The PCMC Journal

An Official Publication of the Philippine Children's Medical Center

CONTENTS

THE USE OF METERED-DOSE INHALER VERSUS NEBULIZATION FOR THE DELIVERY OF SALBUTAMOL IN PEDIATRIC SEVERE ASTHMA EXACERBATIONS: A SYSTEMATIC REVIEW

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ABSTRACT

BACKGROUND: Recent guidelines for the management of asthma have advocated the use of a pressurized metered-dose inhaler (MDI) and spacer in the delivery of salbutamol. However, there is a dearth of research in children with severe exacerbation.

OBJECTIVES: To compare the effectiveness of MDI with spacers versus nebulizers in drug delivery of salbutamol for the management of pediatric severe asthma exacerbations

METHODOLOGY: A systematic search of the Pubmed, Cochrane library, Herdin, WPRIM, ClinicalTrials and reference review databases was conducted for studies containing "severe asthma" using MDI and spacer as an intervention with nebulization as a comparator.

RESULTS: Of 220 articles, 4 met the criteria. In the subgroup analysis, children who received salbutamol through MDI showed no significant difference in hospital admission, pulmonary score, heart and respiratory rate, oxygen saturation, and lung function.

CONCLUSION: In severe asthma exacerbations, there is evidence to support that MDI compared with nebulizer is statistically equal in terms of hospital admission, pulmonary scores, clinical improvement, and side effects

RECOMMENDATIONS: Further randomized controlled trials are suggested to explore the intricacies of drug delivery in management of severe asthma. A meta-analysis may be made possible in the future with more evidence.

KEYWORDS: severe asthma, metered-dose inhaler, nebulizer, salbutamol

INTRODUCTION

Asthma exacerbation is one of the more common reasons for emergency department consult for children. In acute asthma exacerbations, the drug of choice for management is salbutamol (1). In the pediatric population, these are more commonly delivered through a metered-dose inhaler with a holding chamber or spacer or using a nebulizer. The Global Initiative for Asthma (GINA) released interim guidelines for asthma management this 2020 which advocates the use of a pressurized metered-dose inhaler (MDI) and spacer in the delivery of salbutamol, a short-acting beta-agonist (1). Recent randomized controlled trials and reviews have supported the use of the metered-dose inhaler as more effective and cost-effective (2,6). However, there has been some resistance to this movement.

Although latest guidelines have advocated the use of metered-dose inhaler for infection-control purposes, nebulizers have historically been preferred in the management of asthma exacerbation. This may have been due to the difficulty of younger patients to coordinate inhalation and demonstrate proper technique when using the MDI. Studies have shown that some institutions demonstrated a "nebulizer culture' (3,4). Many parents and physicians still prefer to use nebulizers with diverse reasons, among which is the assumption that the nebulizer has a better delivery of medication compared with salbutamol (3). The lack of available information contributed to this misperception. Furthermore, patients with severe asthma were excluded in systematic reviews determining effectiveness. Therefore, this research aims to answer the question: For managing pediatric severe asthma exacerbations, is using a metered-dose inhaler with spacer as effective as using a nebulizer? Asthma remains to be a major cause of morbidity and mortality in the Philippines with a prevalence of 12% in children (4). Theoretically, MDI with spacers can improve drug distribution to the lower airways by

delivering smaller particles and by decreasing side effects by lessening deposition in upper airways by 80% (5). This is supported by systematic reviews that have already concluded that the use of MDI with spacer is as effective as delivery by nebulizer for the treatment of acute illness with lower side effects of tachycardia or tremor (1). However, people with life-threatening disease were excluded from the study thus limiting the applicability in severe cases (1). There is limited information said about using MDI for severe life-threatening disease. As such, this leaves an impression for some physicians that nebulizers may be more appropriate in severe or life-threatening disease. This systematic review aims to analyze available data to resolve conflicts in management and promote physician champions for change who can help with the cultural change.

Asthma is a chronic airway inflammatory disease resulting to hyperresponsiveness, airflow limitations, and disease chronicity (1,4). An asthma exacerbation is an episode characterized as progressive increase in wheezing, chest tightness, cough, or shortness of breath sufficient to require a change of treatment. This is often triggered by viruses, allergens, pollution, or poor adherence with controllers. Diagnostically, this would present as a decrease in peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV1) from baseline. Severe exacerbations would present as a patient who can only talk in words, sits hunched or agitated, with respiratory rate > 30 mins and a pulse rate more than 120, with use of accessory muscles, desaturation, and PEF 50% predicted. Life-threatening exacerbations present with drowsiness or changes in sensorium (1). In circumstances wherein spirometry is not readily available such as in the emergency room or there is difficulty performing expiratory maneuvers such as with younger children, a scoring system can be used to measure severity. The pulmonary score is a validated severity measure for acute asthma

exacerbation that assesses respiratory rate, wheezing, and accessory muscle use on a scale of 0 to 3. A score of more than seven generally connotes severe asthma exacerbation. A decrease in the pulmonary score signifies response to treatment (8). Salbutamol is a short-acting beta-agonist (SABA) that allows rapid reversal of airflow limitation during exacerbation. A good response to initial treatment is described as an increase of PEF to more than 60 to 80% of predicted or personal best a few hours after administration. Clinically, this will present with increasing oxygen saturation, decreased respiratory rate and pulse rate, and less effort in breathing (1). However, the most common identified side-effects of the same drug include fine tremors and tachycardia with a dose-dependent presentation. Evidence also suggests that delivery through MDI with spacer had lesser side-effects compared with nebulizer (2,7).

