw na ipinaliwanag sa iyo ang resulta ng pagsusuring neurodevelopmental	5.00	4.88	Very High
Nagbigay ng sapat na impormasyon ang espesyalista ukol sa pagsusuri sa iyong anak	5.00	4.89	Very High
Tinalakay ang medikal na pagsusuri at iba't ibang paraan ng panggagamot	5.00	4.81	Very High
Sa pangkalahatan, nasiyahan ako sa kalidad ng mga serbisyong ibinigay ng telemedicine	5.00	4.85	Very High

Table 3 shows that there is no significant difference on the level of satisfaction in terms of technical functioning, comfort and perceived privacy, access to care and overall satisfaction with telemedicine visit when grouped according to age of child, gender of child and classification of patient. A comparison of the responses of the caregivers based on the age of the child and the type of visit also showed no significant difference.

Table 3. *Comparison of Satisfaction According to Age of the Child and Type of Visit*

Table 3.1 TECHNICAL FUNCTIONING

	Median	Mean	p value
Age (years)			
3 months to 2 years and 11 months	4.5	4.54	0.3448[ns]
3 to 5 years and 11 months	4.75	4.74	
6 to 9 years and 11 months	5	4.73	
10 years old and above	4.75	4.5	
Gender, n, %			
Male	4.75	4.54	0.2394 [ns]
Female	4.75	4.67	
Classification, n, %			
New	4.75	4.63	0.8502 [ns]
Follow up	4.75	4.61	
Diagnosis			
Autism Spectrum Disorder	4.69	0.36	0.710[ns]
Global Developmental Delay	4.63	0.44	
Infant at Risk for Development Delay	4.53	0.44	
Others	4.58	0.56	
Primary caregiver			
Father	4.75	4.5	0.4018 [ns]
Helper	3.5	3.5	
Myself	4.75	4.66	
Myself and Partner	4.88	4.67	
Others	4.75	4.59	
Marital Status			
Common-law	4.75	4.61	0.4219 [ns]
Married	4.75	4.63	
Others: Boyfriend	4	4	
Separated	5	4.8	
Educational Attainment			
College Graduate	4.75	4.64	0.2968 [ns]
College Undergraduate	4.75	4.77	
High School Graduate	4.75	4.62	
Vocational Graduate	4.63	4.54	
Vocational Undergraduate	3.88	3.88	

Employment status			
Employed	4.75	4.58	
Self employed	5.0	4.96	0.0422*
Unemployed	4.5	4.59	
Monthly income			
<10,000	5	4.75	0.712 ns
10,000 - 20,000	4.63	4.54	
20,000 - 30,000	4.88	4.56	
30,000 - 40,000	4.88	4.69	
40,000 - 50,000	4.88	4.88	
50,000 - 60,000	4.75	4.75	
Don't know	4.75	4.75	
Number of parents working			
One	4.75	4.63	
Both	5.00	4.63	0.2604ns
None	4.25	4.25	

***Significant, ns not significant**

Table 3.2 COMFORT AND PERCEIVED PRIVACY

	Median	Mean	p value
Age (years)			
3 months to 2 years and 11 months	5.00	4.68	
3 to 5 years and 11 months	5.00	4.85	0.6509 ns
6 to 9 years and 11 months	5.00	4.88	
10 years old and above	5.00	4.6	
Gender, n, %			
Male	5.00	4.65	0.6489 ns
Female	5.00	4.81	
Classification, n, %			
New	5.00	4.75	0.4533 ns
Follow up	5.00	4.76	
Diagnosis			
Autism Spectrum Disorder	4.79	0.31	
Global developmental delay	4.76	0.42	0.545ns
Infant at Risk for Development delay	4.60	0.70	
Others	4.82	0.45	
Primary caregiver			
Father	5.00	4.89	
Helper	5.00	5.00	
Myself	5.00	4.72	0.9771 ns
Myself and Partner	5.00	4.83	
Others	5.00	4.76	

Marital Status			
Common-law	5.00	4.71	
Married	5.00	4.79	0.0694 ns
Others: Boyfriend	3.00	3.00	
Separated	5.00	5.00	
Educational Attainment			
College Graduate	5.00	4.77	
College Undergraduate	5.00	4.79	
High School Graduate	5.00	4.74	0.8195 ns
Vocational Graduate	5.00	4.78	
Vocational Undergraduate	4.33	4.33	
Employment status			
Employed	5.00	4.74	
Self employed	5.00	5.00	0.1767 ns
Unemployed	5.00	4.72	
Monthly income			
<10,000	5.00	4.71	
10,000 - 20,000	5.00	4.75	
20,000 - 30,000	5.00	4.72	
30,000 - 40, 000	5.00	4.83	0.9720 ns
40,000 - 50,000	5.00	5.00	
50,000 - 60,000	5.00	5.00	
Don't know	4.67	4.67	
Number of parents working			
One	5.00	4.73	
Both	5.00	5.00	0.6310 ns
None	5.00	4.75	

***Significant, ns not significant**

Table 3.3 ACCESS TO CARE

	Median	Mean	p value
Age (years)			
3 months to 2 years and 11 months	5.00	4.81	
3 to 5 years and 11 months	5.00	4.82	0.1598 ns
6 to 9 years and 11 months	5.00	4.91	
10 years old and above	4.00	4.27	
Gender, n, %			
Male	5.00	4.79	0.9274 ns
Female	5.00	4.79	
Classification, n, %			
New	5.00	4.78	0.3568 ns
Follow up	5.00	4.82	

Diagnosis			
Autism Spectrum Disorder	4.81	0.37	0.369[ns]
Global developmental delay	4.69	0.42	
Infant at Risk for Development delay	4.91	0.20	
Others	4.76	0.43	
Primary caregiver			
Father	5.00	4.89	0.9707 [ns]
Helper	5.00	5.00	
Myself	5.00	4.78	
Myself and Partner	5.00	4.83	
Others	5.00	4.78	
Marital Status			
Common-law	5.00	4.88	0.2699 [ns]
Married	5.00	4.73	
Others: Boyfriend	4.33	4.33	
Separated	5.00	4.93	
Educational Attainment			
College Graduate	5.00	4.80	0.6347 [ns]
College Undergraduate	5.00	4.73	
High School Graduate	5.00	4.84	
Vocational Graduate	5.00	4.83	
Vocational Undergraduate	4.83	4.33	
Employment status			
Employed	5.00	4.80	0.1421 [ns]
Self employed	5.00	5.00	
Unemployed	5.00	4.74	
Monthly income			
< 10,000	5.00	4.81	0.8520 [ns]
10,000 - 20,000	5.00	4.82	
20,000 - 30,000	5.00	4.69	
30,000 - 40,000	4.83	4.71	
40,000 - 50,000	5.00	5.00	
50,000 - 60,000	5.00	5.00	
Don't know	4.67	4.67	
Number of parents working			
One	5.00	4.78	0.9178[ns]
Both	5.00	4.80	
None	4.83	4.83	

***Significant, ns not significant**

Table 3.4 OVERALL SATISFACTION

	Median	Mean	p value
Age (years)			
3 months to 2 years and 11 months	5	4.75	0.6665[ns]
3 to 5 years and 11 months	5	4.81	
6 to 9 years and 11 months	5	4.88	
10 years old and above	4.86	4.54	
Gender, n, %			
Male	5	4.69	0.8200 [ns]
Female	5	4.82	
Classification, n, %			
New	5	4.78	0.9212 [ns]
Follow up	5	4.75	
Primary caregiver			
Father	5.00	4.95	0.6329 [ns]
Helper	4.43	4.43	
Myself	5.00	4.73	
Myself and Partner	4.86	4.88	
Others	5.00	4.83	
Marital Status			
Common-law	5.00	4.79	0.3162 [ns]
Married	5.00	4.79	
Others: Boyfriend	3.00	3.00	
Separated	4.86	4.89	
Educational Attainment			
College Graduate	4.86	4.71	0.4519 [ns]
College Undergraduate	4.71	4.79	
High School Graduate	5.00	4.83	
Vocational Graduate	5.00	4.95	
Vocational Undergraduate	4.79	4.79	
Employment status			
Employed	4.86	4.75	0.0597 [ns]
Self employed	5.00	5.00	
Unemployed	5.00	4.75	
Monthly income			
<10,000	5.00	4.78	0.5320 [ns]
10,000 - 20,000	5.00	4.77	
20,000 - 30,000	5.00	4.82	
30,000 - 40, 000	4.86	4.80	
40,000 - 50,000	4.86	4.86	
50,000 - 60,000	5.00	5.00	
Don't know	4.14	4.14	
Number of parents working			
One	5.00	4.78	0.6329 [ns]
Both	5.00	4.75	
None	4.93	4.93	

***Significant, ns not significant**

DISCUSSION

Measurement of satisfaction has become an important indicator of the performance and outcome of medical services. The primary purpose of measuring the experience and satisfaction with telemedicine is to inform quality improvement efforts at our clinic especially now that there is an increase in its use. It can also reveal important problems like gaps in provider-patient communications that can have broad implications for clinical quality. Implementing a process of quality improvement can increase the likelihood that telemedicine programs will contribute to patient-centered care and be sustained.[15] While it has previously been reported that there are high levels of patient satisfaction with the use of telemedicine in adult patients, there is limited research exploring caregiver satisfaction among pediatric cohorts, in particular children with complex care needs such as those with neurodevelopmental disabilities since it is not commonly practiced in our healthcare setting until the start of the pandemic.[13] Research shows that patients who have positive experiences are more likely to adhere to medical advice and treatment plans, and experience better health outcomes increasing engagement in and adherence to care.[14] This paper provided a systemic assessment of caregivers satisfaction with the use of telemedicine in the neurodevelopmental evaluation of children at PCMC.

In this study, the demographic and clinical profile of caregivers and children who underwent neurodevelopmental evaluation thru telemedicine were obtained and questionnaires were accomplished by the caregivers. The age range of most of the children that caregivers attend to were from 3 months to 2 years and 11 months, consisting of 47.9% of the participants, with a slightly male predominance (64.4%.) Most of the caregivers were mothers (95.9%) who were also the primary caregiver. Most of them were married (60.3%) and college graduates. Fifty-three percent (53%) of the respondents were unemployed. For those who are employed, the average income they receive is from 10,000 – 20,000 per month with only one parent working. As expected, the most common diagnosis was autism spectrum disorder followed by Global Developmental Delay.