General objective

To determine the effectiveness of MDI with spacers compared to nebulizers in drug delivery of salbutamol for the management of pediatric severe asthma exacerbations

Specific objectives

1. To compare the rate of hospital admission and pulmonary scores in patients who were given salbutamol through nebulization versus those who were given through MDI and spacer.

2. To compare oxygen arterial saturation, heart rate, respiratory rate, and lung function test in patients who were given salbutamol through nebulization versus those who were given through MDI and spacer.

3. To compare the most common adverse side effects including tachycardia between MDI with spacer and nebulization

METHODOLOGY

This was a systematic review guided by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)

guidelines for systematic reviews. A literature search from various search engines and electronic databases such as The Cochrane Library, PubMed®, Herdin, and WPRIM was done by the primary investigator. Databases of unpublished trials such as Clinicaltrials.gov were utilized. The search strategy: (metered-dose inhaler OR spacer OR holding chamber) AND (nebuli*) AND (asthma) AND ((pedia*) or (child*)) AND (salbutamol OR albuterol) was used. The Medical Subject Headings (MeSH) was employed when searching a database when available. The bibliographies of included studies were also reviewed to identify other relevant trials. Field experts were asked for reference articles or unpublished studies. After reviewing the results of the search, duplicate studies were removed, and a review of titles and abstracts were done. Two reviewers independently evaluated the abstracts generated by the search strategy for inclusion. Those that met the inclusion criteria as seen in table 1 were retrieved as full text articles. Full text copies of studies included were saved in a Google drive accessible to the investigators. The full text articles were screened again based on the inclusion and exclusion criteria. The two reviewers then compared their list of included studies. Discrepancies were compared and disagreements were resolved through discussion. The studies included in the systematic review was assessed for methodological quality using the Cochrane Collaboration Risk of Bias Tool. Risk of bias scorings and extracted data from the studies was managed using Review Manager (RevMan) 5.4 software. All included randomized trials were evaluated based on randomization, concealment of allocation, blinding, treatment of incomplete outcome data, selective reporting, and other bias. Table 2 demonstrates how rating of 'low risk of bias,' 'high risk of bias' or 'unclear risk of bias' was scored for each category. Two investigators independently assessed each study. Discrepancies were compared and discussed until a consensus among the

investigators was reached. Two investigators independently extracted data from the full-text articles. The information needed included descriptive data (author, year published, age range, number of patients studied), details in the administration of salbutamol (agent, dose, delivery method, duration of therapy, and concurrent treatments) and outcomes assessed, and study details required for appraising the methodological quality of the document. After data collection, the two investigators verified information extracted. A narrative synthesis of all included research based on identified outcomes was done. If possible, pooled estimate of Mean Difference (MD) for continuous variables and Risk Ratio (RR) for categorical variables is planned to be computed along with 95% confidence intervals (CIs). We used RevMan 5.4 for statistical analysis.

RESULTS

The search of articles through databases and other sources yielded 216 references. After deduplication, fifty-seven articles were reviewed based on their title and abstract for eligibility. Out of the fifty-seven, seven articles were found to meet the inclusion criteria and full-text studies were retrieved. Of the seven articles, one article was excluded due to incomplete data as it was an ongoing clinical trial. A total of six studies were included in the analysis. However, one study was also excluded due to difficulty in retrieving an English translation. Another study was excluded since the study population also included adults. A flowchart of study selection is discussed in figure 1.

Four studies are included in this systematic review as seen in table 3. The study of Leversha et al. (2000) is a randomized, double-blind, placebo-controlled trial consisting of 60 children aging one to four years old with moderate to severe exacerbation and a known history of asthma. The study of Vilarinho (2003) was a randomized, single-blinded trial among children presenting with wheezing

crises at the walk-in section of a hospital in Brazil. A total of 54 children with moderate wheezing crisis ages 22 days to 11.7 years were included. On the other hand, Jamalvi et al. (2006) conducted a cross sectional study in the Emergency Room (ER) of National Institute of Child Health (NICH) on a total of 50 children, with ages six months to fifteen years old, and with a history of wheeze and presenting with an acute asthma exacerbation. They were later categorized into mild, moderate, and severe asthma based on medical scoring system. Finally, the most recent among the four studies is the randomized clinical trial conducted by Iramain et al. (2019), The study includes 103 children with severe asthma exacerbations treated in the ED. In total there were 267 children with moderate to severe asthma included in this review. All four studies randomly assigned patients between a spacer group and a nebulizer group. Leversha et al., (2000) divided his study population into the Spacer group (n=30, mean age: 36.0 ± 11.5 months) and the Nebulizer Group (n=30, mean age: 32.3 ± 13.5 months). The spacer group were given 600 ug salbutamol via MDI by spacer (AeroChamber) then placebo by nebulizer, while the Nebulizer Group were given placebo MDI by spacer then salbutamol (2.5 mg) by nebulizer. The treatments were repeated by an interval of 20 minutes up to a maximum of 6 treatments. Until the attending physician decides that the patient does not need further doses of bronchodilator (10). In 2003, Vilarinho et al. after equally dividing his study population between the two groups administered 3 doses of salbutamol (100 mcg/3 kg in the spacer group and 250 mcg/3 kg in the nebulizer group) every 20 minutes until the child was considered to have improved significantly and no longer required any further treatment, or until three doses were done (11). On the other hand, Jamalvi et al (2006), compared effectiveness of administration of salbutamol by Metered Dose inhaler (MDI) with accessory device (AD) by giving 100 mcg for 2 puffs for 3 times versus administration of

salbutamol by small volume nebulizers (SVN) using 0.3 ml/kg as asthma treatment (12). Finally, Iramain et al. (2018) gave salbutamol for two puffs every 10 minutes for 2 hours and subsequently by every 30 minutes for 2 hours through MDI with valved-holding chamber and mask in conjunction with oxygen through a separate cannula (n=52) for his intervention group. For his control group (n=51) nebulization was done with oxygen and salbutamol and ipratropium (1 puff every 20 minutes for 2 hours and subsequently 30 minutes for an additional 2 hours) (13). Outcomes for each study varied. Most studies used clinical outcomes such as heart rate, respiratory rate, oxygen saturation, and effort of breathing to measure effectivity. Measures of cost-effectivity such as hospital admission rate and duration of admission were also measured. Different pulmonary scores were used to measure clinical responsiveness and asthma severity post-treatment. Only Jamalvi et al. (2006) was able to utilize pulmonary function tests such as PEFR to measure asthma response. Side effects of drug administration were measured through presence of tachycardia and hyperactivity. Majority of studies were of low risk of bias as shown in figure 2. Three were double-blinded studies and four had randomize treatment allocation. Only the study of Jamalvi et al. (2003), demonstrated high risk for bias as there was no mention of blinding done in the study for both the participant and the outcome assessment. Participants were also aware of treatment group whether by MDI with spacer or nebulizer. Leversha et al. (2000) found that there was a significantly less admission rate in children treated using MDI with spacer (33% spacer versus 60% nebulizer, p-value = 0.04, adjusted for sex). This is consistent with the findings of Iramain et al. (2018) who found that children who were nebulized had a higher risk for admission versus those who used MDI with spacer (RR 0.21 [0.6-0.69], P=0.003). In contrast, Vilarinho et al. (2003) and Jamalvi et al (2006) both saw no significance in the rate of admission (p-value = 0.19, p-value =

0.185). Table 4 shows that for all studies only mean hospital admission rate was reported and standard deviation was not computed for hence a pooled analysis was not made possible.

While pulmonary scores were used more often to assess response to treatment, different standards were used. The study of Leversha et al. (2000) utilized clinical severity score to determine effect of MDI and spacer versus nebulizer and found that the absolute change in score was similar (-2.9 spacer vs -2.7 nebulizer, P-value = 0.55). This was consistent with a study by Vilarinho et al. (2003) and Jamalvi et al. (2006) which showed no clinical significance between the use of MDI and nebulization in clinical severity scoring. However, of the four included studies, one study demonstrated that the pulmonary score index of children in the spacer group showed significantly better improvement than those in the nebulizer group after 4 hrs. of treatment (2.5±1.0 spacer vs 4.15±0.9 nebulizer, $p<0.00001$) (1,3). The clinical criteria for pulmonary scores used per study were different as demonstrated in table 5 hence pooling cannot be done.

With regards to effect on vital signs, the evidence from available studies also showed varying results. In terms of heart rate, only Leversha et al. (2000) and Iramain et al. (2019) demonstrated a higher heart rate in the nebulizer group compared with the MDI group. In contrast, Jamalvi et al. found no significant difference. In comparison, all studies showed no significant difference in respiratory rate change. Finally, only one study by Iramain et al. (2019) showed that significant improvement in oxygen saturation after treatment with MDI with spacer compared with the nebulizer group. In a study by Leversha et al. (2000), while the 2 groups had similar outcomes for oxygen saturation, respiratory rate, the spacer group developed greater decrease in wheezing (p-value= 0.030). This is consistent with the study of

Vilarinho et al. (2006) and Jamalvi et al. (2003) who both reported that there were no significant differences in outcome measures between the 2 groups in terms of vital signs and related outcomes (respiratory rate: p-value= 0.133; heart rate; p-value= 0.188; dyspnea: p-value= 0.082; cyanosis: p-value= 0.236). On the other hand, the study of Iramain et al. (2019) observed that the metered-dose inhaler group had significantly increased oxygen saturation 90 minutes post-treatment than the nebulizer group (90.5 ± 1.7 vs 88.43 1 ± 1, respectively, p-value< 0.00001). In table 6, only 2 studies published data on standard deviation thus limiting our ability to acquire a collected result.

Only one study utilized lung function tests to measure outcome. The study of Jamalvi et al. (2003) showed that the Peak Expiratory Flow Rate (PEFR) in children more than 5 years old increased significantly in both groups after treatment completion, but it was not statistically significant when compared in between groups (p-value of 0.10 each after 10 minutes, 20 minutes and 2 hours of treatment) (1,2).

Tachycardia was noted to be significantly greater in the nebulizer group within the first treatment compared with the spacer group (p-value< 0.010), based on the study of Leversha et al. (2000). Furthermore, this was found to be continuously higher throughout the rest of the study period (p-value = 0.03). This was supported by the study of Iramain et al. (2018) which found that heart rate was significantly higher in the nebulization group from 30 minutes of treatment until the end of the study (p-value < 0.00001). However, the studies of Vilarinho et al. (2003) and Jamalvi et al (2006) showed no significant difference. The differences in table 7 may lie in the study population wherein Leversha et al (2000) and Iramain et al (2019) both had a baseline mean heart rate of 149 bpm to 156 bpm whereas Vilarinho et al (2003) and Jamalvi et al. (2006) had a mean heart rate of 125 bpm to 136 bpm.