The results of this study showed that caregivers are generally satisfied with the services provided by telemedicine in the neurodevelopmental evaluation of children at our institution. This study identified four domains of satisfaction reported to be highly correlated with global satisfaction for pediatric telemedicine and these are technical functioning, comfort of patient and provider with technology, perceived privacy, timely, geographic access to care, and overall satisfaction. All the respondents had a high level of satisfaction for all the domains mentioned.

Perhaps these results suggest that caregivers are becoming comfortable with the use telemedicine. In terms of the caregiver's responses with the use telemedicine based on the age of the child and the type of visit, there is no significant difference on the level of satisfaction in terms of all domains. This result may not be too surprising, as one of the main reasons for increased use of telemedicine services is driven by necessity since it presented an avenue for the patients to have continuity of care during this unprecedented time. It is bridging the gap between patients, providers, and healthcare systems during this pandemic, enabling communication through virtual channels while staying at home.[16]

Findings also have important implications for the feasibility and acceptability of telemedicine, in addition to key factors to consider in optimizing and sustaining telemedicine neurodevelopmental evaluations beyond the COVID-19. In a study done by Vargas et.al on the feasibility and acceptability of telemedicine among caregivers at the PCMC Neurodevelopmental Pediatrics clinic, it has indicated that the participants showed willingness to use telemedicine in their children's evaluation, follow-up and for other medical and allied services. Reasons include reduced cost and time for travel and preparations for the appointment and to limit exposure to infections.[17] As telemedicine symbolizes the feasibility and practicality of an alternative mode of healthcare in the Neurodevelopmental Pediatrics OPD, caregiver satisfaction needs to be taken into consideration, as this mode of healthcare will be practiced for a long time especially during the time of pandemic.[6] Telemedicine use and satisfaction are influenced by a number of factors including safety during the pandemic, privacy, convenience and accessibility and availability of more avenues of communication. Hilgart et al. (2012) found common factors of satisfaction with technology, education and information provided, communication and avoidance of patient travel.[19] In a study done by Orlando et al. (2019), patient satisfaction in healthcare has been shown to be closely associated to improved patient engagement and treatment compliance for multiple different chronic and acute healthcare conditions.[20] In a local study (Pasco 2016), the findings showed that there was high satisfaction rating by both the healthcare providers and the patients. [18] Some studies viewed that patients were generally satisfied with telemedicine services, with most reporting that this was an efficient and convenient alternative to face-to-face consultations. In a study done by Myers et. Al in 2007 on Child and Adolescent Telepsychiatry, they reported that parent's satisfaction was high across patients' age and increased with return appointments which is similar to the findings of our study. [21] In another large cross-sectional survey study with 1734 patients, 95% were very satisfied

with telehealth quality and found telemedicine to be comparable, if not better than in-office visits with healthcare providers.[22]

Other studies involved not only patient satisfaction but also that of the healthcare provider. These studies conducted during the pandemic examined provider satisfaction with neurodevelopmental telehealth evaluation in children and revealed that most providers are satisfied and comfortable with the process.[23] Similar to other studies reviewed, the reasons for their satisfaction include logistical convenience of the telemedicine assessment, ease of administration, rapport with and expertise of the clinicians, and qualification for intervention services. [23] However, the caregiver satisfaction with the telemedicine platform varies, and many of them still reported a preference for in-person visits compared to telemedicine consultation. Our study is only limited to determining the satisfaction of caregivers and not those of the provider. Nevertheless, our result is consistent with studies presented with the participants showing high level of satisfaction with the use of telemedicine services.

Most of the studies reviewed showed high level of satisfaction with the use of telehealth services on both the provider and the patient's end. However, there was one study conducted that viewed otherwise. In a study done by Masi et al. on the Impact of COVID-19 pandemic on the well-being of children with neurodevelopmental disabilities and their parents, it pointed out that some telemedicine services were either unavailable, not feasible or ineffective for some children with neurodevelopmental disabilities.[24] Some respondents from this study had low ratings of effectiveness, satisfaction, and practitioner confidence with telehealth services received. Probable reasons identified include technological problems, the quality of the patient-provider relationship, the quality of the examination, quality of care, safety, privacy, and accountability.[24] Technical difficulties related to devices, interfaces and internet connectivity have frustrated both providers and patient families as many families simply do not have reliable internet access.[4] There are several implications resulting from these findings. It is essential that there is ongoing service delivery for children and families, especially in the event of more future lockdowns. This includes providing families with technological support and training practitioners in the effective use of telemedicine services for children with neurodevelopmental disabilities. Given the impact of COVID-19 on child and caregiver well-being, targeted services supporting children with neurodevelopmental disabilities and their families are clearly needed.

Even if not directly assessed by our study, the direct experience during the pandemic seems to show that telemedicine produces positive effects for both children and their families.

On the patient's side, telemedicine consultation promoted and enabled continuity of care, maintained social contacts with the physician, and reduced the risk of being exposed to the coronavirus. This complements the widely held view that telemedicine can play an important role to avoid the inconvenience of travel and to avoid exposure to the virus.[2] Given caregivers' satisfaction with telemedicine, health services could feel confident that this form of service enables health care for patients who cannot leave their home because of the restrictions as well as those in rural and remote areas.[20] While telemedicine does not replace face-to-face appointments, it does offer an alternative mode that when integrated into an established service could form part of patient choice when clinically safe and appropriate. Aligning a health care service with caregiver' expectations and needs can lead to overall patient satisfaction.

In summary we showed that telemedicine has an overall positive impact on caregivers' satisfaction in the neurodevelopmental evaluation of children at the PCMC Neurodevelopmental Pediatrics OPD. Despite this being the first time that telemedicine was implemented, the results showed high levels of response to this new service. The result offers reassurance to healthcare professionals that appropriate and satisfactory care and support is being provided through virtual means. This form of consultation is a very adaptable measure for our future service provision.

Given that the current literature of caregiver satisfaction with telemedicine in our country is limited, additional research including comparing the use of telemedicine and in-person assessment can be done, as well as a follow up investigation of caregivers' satisfaction with telemedicine over the long term.

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ARTICLE

The efficacy of oral Micronized Progesterone versus Medroxyprogesterone Acetate in the control of mild to moderate abnormal uterine bleeding – ovulatory Dysfunction (AUB-O) in Adolescents: An Open Label Randomized Controlled Trial

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OBJECTIVES: To determine the efficacy of micronized oral progesterone (OMP) versus Medroxyprogesterone Acetate (MPA) in the control and regulation of mild to moderate abnormal uterine bleeding in adolescents with ovulatory dysfunction.

MATERIALS AND METHODS: This is an open labelled Randomized Controlled Trial. Fifty patients with mild to moderate abnormal uterine bleeding were randomized to treatment with Medroxyprogesterone Acetate or Oral Micronized Progesterone.

RESULTS: There was no significant difference in the control of bleeding for patients with moderate abnormal bleeding. There was no significant difference in the regularity of cycles and length of bleeding once the patients were started on cyclic dosing. There was a difference in amount of bleeding (1-3 pads versus 2-4 pads for MPA and OMP respectively), but both were within normal amount. The adverse effects experienced for patients taking OMP was significantly more compared to MPA.

CONCLUSION: Oral Micronized Progesterone is just as effective as Medroxyprogesterone Acetate in the control and regulation of mild to moderate abnormal uterine bleeding in adolescents with ovulatory dysfunction. However, it was associated with more adverse effects.

KEYWORDS: *Abnormal Uterine Bleeding, Combined Oral Contraceptive Pills, Oral Micronized Progesterone, Medroxyprogesterone Acetate*

INTRODUCTION

Abnormal uterine bleeding is one of the most common reasons for consultation in the adolescent gynecology clinic. Sixty percent of these adolescents will have bleeding caused by anovulatory cycles secondary to immature Hypothalamic-Pituitary-Ovarian axis, while the rest would be caused by bleeding disorders and other non-structural causes[1]. The current treatment regimen for these patients is to give a combined oral contraceptive regimen, or a progestogen, usually in the form of medroxyprogesterone acetate (MPA).

However, both regimens may have significant side effects[2]. In the recent years, a newer preparation of progesterone, oral micronized progesterone (OMP), has been introduced in the market. It is said to be closer to the natural form of progesterone, which is produced by the ovary, rather than the current synthetic progestogens being used. It is already a part of the options for management in the Clinical Practice Guidelines for Abnormal Uterine Bleeding from the Philippine Obstetrical and Gynecological Society, [3,] but these guidelines do not state if they can also be used for adolescents. In this age group there has been no actual study regarding its efficacy, although some treatment guidelines abroad have already included its use in AUB. Thus, we wanted to find a safer alternative for the adolescent age group.

Abnormal uterine bleeding (AUB) has a myriad of possible causes. It is defined as the "departure from a normal menstrual cycle pattern". The FIGO has classified them into 2 categories, the first having structural causes (PALM), and the second having structurally normal anatomy (COEIN) but with abnormal bleeding. For our purposes, the study focused on the category of non-structural causes, because structural causes are very rare in the adolescent age group[4]. We focused specifically on ovulatory dysfunction as a cause for AUB. The normal menstrual cycle in adolescents is typically around 21-45 days, lasting 3-7 days, consuming 3-4 pads per day. A departure from this cycle would be classified as abnormal. In terms of classification of severity of bleeding, we adapted the following classification:

Mild	Longer menses (>7 days) or shorter cycles < 3 weeks for 2 months in succession, with slightly or moderately increased bleeding, a usually normal (>12 g/dL) or mildly decreased (10-12 g/dL) hemoglobin value
Moderate	Moderately prolonged or frequent (every 1-3 weeks) menses, with moderate to heavy bleeding and a hemoglobin level of ≥10 g/dL
Severe	Heavy bleeding with a hemoglobin level of<10 g/dL

There is really no consensus on the treatment for AUB-O for adolescents[1]. Anovulatory AUB can be treated with progestogens alone or oral contraceptive pills (OCPs). There is a paucity of data from randomized trials regarding the treatment of HMB in adolescents. Nonetheless, there are a variety of regimens that appear to be equally effective[5]. Most clinicians utilize combined oral contraceptive pills or progestins/ progestogens for the control of AUB-O. In a study by Munro et al, they compared combined oral contraceptive pills and medroxyprogesterone acetate, and concluded that both medications may be effective and well tolerated[12]. In some treatment protocols for management of acute bleeding in adolescents, oral micronized progesterone is included as well. For adults, it is an accepted part of the treatment protocol. However, there is no evidence on the efficacy of micronized progesterone in the adolescent age group.