DISCUSSION

Overall, results in this study were consistent with previous research. It has been found that comparisons between spacer and nebulizer treatment show that they are equally effective in the delivery of salbutamol to children with mild to moderate asthma in shortening hospital stay (MD: -33.48 minutes; 95% CI:-43.43 to -24.65 minutes, $p<0.001$) with a tendency but without statistical significance on decreasing hospital admission (RR: 0.71, 95% CI: 0.47 to 1.08, $p=0.11$) (2,14). For children with severe asthma, two of the four studies showed no statistical significance in terms of hospital admission rate and pulmonary scores to measure response to treatment between the two study groups in severe asthma.

In terms of secondary outcomes, the result of this study builds on the current recommendations for bronchodilator delivery on MDI use. Outcomes measured included heart rate, respiratory rate, oxygen saturation, lung function tests, and adverse outcomes. Leversha et al. (2000) concluded that a combination of MDI and spacer is as effective as a nebulizer in delivering salbutamol to young children with moderate and severe acute asthma. In the study population, the MDI-spacer combination was the preferred option for treatment for its lower hospital admission rates and lower costs. The spacer offers an effective choice to the nebulizer routine use in the acute setting (10). In Vilarinho et al. (2003), their study revealed that outcomes in the groups do not differ significantly (p-value> 0.05), except for air entering, which scored lower in the MDI group. Furthermore, both the spacer and the nebulizer were equally beneficial when it comes to improving clinical scores and oxygen saturation levels. They were proven to be clinically equal at different doses (100 microg/3 kg with the spacer and 250 microg/3 kg with the nebulizer). It was then concluded that the use of a homemade spacer with a metered-dose inhaler is a more cost-effective option to the use of a jet nebulizer in the

delivery of salbutamol to children experiencing mild wheezing attacks (11). Jamalvi et al. (2003) also observed comparable discharge outcomes in both groups and concluded that the use of MDI in the ER is an effective alternative to nebulizer for the treatment of children with acute asthma exacerbation (12). Finally, one study (Iramain et al., 2019) concluded that MDI was more effective than nebulization in relation to reducing hospital admission, enhanced oxygen saturation and clinical score. However, further studies are needed to support these new outcomes (13).

Remarkable in this systematic review is the differences in salbutamol dosage given between MDI with spacer and nebulizer. In general, a higher dose was provided during nebulization as per clinical guidelines. This was justified by a study done on a model of a neonatal lung on mechanical ventilation which showed that albuterol at 100 mcg given through MDI with a spacer is equivalent to 2500 mcg to 3700 mcg via nebulizer (15). In all studies, uncertainty over the dosage was overcome by repeating treatments at short intervals until a clinical response was observed. Another factor that should be taken into consideration when interpreting this study is that children with severe asthma were further classified to those requiring advanced airway such as mechanical ventilation and those who do not. Some studies excluded those who required advanced airway since decision-making to use an MDI versus nebulization is influenced by other factors such as feasibility and tolerance of the patient. However, a study conducted on twelve intubated infants and children showed no significant difference in respiratory mechanics or hemodynamics between those treated with nebulizer versus MDI plus spacer (p-value = 0.56) (16). It is theorized that small diameter endotracheal tubes influence drug delivery due to deposition of medication but can be overcome with higher doses. Finally, this study also does not take into account the individual preferences of

children in terms of nebulization and use of a spacer. Some children find difficulty in sitting for 5 to 10 minutes during nebulization and find the noise produced by the device as frightening. Whereas some children may have difficulty with maneuvering the valve in some spacers. These factors should be considered by the clinician during decision-making

To summarize, we showed that the metered-dose inhaler (MDI) can be used as an alternative to the nebulizer for the delivery of salbutamol in pediatric severe asthma exacerbations. In majority of studies, it was shown to be comparable in outcomes with nebulization while study authors recommend it because it is convenient to use. The results with respect to lack of significant difference in outcomes was consistent with previously published systematic reviews and meta-analysis (14). Apart from the clinical response, the physician should also consider different individual factors that may influence the choice between the use of MDI with spacer and nebulization.

CONCLUSION AND RECOMMENDATIONS

This study shows that there appears to be no major differences in terms of efficacy and side effects between MDI and nebulization with salbutamol. However, we acknowledge the limitations in the review due to the limited quality of evidence available to come up with a meta-analysis. Furthermore, different standards were used among studies to define asthma severity. It was difficult to compare effects of medication due to the variety of treatment protocols and doses used in the studies included. The lower dose needed in MDI delivery may support favorability due to cost effectivity and efficiency. Also, it may have led us to underestimate the clinical effect of MDI with spacer. In conclusion, despite the lack of evidence showing the superiority of MDI in the treatment of severe asthma, there may be some evidence to support that they are

statistically equal in terms of hospital admission, pulmonary scores, clinical improvement, and side effects. This should guide the clinician in decision making when treating severe asthma amongst other factors such as feasibility, availability, and applicability. Clinical trials have been found underway to provide more evidence in support of the best delivery method for bronchodilators in management of severe asthma. Once enough research is made available, the author recommends revisiting this study for a possible meta-analysis. In addition, parental and child acceptance and tolerance are also factors that influence physician decision-making and may be worth exploring.