Progestogens differ in structure from the natural progesterone produced by the body but is designed to act on progesterone receptors[6]. The effect that is aimed in the uterus is achieved for both, which is stabilization of the endometrium. Progestational agents are an ideal alternative for women who have a contraindication to estrogen. They quickly treat AUB by stabilizing endometrial fragility; inhibiting the growth of the endometrium by triggering apoptosis; inhibiting angiogenesis; and stimulating the conversion of estradiol to the less active estrone. It prevents ovulation and ovarian steroidogenesis, interrupting the production of estrogen receptors and the estrogen-dependent stimulation of the endometrium, leading to an atrophic endometrium[7]. However, side effects for progestogens include irregular bleeding, decrease in bone density, androgenic affects, fluid retention, headache, and mood disturbance. Some studies have shown an increased risk for breast cancer when given in combination with estrogen as hormone replacement therapy for menopausal women[6]. On the other hand, micronized progesterone is progesterone, which is plant based, usually extracted from yams and soybeans[8], unlike the more commonly used progestins which are synthetic progesterone-like compounds. Micronization of progesterone to particle sizes of 10 mm increases the available surface area of the drug and enhances the aqueous dissolution rate and intestinal absorption of progesterone. To enhance intestinal absorption, it is suspended in peanut oil[10]. In studies with adolescents, some current treatment guidelines have included oral micronized progesterone in their algorithms. However, there are no studies documenting its' actual effect on this population.

The main objective of this study is to determine the efficacy of micronized oral progesterone versus medroxyprogesterone acetate in the control and regulation of mild to moderate abnormal uterine bleeding in adolescents with ovulatory dysfunction. The specific objectives were as follows: 1) to describe the demographic profile of adolescents with abnormal uterine bleeding with ovulatory dysfunction in relation to[13] age, menarche, menstrual bleeding patterns and severity of bleeding; 2) to determine the efficacy of progesterone (oral micronized progesterone) versus Medroxyprogesterone Acetate in terms of percentage of adolescents whose bleeding stopped within 5 days (for moderate AUB), mean days until bleeding stopped for those with moderate AUB, timing of next menstrual cycle when cyclic dosing is started (mean interval), number of pads used when cyclic dosing is started (amount of blood, and mean duration of bleeding when cyclic dosing is started. Lastly, we wanted to determine the adverse effects following treatment with oral micronized progesterone and medroxyprogesterone acetate.

METHODOLOGY

This was an open labelled randomized trial that compared the efficacy of micronized oral progesterone versus Medroxyprogesterone Acetate in the control and regulation of mild to moderate abnormal uterine bleeding in adolescents with ovulatory dysfunction seen in the Pediatric and Adolescent Gynecology in the Philippine Children's Medical Center from July 2021-July 2022.

Inclusion criteria included all adolescent girls aged 10-18 complaining of mild to moderate abnormal menstrual bleeding who were assessed and interviewed by the pediatric and adolescent gynecology fellows in the clinic from July 2021-July 2022. Patients who had a probable coagulation disorder (with history of gum bleeding, epistaxis, prolonged bleeding from minor wounds or for dental extractions), were hemodynamically unstable, tagged as with severe bleeding or those who needed admission were excluded from the study. Micronized progesterone contains peanut oil, so those with allergies were not included.

The minimum number of participants was determined at 48 to achieve 80% power to detect a difference in regularity of cycles between the 2 groups using a two-sided two sample t-test. Twenty-five patients who received micronized oral progesterone (OMP) and twenty-five who had taken Medroxyprogesterone Acetate (MPA) were included in the study.

The informed consent/assent was presented to all eligible patients and their guardians. Those whose guardians agreed and signed the informed consent were randomized to one of two groups: oral micronized progesterone and medroxyprogesterone acetate. Randomization sequence was prepared by a third party, the allocation of the eligible patients was placed in sequentially numbered sealed envelopes with specific interventions. Only the co-investigator knew which intervention corresponded to the specific number. Depending on the severity of bleeding, the dosing was as follows. If mild, she received cyclic micronized oral progesterone at 200 mg per capsule on day 16 -25 of the menstrual cycle or started on medroxyprogesterone acetate 10 mg/tab on day 16-25 of the menstrual cycle. If bleeding is moderate, she was started on oral micronized progesterone 1 capsule until the bleeding stopped for at least one month, then was started on cyclic dosing once the bleeding has been controlled. For medroxyprogesterone acetate, she took 1 tablet daily for 1 month then started on cyclic regimen on day 16-25 of each cycle. Dosing was the same regardless of the age of the patient.

The baseline characteristics obtained from the patient are as follows: the age of the patient at present, the age of menarche, the menstrual bleeding pattern which led to the consult (prolonged bleeding, intermenstrual bleeding, heavy bleeding, amenorrhea, irregular menses), and the severity of bleeding.

Patient and mother were instructed to take the capsule on the same time each day, and to take note of when the bleeding stopped, the date of her next menstrual cycle, number of pads used per day, the number of days for the cycle and if there were any adverse effects noted. They were also given instructions on how to fill out a menstrual diary and to fill out the information during the duration of the study. They were given the medications for free after the process has been explained and the consent and assent forms have been signed. Medications were distributed by the Co-Investigator.

The primary investigator kept in touch with the mother and patient to monitor progress thru phone call or social media messengers. Re-evaluation was done if the bleeding persisted or increased in severity. They were contacted every month for two months via phone call. The third month marked their follow up in the clinic where data was reviewed by the investigator. A travel allowance of Php 500 for their return visit was given after the 3rd month of medication.

The costs of the medications were shouldered by 3 parties: Medroxyprogester-one Acetate was shouldered by Philippine Children's Medical Center; Oral Micronized Progesterone cost was shouldered by the main investigator, since it is not in the Philippine National Drug Formulary. Drug samples of Oral Micronized Progesterone from Besins Healthcare were also utilized for 10 of the participants.

The patient and the mother were asked to record information in a menstrual diary. For moderate bleeding, outcomes were measured as follows. First, how many days it took until the bleeding stopped, and the percentage of those whose bleeding stopped within 5 days. After one month, medication was stopped, and patients were instructed to wait for the start of the next cycle (Day 1 of menses). The patient and mother were asked to record when the first day of menses started, the number of pads per day, and how many days the menses lasted. Cyclic dosing was then started on Day 16-25 of the cycle.

For mild bleeding, cyclic dosing was started, meaning the tablets were taken on day 16-25 of each cycle. As in the protocol for moderate bleeding, patient and mother were asked to record when the first day of next menses started, the number of pads per day, and how many days the menses lasted.

Patients were also instructed to take note of perceived adverse effects in the menstrual diary. They were also instructed to note any other symptom that they perceive which is not included in the list of possible adverse effects.

The primary outcomes for the intervention were as follows: the days until the bleeding stopped for moderate bleeding

and the interval until the next menstrual cycle once cyclic dosing is started. Compliance to the medication was monitored thru the information they will log in their menstrual diary. The study was started once it was approved by the Institutional Research - Ethics Committee of this institution.

RESULTS

Out of the 25 patients per arm that were randomized, some were lost to follow up. For the MPA group, 3 patients were lost to follow up, and 1 patient had to be shifted to another medication as the bleeding did not stop after 5 days. For the OMP group, 5 patients were lost to follow up, 1 was shifted to severe dizziness after intake of the medication, and 1 had to be shifted to another medication as bleeding did not stop after 5 days of OMP. All in all, the drop out rate was 16%. Patients who were shifted to another medication were withdrawn from the study and not included in the calculation of the drop out rate. This can be seen in Figure 1.

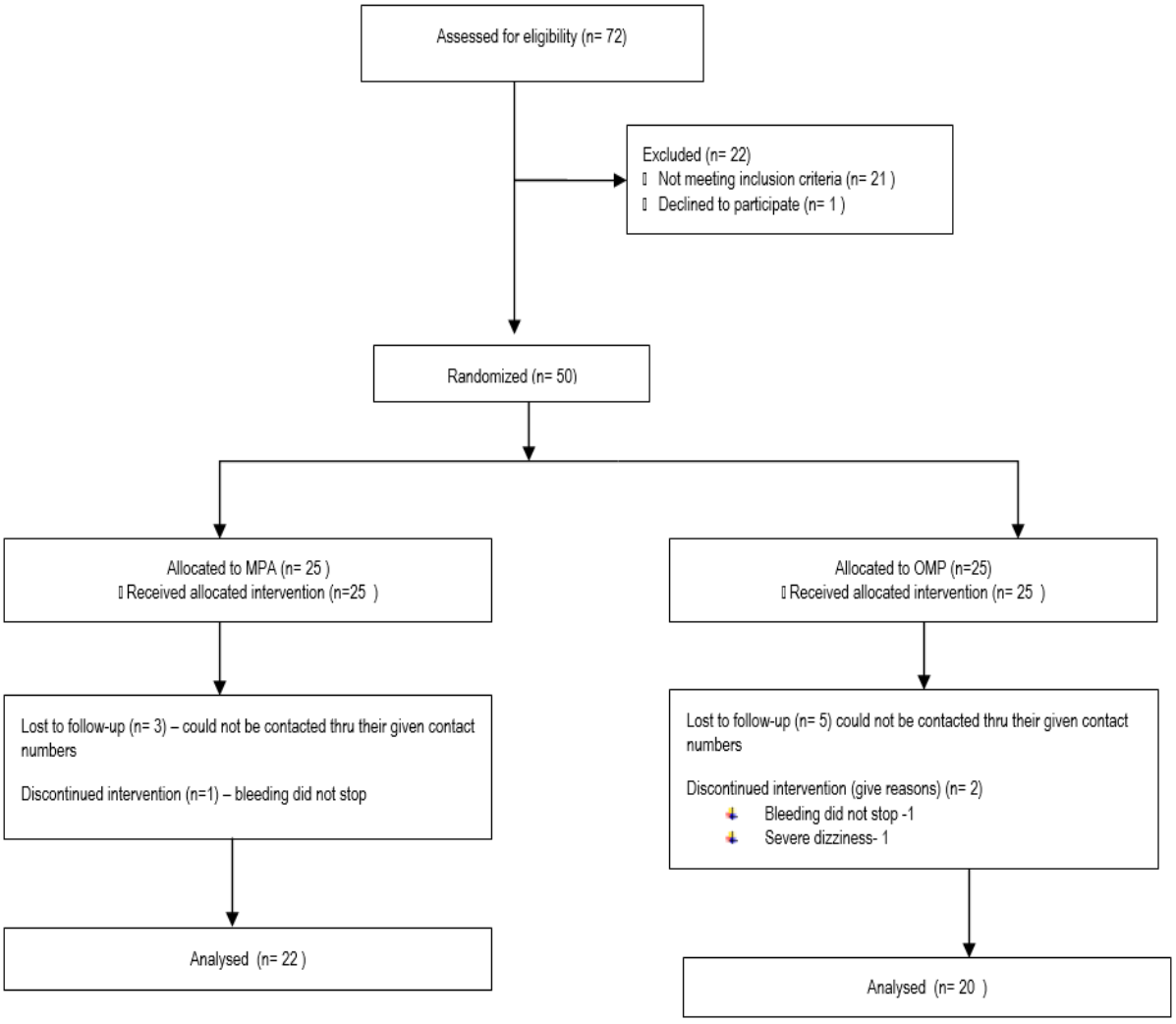

Figure I. *CONSORT Diagram*

Twenty-five patients who received micronized oral progesterone (OMP) and 25 who took Medroxyprogesterone Acetate (MPA) were included in the study. Though there were some who dropped out from the study, the information regarding their demographics was still used for the demographic profile. Table 1 shows that the two groups have no significant difference on their characteristics as both groups are around 15 years old with a mean age of menarche at around 11 years old. For both groups, the most common presentation was irregular menses and prolonged menses. On severity of AUB, we included 33 patients with mild bleeding, and 17 patients for moderate bleeding. For both groups, there was no significant difference in the number per group, per treatment arm. The study population was homogenous.

Table 2. Presence of Adverse Effects for Oral Micronized Progesterone (OMP) Versus Medroxy-progesterone Acetate (MPA) and Breakdown

	OMP (n=20)	**MPA (n=22)**	**p value**
Bleeding stops in 5 days, n, %			
Yes	5 (83.0)	8 (88.9)	1.000[ns]
No	1 (16.0)	1 (11.1)	
Days until bleeding stop, mean ± SD	4.5 ± 1.0	4.4 ± 1.5	0.939 [ns]
Timing of next cycle (interval)			
Regular	15 (88.2)	17 (77.3)	0.438 [ns]
Irregular	2 (11.8)	5 (22.7)	
Number of Pads, n, %			
1 to 2 / 1 to 3	1 (5.3)	10 (45.5)	0.009*
2 to 3 / 2 to 4	12 (63.2)	6 (27.3)	
3 to 4/ 3 to 5	6 (31.6)	6 (27.3)	
Duration of Bleeding, mean ± SD	4.8 ± 1.4	5.4 ± 2.6	0.448 [ns]

*Significant, ns not significant

Table 3 shows the presence of adverse effects was significantly higher in OMP group as 56% of them experienced it, as compared to only 12% in the MPA group. Some of the adverse effects felt in the OMP group are dizziness, sleepiness, weakness, and headache, while the patients with adverse effects in MPA group all experienced sleepiness.

TABLE 3. *Efficacy of Oral Micronized Progesterone (OMP) Versus Medroxyprogesterone Acetate (MPA)*

	OMP (n=20)	MPA (n=22)	p value
Adverse effects, n, %			
Yes	14 (56.0)	3 (12.0)	0.001*
No	11 (44.0)	22 (88.0)	
Adverse effects breakdown			
Sleepiness	8	3	
Dizziness	11	0	
Weakness	2	0	
Headache	1	0	

DISCUSSION

Out of the 50 patients included in this study, the mean age was 14-15 years old. Most of them had their menarche at a mean age of 11-12 years old. There has been a decreasing trend of age at menarche over the years due to several factors. According to Tey et al, in the Philippines, the mean and median ages at menarche declined from 13.2 years and 12.6 years, respectively, among young women born in 1973-1977, to 12.9 years and 12.3 years, respectively, among those born in 1993-1997". [15] This is comparable to age of menarche in other Asian countries, with studies stating that Korean girls have menarche at an average age of 12.27 years and Chinese girls at 11.38 years old.

The most common presentation of abnormal bleeding in adolescents was irregular menses at 34 percent, which was followed by prolonged menses in 26% of the patients. This is comparable to a prospective cohort study done by Chung et al, where they reviewed menstrual disorders in 577 adolescents. Out of these, 47% presented with menorrhagia, prolonged menstruation, and short menstrual cycles, while the rest presented with amenorrhea or oligomenorrhea. [18]

In adolescents, structural causes of abnormal uterine bleeding are rare. Out of the non-structural causes, the most common reason of AUB in adolescents would be immaturity of the hypothalamic-pituitary-ovarian axis and associated anovulatory cycles. Usually, regular cycles are achieved within 2-3 years from menarche[4]. The pathophysiology during an anovulatory cycle is that estrogen continuously stimulates the endometrium but there is no ovulation, hence no progesterone production occurs. Progesterone is needed for stabilizing the endometrium, hence leading to unpredictable and heavy bleeding.[14] Aside from immaturity of the HPO Axis, other conditions which influence ovulation such as PCOS, systemic diseases and stress can cause ovulatory AUB [4].

There is really no consensus on the treatment for AUB-O for adolescents[1]. There is a paucity of data from randomized trials regarding the treatment of HMB in adolescents. Most clinicians utilize combined oral contraceptive pills or progestins/ progestogens for the control of AUB-O. Both progesterone and OCPS seem to be equally effective in treating the condition[5,12]. Whatever the treatment plan chosen, the main goals are the same. These are: to stop the acute episode of bleeding, prevent anemia, prevent absences from school and other activities, and to prevent the recurrence of heavy, prolonged or irregular bleeding[4]. In this study we chose to focus on progesterone as the treatment modality as other studies have already compared OCPs and synthetic progesterone.

Among the progesterones used to treat AUB, Micronized progesterone is one of the newer modalities. It is a progesterone which is plant based, usually extracted from yams and soybeans[8], unlike the more commonly used progestins which are synthetic "progesterone-like" compounds. Currently, OMP is utilized for conditions such as secondary amenorrhea, treatment for dysfunctional uterine bleeding, support for luteal phase deficiency, hormone replacement therapy, treatment for endometrial hyperplasia and other clinical conditions which would need progesterone[11] which makes it ideal for treatment of anovulatory AUB.

On studies with adolescents, some current treatment guidelines have included oral micronized progesterone in their algorithms. However, a search for studies documenting its' actual effect on this population was unsuccessful. In our study, there was no significant difference in the results for both the moderate and mild groups who were randomized to OMP and MPA. For moderate bleeding, OMP was just as effective as MPA in stopping acute bleeding within five days, as both were able to stop bleeding in 4.5 and 4.4 days respectively.

The data for cyclicity, bleeding duration and amount of bleeding was also comparable. For those on OMP, 88.2% were

able to achieve regular cycles while on the medication, lasting for a mean of 4.8 days consuming 2-4 pads per day. On the other hand, those on MPA had regular cycles in 77.3% of patients, lasting for 5.4 days and consuming 1-3 pads per day. Though not statistically significant, patients in the MPA group experienced more irregular cycles. Progestogens are different in structure from natural progesterone produced by the body but the effect of stabilizing the endometrium is there.[6] However, it is also known that progestogens such as MPA do have a tendency to cause irregular bleeding.[6,19] Various studies and articles comparing treatment for abnormal uterine bleeding in adults show that Oral Micronized Progesterone is just as effective in regulating menses by helping patients achieve a more predictable cycle and reducing menstrual flow[20,21]. Review of literature did not show specific studies on exact amount of bleeding or number of pads used for MPA and OMP, though the results still showed that bleeding was controlled and pads used were still within normal amount.

There was a significant difference in adverse effects, as patients in the OMP group complained more of dizziness and sleepiness, which was one of the expected adverse effects for OMP, even in the adult population.[8,21] Out of all the participants, only one dropped out because she was unable to tolerate the dizziness after taking the medication. No participant had to be brought to the emergency room for treatment due to adverse effects.

According to Carswell et al, micronized oral progesterone is one of the options in ensuring that there is no uterine bleeding for adolescent patients using the dose of 100-200 mg of micronized progesterone per day[9]. They also state that the adverse effects for OMP may be limited to sedation and fatigue hence the rationale for giving the dosage at night[9]. One of the recommendations of this study is to utilize a dose of 100 mg instead of 200 mg since this was also effective for patients in the study of Carswell.

Adverse effects for Medroxyprogesterone Acetate include decrease in bone density (which can be reversed), androgenic effects, fluid retention, headache, and mood disturbance[7,19]. These adverse effects were mostly not reported by the patients using Medroxyprogesterone Acetate in this study. Instead, they noted sleepiness as an adverse effect. A review of literature did not come up with sleepiness as a adverse effect for MPA. This leads us to believe that this is a possible side effect for younger patients, although the percentage who complained of this was not significant. A greater study population is needed to make this conclusion. Another possibility is that since it was once the adverse effects listed in the menstrual diary, the patients may have been influenced by the existing chart of adverse effects.

Conclusion and Recommendation

Both oral micronized progesterone and Medroxyprogesterone acetate are effective in the control and regulation of menses for patients with Mild to Moderate Abnormal Uterine Bleeding. Our study showed that there was a comparable effect on stopping acute AUB within 5 days and helping in achieving regular cycles with normal duration and amount of flow. Significantly, there were more complaints of adverse effects for the OMP group.

Limitations of the study include the small sample size and follow up period of 3 months. Since this was done in the time of the pandemic, the sample size was expected to be small and just barely reached the minimum. Also, some of the data collected was subjective such as the assessment of the napkins used, and the adverse effects noted. A more systematic approach in recording, such as use of the Pictorial Blood Assessment Chart may be recommended. Also, since there are no studies utilizing OMP in the adolescent, we recommend that a lower dose such as 100 mg might also be favourable to this population and may bring about less adverse effects. Lastly, further studies should focus on one group (mild or moderate) rather than combining them both in one study.