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TABLE 1: INCLUSION AND EXCLUSION CRITERIA FOR INCLUDED STUDIES

Inclusion Criteria	Exclusion Criteria
Target population Children 0 to 18 years old diagnosed with asthma in moderate to severe exacerbation consulting at a primary or tertiary care institution **Type of intervention** Salbutamol delivery through MDI with spacer Comparator: Salbutamol delivery through nebulizer **Type of studies** Randomized controlled study **Types of outcomes** Hospital admission rate, pulmonary score, change in respiratory rate, pulse rate, and oxygen saturation, immediately after intervention, incidence of tachycardia, and lung function.	Articles published in non-English language Observational studies or randomized trials which are cross-over in design

TABLE 2. RISK OF BIAS JUDGEMENT FOR A SPECIFIC OUTCOME

Overall risk of bias judgment	Criteria
Low risk of bias	The study is judged to be at low risk of bias for all domains for this result
Unclear risk of bias	The study is judged to be at some concerns in at least one domain for this result
High risk of bias	The study is judged to be at high risk of bias in at least one domain for this result OR the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result

TABLE 3. CHARACTERISTICS OF STUDIES INCLUDED

STUDY ID (Author, year, location)	Study title	Population	Method/Design	Comparator	Intervention	Study outcomes
A Leversha A.M., Campanella, S.G., Aickin, R.P., Asher, M.I. 2000 Starship Children's hospital in Auckland, New Zealand	Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma	Inclusion 1 to 4 yrs. old in moderate to severe exacerbation, known history of asthma Exclusion -Received inhaled bronchodilator 1 hr. prior to admission - coexisting pneumonia	Randomized, double-blind, placebo-controlled trial	Nebulizer of 600 mcg salbutamol + NSS	MDI with spacer of 2.5 mg salbutamol	Heart rate, respiratory rate, oxygen saturation, clinical severity score, wheezing, tremor, hyperactivity, admitted or discharged
B Vilarinho, L.C.S, Mendes, C.M.C, Souza, L.S.D 2003 Centro Pediatrico Prof Hossana de Oliveira, Brazil	Metered-dose inhalers with home-made spacers versus nebulizers to treat moderate wheezing attacks in children	Inclusion Children up to 12 yrs. of age, with moderate wheezing crisis Exclusion Use of bronchodilators or corticosteroids, severe chronic disease such as GERD, cystic fibrosis, cardiopathy, immune deficiency	Randomized, single-blinded trial	Nebulizer with 250 mcg/3kg in 5ml saline solution	MDI with spacer of 100mcg/ /3kg weight of salbutamol	Level of consciousness, skin color, intensity of dyspnea and retractions of the chest muscles, expiratory period, air entry, wheezing, o2saturation
C Jamalvi, S.W., Raza, S.J., Naz, F., Shamim, S., Jamalvi, Z. 2006 National Institute of Child Health, Pakistan	Management of acute asthma in children using metered dose inhaler and small volume nebulizer	Inclusion 6 months to 15 years with acute asthma exacerbation Exclusion ICU requiring, PEFR <20% or >70%, O2 saturation < 90%, received daily treatment with corticosteroids	Cross-sectional study	Nebulization of salbutamol (0.3 mg/kg) with 2ml normal saline	MDI with spacer of salbutamol 100mcg, 2 puffs for 3 times	Dyspnea and retractions, respiratory rate, heart rate, wheeze, blood pressure, o2 saturation, PEFR, pulmonary score
D Iramain, R., Castro-Rodriguez, J.A., Jara, A., Cardozo, L., Bogado, N., Morinigo, R., De Jesus, R. 2018	Salbutamol and ipratropium by inhaler are superior to nebulizer in children with severe acute asthma exacerbation: randomized clinical trial	Inclusion 2-18 yrs. old with severe acute asthma exacerbation Exclusion Radiologic pneumonia, pulmonary and or cardiac congenital malformations,	Randomized, double-blinded	Nebulization of salbutamol (0.15 mg/kg) in 5ml Normal saline, 7mins every 20 mins for 2h then every 30 mins for 2 more hrs.	MDI with spacer of salbutamol 100mcg, 2 puffs every 10 mins for 2 hrs. then every 30 mins for 2 hrs.	Pulmonary score, oxygen saturation

Hospital Clinicas and Instituto Privado del Nino, Paraguay		chronic pulmonary disease, foreign body aspiration, neurologic alteration, very severe acute asthma exacerbation requiring intubation				

TABLE 4. SUMMARY OF OUTCOMES FOR HOSPITAL ADMISSION

Study	Outcome	p-value
A (Leversha et al.)	33% required hospital admission with MDI and spacer 60% required admission with nebulizer	=0.04
B (Vilarinho et al.)	9% required hospital admission with MDI and spacer 15 % required hospital admission nebulizer	=0.19
C (Jamalvi et al.)	4.8% required hospital admission with MDI and spacer 10.6% required hospital admission with nebulizer	=0.185
D (Iramain et al.)	Higher hospitalization in the nebulization group versus the NBI group (RR 0.21 [0.6-0.69])	=0.003

TABLE 5. SUMMARY OF OUTCOMES FOR PULMONARY SCORES

Study	Outcome	p-value
A (Leversha et al.)	Clinical severity score based on wheeze, heart rate, and accessory muscle use Less 2.9 in MDI with spacer group Less 2.7 in nebulizer group	0.55
B (Vilarinho et al.)	Global score based on level of consciousness, skin color, retraction, dyspnea, expiratory period, air entry, wheezing, and oximetry Less 3.68 for MDI with spacer group Less 3.15 for nebulizer group	0.55
C (Jamalvi et al.)	Medical scoring system based on heart rate, respiratory rate, pulsus paradoxus, dyspnea, accessory muscle use, wheeze Less 3.8 for MDI with spacer group Less 3.7 for nebulizer group	n/a
D (Iramain et al.)	Pulmonary score based on wheeze, heart rate, and accessory muscle use Less 4.54 for MDI with spacer group Less 2.91 for nebulizer group	<0.00001

TABLE 6. SUMMARY OF OUTCOMES FOR VITAL SIGNS

STUDY	OUTCOME	P-Value
	Heart rate change compared with baseline	
A (Leversha et al.)	Higher 2.4 bpm in MDI with spacer group Higher 10.5 bpm in nebulizer group	<0.01
B (Vilarinho et al.)	Not reported	
C (Jamalvi et al.)	Lesser 18 bpm in MDI with spacer group Lesser 17 bpm in nebulizer group	=0.188
D (Iramain et al.)	Lesser 11.86 bpm in MDI with spacer group Higher 15.66 bpm in nebulizer group	<0.00001
	Respiratory rate change compared with baseline	
A (Leversha et al.)	Higher 0.3 cpm in MDI with spacer group Lesser 0.9 cpm in nebulizer group	insignificant
B (Vilarinho et al.)	Lesser 7.4 cpm in MDI with spacer group Lesser 8.8 cpm in nebulizer group	=0.93
C (Jamalvi et al.)	Lesser 22 cpm in MDI with spacer group Lesser 21 cpm in nebulizer group	=0.133
D (Iramain et al.)	Not reported	
	Oxygen saturation percent change compared with baseline	
A (Leversha et al.)	Higher 0.7% in MDI with spacer Higher 1% in nebulizer group	insignificant
B (Vilarinho et al.)	Higher 2.52% in MDI with spacer Higher 1.3% in nebulizer group	=0.29
C (Jamalvi et al.)	Not reported	
D (Iramain et al.)	Higher 10% in MDI with spacer Higher 6.75% in nebulizer group	<0.00001

TABLE 7. SUMMARY OF SIDE EFFECTS

Study	Outcome	p-value
A (Leversha et al.)	HR higher by 0.17 bpm with MDI group HR higher by 11 bpm with nebulizer group	<0.010
B (Vilarinho et al.)	Not reported	<0.06
C (Jamalvi et al.)	HR 110 bpm with MDI group HR 107 bpm with nebulizer group	=0.188
D (Iramain et al.)	HR 144.7692 bpm with MDI group HR 172.2 bpm with nebulizer group	<0.00001

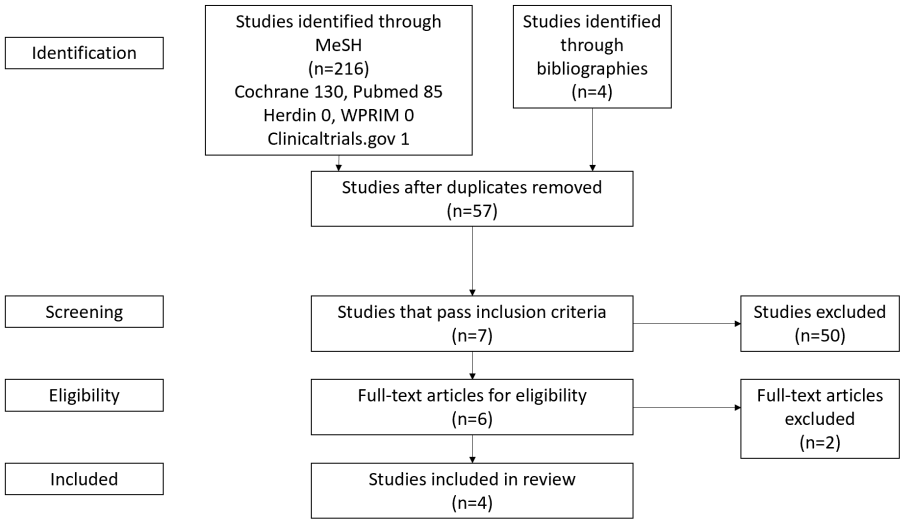

FIGURE I: PRISMA FLOW DIAGRAM OF STUDY SELECTION PROCESS

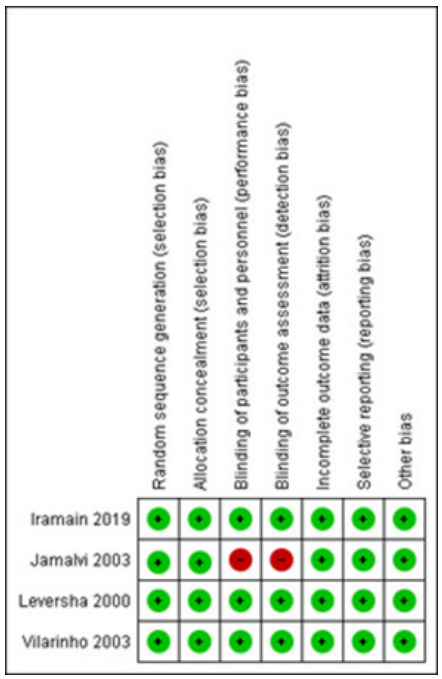

FIGURE II: RISK OF BIAS ASSESSMENT

THE UTILITY OF A CHEST RADIOGRAPH IN SCREENING COVID-19 PATIENTS IN A PEDIATRIC TERTIARY GOVERNMENT HOSPITAL

JANELLA M. TIU, FATIMA I. GIMENEZ

ABSTRACT

Background: COVID-19 continues to be a pandemic to this time, and chest radiography has been used as a first-line triage tool due to long turnaround times of real-time reverse transcription polymerase chain reaction (RT-PCR). Chest x-ray (CXR) alone has poor sensitivity in diagnosing COVID-19, though pediatric studies on this are scarce.