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CASE REPORT

Co-infection of Coronavirus Omicron variant and Salmonella Meningoencephalitis

Efraim Culminas, Lucy Kathrina Banta- Banzali, Jay Ron Padua

ABSTRACT *:* It has been considered that viral infections predispose patients to bacterial infections due to immunosuppression.[3] However, it is still unclear what exact roles co-infections play in patients with COVID-19 infection[1]. Centers for Disease Control and Prevention defines co -infection as an infection concurrent with the initial infection. This report discusses a case of meningoencephalitis presenting with seizures. Notable in this case was the detection of SARS-CoV-2 RNA and Salmonella in the CSF.

CASE REPORT

A previously well three-month-old Filipino girl presented with one-day history of fever. A day prior to admission, the patient had difficulty of breathing and seizures described as persistent upward gaze which lasted for two minutes. Pertinent neurologic findings were irritability and nuchal rigidity. Initial work up including a complete blood count, showed elevated white blood cell count (WBC) with segmenter-predominance. C-reactive protein and procalcitonin were also elevated. Chest x-ray showed pneumonia for which she was treated with Ceftriaxone at 100 milligram per kilogram per day (mkd). Bedside cranial ultrasound showed bacterial meningitis with ependymitis. Blood culture showed presumptive gram-negative bacilli, hence, Amikacin was started.

The patient was then noted to have myoclonic jerks of upper and lower extremities. Levetiracetam at 20mkd was started with resolution of seizure. The nasopharyngeal SARS-CoV-2 RT-PCR revealed positive and she was started on Dexamethasone.

Lumbar CSF analysis showed a slightly turbid CSF, elevated WBC with lymphocytic-predominance, elevated protein and hypoglycorrhachia. The CSF co-agglutination test, Acid Fast Bacilli, and gram stains were all negative. The CSF SARS-CoV-2 RT-PCR result was positive and on gene sequencing revealed Omicron variant. The blood culture yielded growth of Salmonella group hence antibiotics were shifted to Amikacin, Cefepime and Ciprofloxacin. Patient was also started on Remdesivir.

On the fifth hospital day, she had four episodes of seizure described as right versive gaze, tonic flexion of left upper extremity, and tonic extension of the right upper extremity. Levetiracetam was increased to 60mkd and Phenobarbital at 5mkd was added. The patient was then hooked to non-invasive positive pressure ventilation due to episodes of tight air entry and respiratory distress.

On the sixth hospital day, the CSF culture grew Salmonella group with the same susceptibility pattern as the blood isolate. Baseline work-up for COVID-19 severe infection showed slightly elevated ferritin, D-dimer, and Creatine Kinase-MB.

After twenty-one days of antibiotic treatment, cranial magnetic resonance imaging (MRI) showed pachymeningitis with minimal communicating hydrocephalus (Figure). A repeat lumbar CSF analysis showed normal WBC with lymphocytic predominance, an improved protein and hypoglycorrhachia. The repeat CSF culture and SARS-CoV-2 RT-PCR were negative. Intravenous Cefepime and Ciprofloxacin were completed for 28 days. Before discharge, a repeat COVID ECLIA was reactive for IgG and nonreactive for IgM. The immunodeficiency panel were within normal for age. On discharge, the patient had no seizure recurrence with no neurologic deficits. On follow-up, neurologic examination was normal with developmental milestones at par with age.

Discussion

Co-infection is the simultaneous infection of a host by multiple pathogens resulting in a delay in diagnosis and poor prognosis. Currently, coronavirus infection is a global health concern. In children, coronavirus with concomitant infections is rarely reported. During this pandemic, acute illnesses in children may be associated with coronavirus infection. An acute illness non-responding to conventional treatment, or that which presents atypically or leads to further deterioration, might be associated with coronavirus infection. COVID-19 symptoms may mimic various other diseases. The febrile phase of dengue, typhoid, malaria, and many other diseases may overlap with the coronavirus infection which may lead to substantial misdiagnosis.[2] Based on the available literatures, there is one case report of a 5-year-old girl diagnosed with acute SARS-CoV-2-associated meningoencephalitis based on the detection of its RNA on a nasopharyngeal swab and CSF, and on cerebellar biopsy, *Mycobacterium tuberculosis* complex DNA was detected by PCR.[5]

Salmonella meningitis accounts for <1% of confirmed cases in infantile age group. Despite being an uncommon it is associated with higher rates of complications when compared to other forms of gram-negative rods meningitis.

Its mode of transmission is mainly fecal-oral.[6] The first COVID-19 and enteric fever co-infection was a case of a 56-year-old male who was admitted due to fever, shortness of breath, and myalgia with positive nasopharyngeal SARS-CoV-2 RT-PCR and blood culture for salmonella.[7]

SARS-CoV-2 involves multiple organs including the central and peripheral nervous system. Since the outbreak of the COVID-19, there have been reports of neurologic manifestations of COVID-19 mostly seen in adults, with a few cases described in children which include encephalopathy, encephalitis, stroke, hemorrhage, acute disseminated encephalomyelitis, and Guillain-Barré syndrome.[8]

Both viral and autoimmune meningoencephalitis have been reported in COVID-19 but these complications are rare.[9] Currently, most of the patients with SARS-CoV-2 infection with neurological complications are elderly.[10] In a systematic review by Liang Huo, the incidence of SARS-CoV-2-associated encephalitis/ meningitis is relatively low in children, which may be related to the relatively mild illness of COVID-19.[8]

The underlying mechanisms of neurologic complications in patients with COVID-19 are diverse and multifactorial. Neurologic complications arise most frequently from systemic response to the infection. Distinct mechanisms include: neurologic injury from systemic dysfunction, renin-angiotensin system dysfunction, immune dysfunction and direct viral invasion of the nervous system. Recent evidence suggest that disruption of the blood brain barrier might be one of the potential routes for viral transport and entry to the brain regions. Overall, huge research work is still needed to investigate these processes and mechanisms as no convincing evidence is available that could prove these proposed mechanisms.[11]

The sensitivity of RT-PCR nasopharyngeal swabs of SARS-CoV-2 to detect acute COVID-19 is high, but current data are limited to evaluate the sensitivity of this technique in CSF in patients with neurological disease. Due to the time limit of transmission of COVID-19, its CSF titer may be extremely low which makes it difficult to diagnose SARS-CoV-2-related encephalitis.[12]

By definition, SARS-CoV-2-associated encephalitis/meningitis is an inflammatory process. Supporting evidence includes the presence of COVID-19 with CSF pleocytosis and elevated protein.[13] Definitive evidence about direct neuro-invasiveness of SARS-CoV-2 would include SARS-CoV-2 RNA PCR positive tests in CSF, SARS-CoV-2-specific antibodies positive tests in CSF, or SARS-CoV-2 RNA or antigen positive tests in brain tissue obtained at autopsy or biopsy. Although SARS-associated encephalitis have been reported, few actually meet the strict

criteria for direct SARS-CoV-2-associated encephalitis. In the majority of reported patients with COVID-19-associated encephalopathy, CSF was reported as normal. Thus, detailed nervous system physical examination, ancillary examination, and positive rate of SARS-CoV-2 detection in CSF are very important to provide direct neurotropic evidence of SARSCoV-2.[8]

In SARS-CoV-2-associated encephalitis may involve any part of the brain, especially the temporal lobe, white matter, frontal lobe, and corpus callosum. Neuroimaging abnormalities usually present with high T2/FLAIR signal hyperintensity in the subcortical white matter or other parts of brain injury. There are a myriad of patients without neuroimaging changes. On the other hand, EEG findings of monomorphic biphasic high amplitude delta waves with occasional myoclonic has been suggested as a direct effect of COVID-19 infection.[8]

Patients with encephalitis generally need intensive care and mechanical ventilation. In most of the patients with SARS -CoV-2-associated encephalitis/meningitis were treated with antibiotics and antiviral drugs. Some patients were also treated with IVIg and corticosteroids. Anticonvulsant medications were used in the patients with seizure.[8]

In general, the presence of neurological disease in COVID-19 patients is associated with higher mortality, disturbance of consciousness, refractory epilepsy, and severe physical disability. However, in a review of published case reports by Liang Huo and colleagues found that most COVID-19 patients with encephalitis/ meningitis improved after systematic treatment. Although the literatures available are mostly in adults.[8]

Currently there is no recommended vaccine in children less than 5years old. Vaccination reduced a significant number of infections in the pediatric population, including symptomatic and severe COVID-19. Vaccination of family members and household members may also contribute in achieving herd immunity. At present, there are no published studies showing the effectiveness of COVID vaccine on covid infection with neurologic manifestation.

Locally, there is only one case report of a 12-year male diagnosed with focal encephalitis with documented SARS-CoV-2 in the CSF.[14] However there have been no reports of meningoencephalitis co-infection with SARS-CoV-2.

CONCLUSIONS

COVID-19 co-infections with bacterial pathogens are not well documented.[15] Signs and symptoms of COVID-19 in children may mimic or may overlap with other diseases. Moreover, due to overburden in health services, the diagnosis of co-infections becomes difficult and treatment may be delayed.