Objective: To evaluate the usefulness of a routine CXR as an adjunct to diagnosing suspected pediatric COVID-19. The radiographic characteristics in pediatric COVID-19 patients are also presented.

Methods: A cross-sectional study involved a retrospective chart review of 259 pediatric patients admitted in a tertiary hospital with COVID-19 signs and symptoms, with baseline CXR and SARS-CoV2 RT-PCR tests. Correlation of signs and symptoms with CXR findings to RT-PCR positivity was determined using univariate and multivariate logistic regression analysis.

Results: The study was composed of 259 pediatric patients (ages 0-18 years old). Of these, 35 had positive findings with RT-PCR (15%). Sensitivity of a CXR with pneumonia is at 62.9%, while specificity is at 39.3%. Overall accuracy of CXR findings leading to RT-PCR positivity is 42.5%. Ground glass or hazy opacities was the most common radiographic finding (45.5%), followed by reticular opacities (31.8%). Abnormalities were mostly distributed in the inner lung zone distribution with bilateral involvement (90%). Those with difficulty of breathing were more likely to have pneumonia on their CXR, though a finding of pneumonia on CXR did not significantly correlate to a positive RT-PCR.

Conclusion: Findings of pneumonia on a pediatric CXR may not necessarily lead to a positive SARS-CoV2 RT-PCR but correlating this with the patient's clinical course and symptoms may be beneficial in effectively triaging patients at the emergency room.

Keywords: covid-19, coronavirus, pediatric, children, radiograph, chest x-ray, CXR, screening, sensitivity, specificity

INTRODUCTION

COVID-19 was declared by the World Health Organization as a pandemic last March 2020 and since then, cases continue to rise worldwide with over 140 million cases in 219 countries and 3 million deaths as of April 2021.[1] In the Philippines, there have been over 900,000 COVID-19 confirmed cases with a ranking of 26th in countries with most cases, with over 15,000 deaths since the last year. The pandemic is still ongoing, and in the last 12 months, various advances in medical knowledge about the disease course, diagnostics and treatment regimen have been done globally. Diagnostic technologies have become widely available, but the gold standard remains to be the reverse-transcription polymerase chain reaction (RT-PCR). This method has several limitations: a relatively slow turnaround time (average of 2-7 days), with high cost and limited testing capacity in many countries.[2] Other imaging modalities, such as the chest radiograph, chest CT scan[3] and lung ultrasound[4,5] was found to be useful to assess clinical features, predict likelihood of COVID-19, and detect disease severity and progression in various studies in adults.

In the pediatric population, chest findings are mostly nonspecific. Children seem to have milder forms of the disease, with a wider spectrum of clinical findings, lower hospitalization rates and lower mortality.[6] Because children appear to be less infected with COVID-19, studies are scarce as to the use of chest imaging in this population. Meanwhile, the recommendations from the American College of Radiology still do not include chest CT or CXR as an upfront test to diagnose pediatric COVID-19, but they may still have a role in clinical monitoring.[7] A chest CT is also not recommended as an initial diagnostic test for children with known or suspected COVID-19 pneumonia due to increased radiation sensitivity in children, as compared to adults, and increased cost and unavailability of CT scan machines.[8] A CXR

can be useful in the clinical decision and management of children with suspected COVID-19, with lesser radiation risks and more readily available results.

Cases of COVID-19 in both the adult and pediatric population remain a problem in the country and worldwide. Problems with classification of these patients become inevitable, requiring immediate availability of RT-PCR results. Turnaround time of RT-PCR results is usually slow ranging from 24 hours to several days. A more readily available option is the chest x-ray with results becoming available within three to six hours. As an admission policy of the Philippine Children's Medical Center formulated in response to the pandemic, all patients to be admitted will have to be assessed at the triage if he/she is a COVID-19 suspect. This will determine where the patient will be admitted, either in the COVID ward or in the regular ward. Whether or not the patient presented with COVID-19 symptoms or not, all are required to have a baseline chest x-ray. If the chest x-ray result shows pneumonia, he/she is tagged as a COVID-19 suspect. In local hospital data, patients with a normal CXR eventually turn out COVID-19 positive on RT-PCR upon subsequent testing. On the other hand, some admitted patients with abnormal CXR results subsequently turn out COVID-19 negative. It is left to the clinician's discretion for the treatment of these cases. We aimed to evaluate the usefulness of a routine chest radiograph as an adjunct to screening COVID-19 suspect patients upon admission, while awaiting the result of the RT-PCR.

OBJECTIVES OF THE STUDY

General Objective

- To evaluate the usefulness of a routine chest radiograph as an adjunctive screening tool in diagnosing suspected COVID-19 in a pediatric population

Specific Objectives

1. To describe the most common radiographic findings among confirmed COVID-19 pediatric patients
2. To determine the sensitivity, specificity, positive and negative predictive values, and likelihood ratio of a CXR finding and correlate it with the signs and symptoms of confirmed COVID-19 pediatric patients
3. To determine the risk factors for COVID-19, correlating the most common signs and symptoms, comorbidities and a positive CXR finding.