Therefore, infection accompanying COVID-19 may lead to misdiagnosis and sudden deterioration of the patient's general condition that leads to increase in morbidity and mortality.[7] Hence, not only bacterial pathogens, but also COVID-19 infection should be considered in patients with presenting with meningitis. In this view, a high index of suspicion, careful attention to the clinical course, and RT-PCR are necessary to identify the coronavirus infection with recent illnesses. Delay in diagnosis of associated COVID-19 results in poor prognosis.[2]

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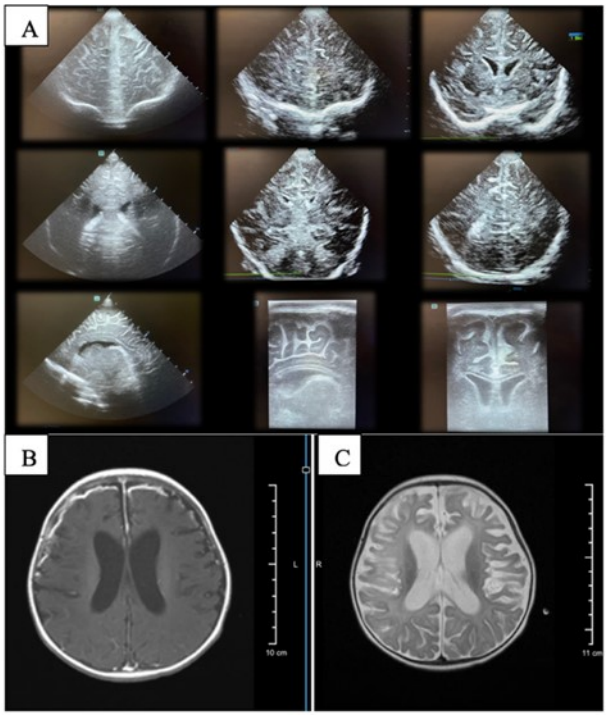

Figure. A. Cranial Ultrasound. The sulci are thick, irregular and hyperechoic, within the interhemispheric fissure and bilateral convexity consistent with Bacterial meningitis with ependymitis. **Cranial MRI plain with contrast (T1 with contrast (B) and T2(C)).** There is abnormal enhancement of the dura overlying both anterior frontal and left medial frontal lobes suggestive of Pachymeningitis.

CASE REPORT

Case report of a child with Myelin Oligodendrocyte Glycoprotein Associated Disease (MOG-AD)

Jenniel Lovely Z. Poyaoan, Jean Marie B. Ahorro

ABSTRACT *:* Myelin oligodendrocyte glycoprotein associated disease (MOG-AD) is an inflammatory disorder of the central nervous system characterized by immune-mediated demyelination. We present a case of a patient with subacute to chronic progressive bilateral motor weakness associated with encephalopathy, which led to the diagnosis of MOG-AD. This case highlights the importance of recognizing the diverse clinical manifestations and the need for a multidisciplinary approach in the diagnosis and management of MOG-AD. In this review, we discuss the pathophysiology, diagnostic criteria, imaging findings, treatment strategies, and prognosis of MOG-AD based on the available literature.

CASE REPORT

This case involves a 9-year-old male who presented with progressive motor weakness. The history began five weeks prior to admission with a two-day episode of cold symptoms, without cough or fever. Two weeks later, he experienced a left temporal headache that resolved after 30 minutes without medication. There were no associated symptoms such as nausea or vomiting, and no consultation was sought.

Three weeks prior to admission, weakness of the right hand was noted, affecting the patient's handwriting. He became unusually quiet, preferred to be alone, and had decreased verbal output. Although he could recognize his parents, he was unable to say their names. Two days later, there was further progression of weakness involving the right extremity such as patient can't hold objects anymore with the right hand, accompanied by facial asymmetry. A child neurologist was consulted, and a cranial MRI was ordered. The following day, the patient experienced a severe left temporal headache without vomiting, and weakness progressed to the right lower extremity. This prompted admission to a nearby hospital.

Initially, the patient was assessed for acute pediatric stroke, but the cranial MRI revealed abnormal signals in the bilateral frontal, temporal, and parietal lobes, more prominent on the left. The radiological interpretation suggested an infectious or

inflammatory process, possibly encephalitis with the beginning of abscess formation. The patient was treated as a brain abscess with ceftriaxone and metronidazole.

During the hospitalization, there was further progression of weakness involving the right upper and lower extremities, rendering him nonambulatory. Behavioral changes were also observed, including irritability, inconsistent responses to questions, and difficulty following commands. The patient experienced visual hallucinations when perceiving shadows in front of him. Urinary retention and constipation were noted as well.

A repeat cranial MRI performed on the 14th day of antibiotic treatment showed progression of the previously seen abnormal signals, with involvement of most of the left lower and capsulothalamic regions. Additionally, patchy enhancement was observed in the left frontoparietal lobe, as well as cortical ovoid foci in the bilateral frontal and left temporal lobes (Figure 1). Two days prior to admission to our institution, the patient developed an inability to eat and exhibited no verbal output, necessitating the transfer.

Pertinent findings on physical examination included stable vital signs, hypoactive bowel sounds, a distended bladder, and good sphincteric tone. On neurological examination, the patient was awake but irritable, with no verbal output or ability to follow commands. Cranial nerve examination revealed responses to visual threat and normal fundoscopic findings. The pupil size was 5-6 mm bilaterally, sluggishly reactive to light. The patient exhibited intact oculocephalic reflexes, right central facial palsy, no head turning in response to sound, and a weak gag reflex. Motor strength was assessed as 1/5 in the right upper extremity, 3/5 in the right lower extremity, and 4/5 in the left upper and lower extremities. Increased tone was noted in both the right upper and lower extremities, and the patient cried in response to pain during the prick examination. Hyperreflexia was observed in the right upper and lower extremities, as well as in the left lower extremity, accompanied by bilateral Babinski signs and clonus. Bladder retention with good sphincteric tone was also noted.

Based on the clinical presentation and investigations, the initial impression was acquired demyelinating syndrome, possibly acute disseminated encephalomyelitis (ADEM). Cerebrospinal fluid (CSF) analysis was normal, but the patient tested positive for anti-MOG antibodies. The electroencephalogram (EEG) showed continuous slowing of background activity at 0.5 to 2 Hz over the left hemisphere, predominantly in the left frontotemporal, mid-temporal, and frontocentral regions. The background activity in the right hemisphere was also slow for the patient's age. A spinal MRI revealed T2 hyperintense, non-enhancing, intramedullary signals in the center of the spinal cord at the C2-C4 and T11-T12 levels. (Figure 2)

Treatment was initiated with methylprednisolone at a dose of 30 mg/kg/day for five days, followed by a switch to prednisone at a dosage of 1 mg/kg/day. Minimal improvement was observed, leading to the decision to perform therapeutic plasma exchange (TPE) every other day for six cycles. The TPE sessions were uneventful, and the patient was discharged with a final diagnosis of MOG-IgG-associated disease, specifically acute disseminated encephalomyelitis

On follow-up, the patient showed some improvement. He was able to say "mama" and "papa," indicating some improvement in his verbal output. Motor strength in the right upper extremity also improved to 3/5, suggesting some recovery. However, the left upper and lower extremities maintained a strength of 4/5, without significant changes.

Encouragingly, there was resolution of the right central facial palsy and drooling, indicating improvement in the facial muscle weakness. No new onset neurological deficits were observed, which suggests that the disease progression may have stabilized or slowed down.

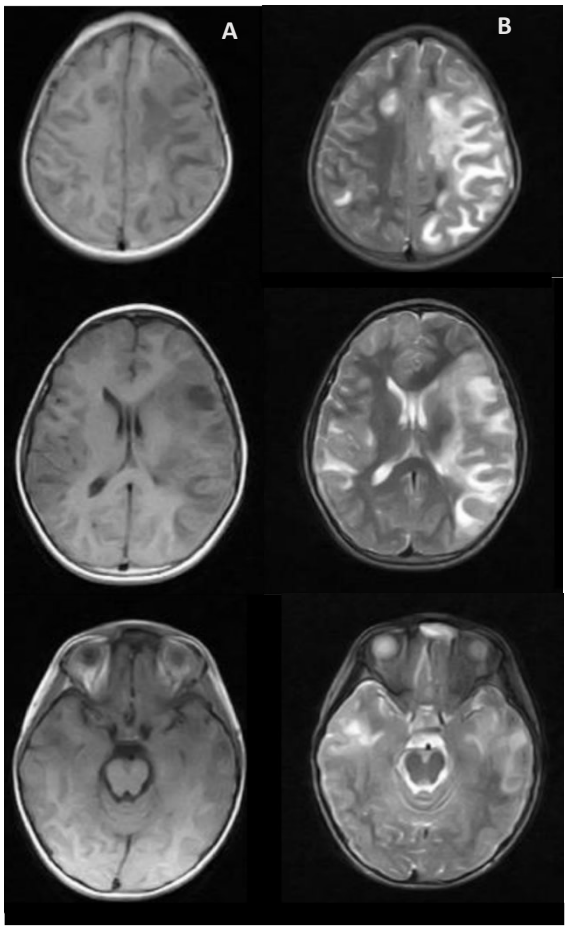

Figure 1. *Cranial MRI showing T1 hypointensity (A) and T2 hyperintensity (B) over the left frontal, parietal, temporal, thalamocapsular region and right temporal*

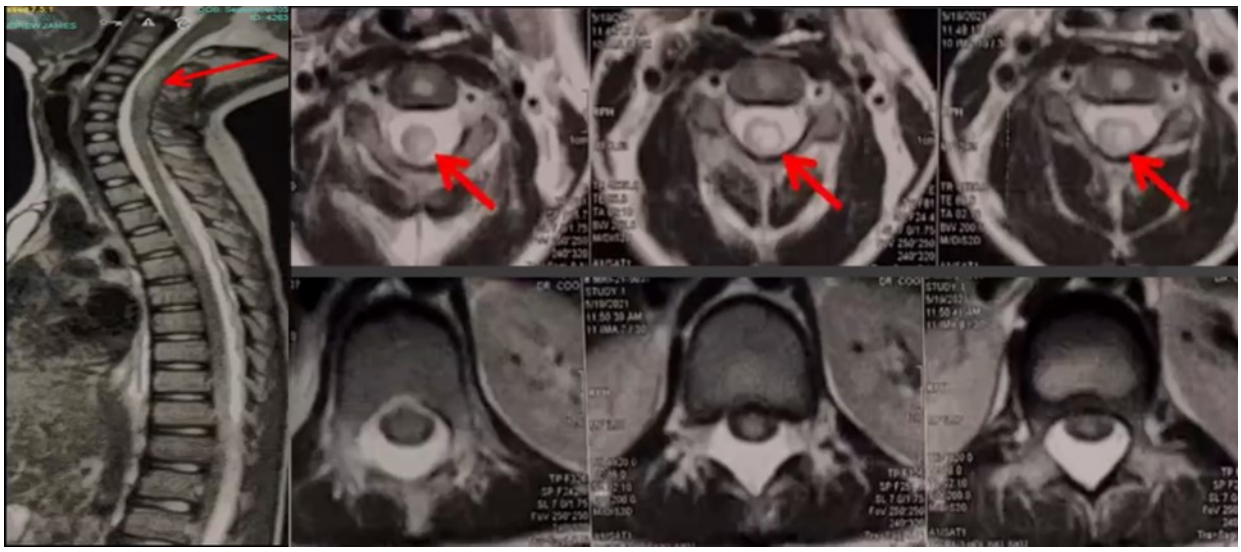

Figure 2. *Spinal MRI showing T2 hyperintensity over the levels T5, T11-T12 (red arrow)*

Discussion

MOG (myelin oligodendrocyte glycoprotein) is primarily produced by oligodendrocytes, the cells responsible for forming and maintaining the myelin sheaths in the central nervous system (CNS). MOG plays a crucial role in the development, stability, and integrity of myelin.

While MOG is found in relatively small amounts within the myelin sheaths, its structure and external location make it susceptible to interactions with the immune system. This accessibility can lead to potential antibody and T-cell responses against MOG, resulting in immune-mediated demyelination and inflammatory disorders such as MOG-associated diseases.

MOG-associated disease (MOG-AD) is an inflammatory disorder of the central nervous system (CNS) characterized by immune-mediated demyelination that primarily affects the optic nerves, brain, and spinal cord. MOG antibodies are the most common autoantibodies in acute disseminated encephalomyelitis (ADEM) and can be present in up to 68% of cases at initial presentation with MOG-AD.[1]

The coexistence of cortical and subcortical demyelinating lesions in MOG-AD is thought to be the result of an immune response involving serum IgG antibodies selectively binding to MOG. This immune response is accompanied by CD4-dominant T-cell and granulocytic inflammatory infiltrates.[2]

The suspicion of MOG-AD arises when a patient presents with optic neuritis, ADEM or ADEM-like presentations with large, poorly demarcated T2 hyperintense lesions in the brain and spinal cord, unilateral cortical encephalitis or other focal neurological findings with cortical T2 hyperintensity and swelling, or a complete spinal cord syndrome, especially with prominent bowel, bladder, or erectile dysfunction symptoms.

Cranial MRI findings in MOG-AD are typically characterized by extensive bilateral cortical encephalitis, while spinal cord MRI may reveal patterns such as extensive involvement of the spinal cord with abnormal hyperintense signals within three vertebral body segments and an H-shaped T2 hyperintensity in axial sequences. Localization of lesions over the medullary cone is highly specific for MOG-AD diagnosis. However, there are no clinical or neuroimaging findings highly specific for MOG-AD, highlighting the importance of the presence of MOG IgG antibodies for diagnosis.[3]

CSF analysis is useful in MOG-AD, showing pleocytosis in cases of myelitis and ADEM, and a potential increase in CSF protein in 50% of cases. The presence of MOG IgG antibodies in serum is crucial for diagnosis, with higher concentrations observed during acute attacks and lower concentrations during remission or the chronic phase. The specificity of MOG IgG testing ranges from 97.8% to 100%, with a positive predictive value of 72% to 94%.[4, 5, 6]

Treatment for MOG-AD involves managing acute exacerbations with high-dose intravenous methylprednisolone. Severe attacks may require therapeutic plasma exchange (TPE) or intravenous immunoglobulin (IVIG). Strategies for preventing attacks include immunomodulating and immunosuppressive therapies, such as long-term use of oral corticosteroids, steroid-sparing medications, and repeated cycles of IVIG.[5]

Studies have reported relapses in 50% of cases over a 2-year period. Gradual tapering of oral corticosteroids is used for relapse prevention, with low-dose prednisolone (10 mg daily) showing effectiveness in some studies. However, due to long-term side effects, treatment is often shifted to steroid-sparing medications.[1]

Two clinicoradiological patterns associated with poor outcomes in MOG-AD are patients who present with ADEM, frequent relapses, and progression, and those who present with non-ADEM encephalitis.

In multicenter observational studies, MOG-AD has been shown to follow a monophasic or relapsing course, with lower long-term disabilities compared to neuromyelitis optica spectrum disorder (NMOSD) or multiple sclerosis (MS). Around 4% of patients may develop MS on follow-up. MOG-AD is not associated with a primary or secondary progressive course, and mortality is low.[1]

Summary

We present a 9-year-old male with progressive hemiparesis that later progressed bilaterally and was associated with encephalopathy. Imaging studies revealed diffuse white matter lesions in the bilateral frontal, parietal, and temporal lobes, as well as the left capsulothalamic region on cranial MRI. Patchy lesions were also seen in the thoracic area (T5, T11-12) on spinal MRI. The presence of serum MOG antibodies confirmed the diagnosis of Myelin oligodendrocyte glycoprotein antibody disease.

The first-line treatment for MOG-AD typically involves intravenous corticosteroid therapy followed by oral corticosteroids. However, in this case, a poor response to initial treatment necessitated the initiation of second-line therapy. Despite the initial challenges, the patient showed improvement in motor and other cortical functions on follow-up, and no new onset focal neurological deficits were noted.

Advances in technology have facilitated the diagnosis of MOG-AD in children presenting with acute disseminated encephalomyelitis (ADEM). Due to the complexity and diversity of clinical, radiologic, and pathologic features associated with MOG-AD, a thorough history and examination of patients is crucial for accurate diagnosis.

Treatment strategies for MOG-AD aim to address acute attacks and prevent relapses. The prognosis of patients with MOG -AD varies depending on the extent of disease progression. Regular follow-up and monitoring of these patients are essential, as a small percentage may go on to develop multiple sclerosis (MS).

It is important to continue close monitoring and follow-up to assess further improvements and any potential recurrence or new symptoms. Rehabilitation therapies and supportive care may be beneficial in helping the patient regain strength and function in the affected limbs.

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CASE REPORT

Case report of Neuroschistosomiasis in a Child

Jenniel Lovely Z. Poyaoan, Marilyn H. Ortiz

ABSTRACT *:* Neuroschistosomiasis is a serious complication of schistosomiasis, where Schistosoma parasites migrate to the central nervous system. It is often overlooked but can cause significant neurological symptoms. We present a 10-year-old male with headache and papilledema, emphasizing the importance of considering neuroschistosomiasis in patients with neurological symptoms and a history of schistosomiasis exposure. Early diagnosis and timely treatment with antischistosomal drugs and corticosteroids are crucial for positive outcomes. Raising awareness and implementing appropriate management approaches can improve the prognosis of neuroschistosomiasis.

CASE REPORT

This case involves a 10 y/o male from Tacloban, Leyte who presented with headache. He was apparently well until 11 months prior to admission, when the patient experienced intermittent rashes characterized by erythematous maculopapular lesions with raised borders, pruritus, and burning sensation on the extremities. He consulted an allergologist and was diagnosed with Acute Urticaria. After 1 month of antihistamine treatment without resolution of symptoms, the possibility of Cercarial Dermatitis was considered due to the presence of recurrent rashes and the high prevalence of schistosomiasis in the area. However, the family did not proceed with the recommended stool examination.

Nine months prior to admission, due to the persistence of symptoms a stool examination was finally conducted, leading to a diagnosis of Intestinal Schistosomiasis in the patient. The patient was given two courses of praziquantel computed at 42mg/kg/day, divided into two doses administered four hours apart. The first course was given immediately upon the initial diagnosis, and the treatment was repeated one month later.

The patient remained asymptomatic until 25 days prior to admission, when he complained of non-radiating dull periumbilical abdominal pain with a severity of 5/10, along with two episodes of non-projectile vomiting of previously ingested food.

No other associated symptoms were reported. A teleconsultation was conducted with a private pediatrician who managed the patient's condition as a case of Acute Gastroenteritis and prescribed probiotics. However, two days later, the abdominal pain and vomiting persisted, and the patient developed an associated bilateral frontotemporal headache with a severity of 5/10. The headache was described as non-radiating and squeezing in character, and there were no associated symptoms of dizziness or blurring of vision. Another teleconsultation took place, during which a complete blood count and urinalysis were requested and yielded normal results. He was then prescribed Omeprazole to be taken for two weeks, which provided temporary relief of the abdominal pain.

Twenty-one days prior to admission, the patient experienced a severe frontotemporal headache upon waking up, with a pain scale of 10/10. The headache was accompanied by transient slurring of speech lasting for about 5 minutes and one episode of vomiting. There were no associated seizures or focal weakness. The patient was taken to a nearby hospital, where the symptoms resolved during the stay in the emergency room. He was then advised to consult an ophthalmologist. Upon examination bilateral papilledema was observed during fundoscopy. As a result, patient was admitted to a hospital in Leyte for four days. The impression was Neuroschistosomiasis, and he received three doses of praziquantel, given four hours apart, at a calculated dosage of 45mg/kg/day. A Circumoval Precipitin Test (COPT) was performed during this admission, but the results were expected in two weeks. The patient was discharged in a well condition and advised to have child neurology consult in our institution which was scheduled approximately three weeks later.

Eight days prior to the current admission, the patient had no subjective complaints, but the mother decided to seek a second opinion from another Ophthalmologist regarding the previously noted papilledema. There was a concern about the possibility of leukemic infiltrates, and a complete work-up was recommended. After this consultation, the COPT result came in and was positive.

Three days prior to the current admission, the patient complained once again of a frontotemporal headache with the same character as before, but with a pain scale of 3/10. The patient also experienced two episodes of non-projectile vomiting. As a result, the patient was advised to be transferred to our institution for further evaluation and management.

The patient has a history of living in a flood-prone area during his early childhood. They lived in a rented bungalow house near a river that frequently floods during heavy rains and typhoons. The patient's mother mentioned that they occasionally had to wade through the floodwaters.

To avoid the frequent flooding, they eventually moved to a different house situated in a higher location. Additionally, the patient's school is also frequently affected by floods, indicating that the local area has a recurring issue with flooding. However, the last exposure to floodwater occurred before the COVID-19 pandemic.

The patient's vital signs are stable, and the physical examination does not reveal any significant abnormalities. Neurologically, the patient has intact mental status and higher cortical functions. The cranial nerve examination reveals bilateral papilledema, but the rest of the cranial nerve examination was normal. The motor examination does not show any notable abnormalities. There are no sensory deficits observed across all modalities, indicating that the patient's ability to perceive touch, pain, temperature, and other sensory stimuli is intact. The patient exhibits hyperreflexia in the bilateral lower extremities. The examination of cerebellar function and meningeal signs, as well as the autonomics, does not reveal any noteworthy abnormalities.

Based on the clinical presentation, the initial impression was Increased Intracranial Pressure secondary to Cerebral Neuroschisto-somiasis. Laboratory tests revealed an elevated erythrocyte sedimentation rate, which can be indicative of inflammation. Blood culture did not yield any growth, ruling out an acute bacterial infection. Other laboratory tests, including complete blood count, inflammatory markers, serum electrolytes, kidney and liver function tests, urinalysis, and stool examination, did not reveal any significant abnormalities. A chest X-ray was normal, suggesting no apparent lung involvement.

Ophthalmology consultation confirmed the presence of chronic papilledema in both eyes, further supporting the diagnosis. Cranial MRI was performed and revealed subcortical and sulcal lesions in the parietal lobes of both cerebral hemispheres, as well as vasogenic edema in the right frontal and bilateral parietal lobes (Figure). These findings were interpreted as cerebral tuberculomas. He was then initiated on anti-TB medication. TB work-up, including a purified protein derivative (PPD) test and sputum gene x-pert, yielded normal results.

A neuroradiologist reviewed the images and confirmed compatibility with neuroschistosomiasis. To further evaluate the possibility of seizures associated with neuroschistosomiasis, a 6-hour video EEG was performed, which was normal. A craniospinal MRI with contrast was also conducted, showing no remarkable findings in the spinal region.

Methylprednisolone was started at 15 mg/kg/day to manage the inflammation and reduce intracranial pressure, along with praziquantel at 50 mg/kg/day to target the schistosomiasis infection.

Subsequently, methylprednisolone was shifted to oral prednisone at 1 mg/kg/day after seven doses and tapered over the course of a month. Praziquantel was completed for five days, while anti-TB medication (HRZE) was continued and planned for a year.

The patient was also referred to the Hematology service to rule out the possibility of leukemic infiltrates. Lactate dehydrogenase and reticulocyte count were normal, and bone marrow aspiration revealed a normocellular marrow with complete trilineage hematopoiesis, effectively ruling out leukemia.

With no subjective complaints, stable vital signs, and no new onset neurological deficits, he was discharged on the 14th hospital day.

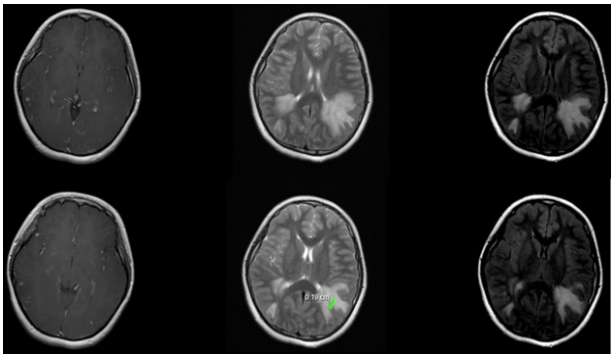

Figure: *T1-weighted hypointense and T2-weighted hyperintense subcortical and sulcal lesions on the parietal lobe of both cerebral hemispheres. There was also significant vasogenic edema in the right fontal and bilateral parietal lobes.*

DISCUSSION

Schistosomiasis is a parasitic disease caused by blood flukes of the genus Schistosoma. The granulomatous reaction is the main mechanism of disease in schistosomiasis. The eggs of the Schistosoma parasite that are not excreted can become trapped in the intestinal or bladder wall or can be carried by the bloodstream to the liver and other sites, including the central nervous system (CNS).

Clinical forms of schistosomiasis include acute and chronic infections. Acute infections can manifest as cercarial dermatitis (swimmer's itch) or as Katayama syndrome (acute schistosomiasis syndrome). Chronic infections can result in intestinal schistosomiasis, hepatosplenic schistosomiasis, genitourinary schistosomiasis, or neuroschistosomiasis (schistosomal involvement of the CNS).[1,2]

Neuroschistosomiasis is a severe complication of schistosomiasis, characterized by the involvement of the central nervous system (CNS). It is an underrecognized complication and affects a small percentage of individuals with systemic schistosomal infections. There are two main types of neuroschistosomiasis depending on the species of Schistosoma involved. Spinal cord schistosomiasis is predominantly associated with Schistosoma mansoni and Schistosoma haematobium infections, while brain involvement, such as acute schistosomal encephalopathy and

and pseudotumoral encephalic schistosomiasis, is typically associated with Schistosoma japonicum infections.

Spinal cord schistosomiasis commonly presents with lower back pain that radiates to the lower limbs, lower limb weakness, bladder dysfunction, lower limb paraesthesia, hypoaesthesia or anaesthesia, deep tendon reflex abnormalities, constipation, and sexual impotence. The conus medullaris and cauda equina are often affected. The severity and distribution of symptoms can vary, and the medullary level identified by clinical examination is typically equal to or below T6, particularly at T11–L1. It is classified into three clinical forms: medullary, conus-cauda equina syndrome, and myeloradicular.

In cases of brain involvement, acute schistosomal encephalopathy (ASE) may occur. ASE presents with symptoms such as headache, altered mental status, seizures, sensory disturbances, weakness of extremities, ataxia, and transient visual and speech disturbances. Meningeal signs are less common in ASE.

Pseudotumoral encephalic schistoso-miasis, which predominantly occurs in individuals without other symptoms of schistosomiasis, is characterized by slow-expanding lesion-like masses in the brain. These masses cause increased intracranial pressure and can lead to severe and persistent headaches, focal neurological signs depending on the lesion site, and various types of seizures. The cerebellum is the most commonly affected site, followed by the occipital and frontal lobes.[3]

For the diagnosis of active schistosomiasis, the gold standard is the identification of schistosome eggs in stool or urine samples using microscopy. However, microscopy has limitations, particularly in cases of light infections or acute infections. The Kato-Katz method is commonly used for stool examination in endemic settings, but it may lack sensitivity in light infections. Serologic tests, such as the Circumoval Precipitin Test, can be useful in the absence of egg detection, especially for travelers with low parasite burden. Biopsy, particularly superficial rectal biopsies or "rectal snips," can be more sensitive than stool microscopy in certain cases.[4]

Regarding neuroschistosomiasis, MRI is a sensitive imaging modality for detecting abnormalities. In spinal cord schistosomiasis (SCS), the most common findings include signal hyperintensity on T2-weighted images, spinal cord enlargement (particularly lower cord and conus medullaris), thickening of spinal roots (especially cauda equina roots), and heterogeneous contrast enhancement on T1-weighted images. In acute schistosomal encephalopathy (ASE), edema and multifocal small contrast-enhanced lesions can be observed in the frontal, parietal, occipital lobes, and brainstem on MRI. Pseudotumoral encephalic schistosomiasis (PES) typically presents as a non-specific tumor-like lesion

surrounded by edema, with mass effect and heterogeneous contrast enhancement on MRI.

CSF examination in neuroschistosomiasis can show slight-to-moderate increases in total protein concentration and lymphocyte count. Eosinophils may be present in the CSF in approximately 50% of patients with spinal cord schistosomiasis. In ASE and PES, CSF findings can be normal or non-specific.

Treatment approaches for neuroschistosomiasis are not yet standardized. However, antischistosomal drugs, corticosteroids, and surgery are the available modalities. Prompt corticosteroid treatment, such as prednisone at a dose of 1 to 2 mg/kg per day, is essential to limit tissue damage caused by the intense inflammatory response to embolized eggs. Even if the diagnosis of neuroschistosomiasis is suspected but not confirmed, corticosteroid therapy should be initiated. The duration of corticosteroid therapy is uncertain, but it is generally continued for several months and then gradually tapered based on individual circumstances. Premature discontinuation or rapid tapering of steroids may result in clinical relapse.[3]

Control strategies for schistosomiasis in endemic areas include several approaches. Periodic mass treatment with antischistosomal drugs, particularly praziquantel, is a key intervention to reduce the parasite burden and prevent the development of severe disease. Water sanitation programs aim to minimize exposure to contaminated freshwater sources, which are the habitat of the intermediate snail hosts. Vaccine development is also an important area of research to provide long-term protection against schistosomiasis.

Interventions such as community education play a crucial role in raising awareness about preventive measures, including the use of protective clothing and footwear to reduce contact with contaminated water. Eradication of snail species, which act as intermediate hosts for the parasites, can also be a part of control efforts to disrupt the life cycle of the parasites.[4]

The prognosis of neuroschistosomiasis largely depends on early diagnosis and treatment initiation. With the advent of praziquantel and the addition of corticosteroids, the rates of recovery have significantly improved. In cases treated early with praziquantel and steroids, neurological symptoms have shown complete resolution in most patients. Before praziquantel became widely available, the rates of recovery were lower, with only 13% achieving full recovery, 74% experiencing partial recovery, and 13% having a poor recovery.[3]

Summary

Neuroschistosomiasis is a severe and underrecognized complication of schistosomiasis, a parasitic disease caused by blood flukes of the genus Schistosoma. It is characterized by the involvement of the central nervous system, including the spinal cord and brain.

This abstract summarizes the case of a patient with neuroschistosomiasis presenting with increased intracranial pressure and exhibiting symptoms such as bilateral papilledema, hyperreflexia, and subcortical lesions on imaging.

The patient, who had a history of living in a flood-prone area, underwent various diagnostic tests, including laboratory investigations, imaging studies, and cerebrospinal fluid examination. The diagnosis of neuroschistosomiasis was confirmed based on the presence of schistosome eggs in the stool and the characteristic findings on imaging, which showed T1-weighted hypointense and T2-weighted hyperintense lesions in the parietal lobes and significant vasogenic edema. Treatment was initiated with anti-kochs medication, including methylprednisolone and praziquantel. The patient showed improvement in symptoms and stable vital signs during the hospital stay. Follow-up evaluations, including a bone marrow aspiration, were performed to rule out other potential conditions.

Our report highlights the importance of early diagnosis and treatment in neuroschistosomiasis, as prompt administration of corticosteroids and antischistosomal drugs can lead to favorable outcomes and complete resolution of neurological symptoms. Control strategies for schistosomiasis in endemic areas, such as mass treatment, water sanitation programs, and community education, are crucial in preventing and managing this debilitating condition.

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