METHODS

This was a cross-sectional diagnostic study design which included a chart review of COVID-19 suspect admissions from March to December 2020 in a pediatric tertiary government hospital. Target population were pediatric patients admitted as COVID-19 suspects at a tertiary government hospital from March to December 2020, who had a CXR and SARS-COV2 RT-PCR done during admission. Inclusion criteria were all pediatric patients 0 to 18 years of age of either sex, who presented at the triage/ER with signs and symptoms of COVID-19 (fever, cough, dyspnea, sore throat, coryza, diarrhea, myalgia, anorexia, nausea, vomiting, headache, altered mental status), with or without co-morbidities, who were admitted as a COVID-19 suspect case, with a chest x-ray and SARS-COV2 RT-PCR test done during admission. Admitted patients who had no COVID-19 symptoms but had a standalone finding of pneumonia on chest x-ray were also included in this study. Exclusion criteria were those who did not consent for admission to COVID ward, those who refused to undergo a chest x-ray and a SARS-COV2 RT-PCR test at admission, those with inaccessible CXR and SARS-COV2 RT-PCR results, and those who died at the triage and had no chest x-ray and

RT-PCR test done. Those who were admitted initially as a non-COVID-19 case, but subsequently developed COVID-19 symptoms and was tagged as a COVID-19 suspect during their hospitalization were excluded from this study. Considering all admissions to COVID ward from March to December 2020 as the total population of n=794, sample size was computed at 95% confidence level and 0.05 margin of error which requires a minimum of 259 subjects. Random sampling was applied to choose the 259 subjects and there were n=35 COVID-19 confirmed patients within the sample.

All admitted COVID-19 suspect patients were included until sample size was reached using systematic random sampling. The patient's demographics, including age, sex, signs and symptoms, comorbidities, date of admission, working diagnosis, chest x-ray result, SARS-COV2 RT-PCR result, and patient disposition (whether died or discharged) were recorded. The primary investigator obtained the list of patients from the hospital records, noting the demographics, signs and symptoms and comorbidities, official chest x-ray results and the SARS-COV2 RT-PCR results (positive or negative) upon admission. The description of the chest x-ray findings solely relied on the official result released by the primary reading radiologist. Any abnormal finding noted on the CXR, aside from the finding of pneumonia, was recorded as well. These were all gathered in a tabular form. From these data, the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio of the signs and symptoms together with the chest x-ray findings in those with positive SARS-COV2 RT-PCR results were computed.

Data was collected using random sampling of all COVID-19 suspect patients admitted in the institution from March to December 2020 until the sample size was reached. Instruments included the hospital's in-patient census, patient medical records, review of chest x-ray description and official results via the RAMSOFT application of the hospital, and the SARS-COV2 RT-PCR results via the COVID

laboratory list. All data was typed in a Microsoft Excel document and stored in the researcher's laptop. Information in the worksheet included the patients' identifiers (age, sex) with date of admission, admitting signs and symptoms, comorbidities, initial working diagnosis, official chest x-ray result and description, SARS-COV2 RT-PCR result and patient's disposition.

Descriptive statistics, such as mean and standard deviation were used to present continuous variables, while frequency and percentage were used for categorical data. Univariate and multivariate logistic regression were applied to determine risk factors for COVID-19, which included the signs and symptoms, comorbidities and a positive CXR finding. Correlation between these factors and a positive RT-PCR results was done via chi square test. Additionally, diagnostic values such as sensitivity, specificity, accuracy, AUC (Area under the curve) and likelihood ratio was provided to show the discriminatory capability of CXR in predicting positive RT-PCR results. Level of significance is at 5% while Medcalc Statistical software was used to carry out statistical calculations.

RESULTS

Among the 259 COVID-19 suspect patients, 35 (15%) were confirmed COVID-19 positive cases, while 224 patients (85%) were negative for COVID-19. The mean age of these patients (139 boys, 120 girls) was six years old, with a median of four years old (range 0 days to 18 years of age). Gender distribution is not significantly different, as both groups are mostly males. Among the total subjects, 62% had pre-existing comorbidities. Of these, 12% eventually turned out to be positive for COVID-19, while 88% were negative for COVID-19. The most common comorbidities were that of hematology/oncology, such as acute leukemia and solid organ tumors, followed by neurology, with epilepsy as the most common disorder. The top three most

frequent symptoms at the triage were difficulty breathing, fever and seizure. These are summarized in table 1.

Table 1. Profile of COVID-19 Suspects

	All (n=259)
Age (years), mean ± sd, (median)	5.98 ± 6.0
Sex, n, %	
Male	139 (53.7)
Female	120 (46.3)
Comorbidities	
With	161 (62.2)
Hematology/Oncology	47 (18.1)
Neurology	30 (11.6)
Gastroenterology	25 (9.7)
Renal Disease	19 (7.3)
Congenital Anomalies	13 (5.0)
Cardiovascular system	5 (1.9)
None	98 (37.8)
Signs and Symptoms	
Difficulty of breathing	65 (25.1)
Fever	52 (20.1)
Seizure	39 (15.1)

Table 2 summarizes the characteristics of the COVID-19 confirmed patients. 37% of these patients belonged to the one month to one year age group (13 of 35 patients), followed by those ages seven to 12 years at 20%. For the most common signs and symptoms at admission, nine of 35 (25.7%) presented with difficulty of breathing, six patients (17.1%) had fever, and five patients presented with seizure (14.3%). 57% of the confirmed COVID-19 patients have co-morbidities. The most common comorbidities associated with these patients include chronic liver disease and leukemia at 20%, followed by solid organ

tumors at 15% (ependymoma, Wilms tumor and teratoma). In the clinical classification of these patients, six patients were evaluated as having mild disease, 15 patients had moderate disease, three patients had severe disease, and 11 patients were considered critical. COVID-19 severity and outcomes are seen in table 2 with moderate classification being the most common among the subjects and 71% recovered from the illness.

Table 2. CHARACTERISTICS OF COVID-19 CONFIRMED PATIENTS

Parameters	N = 35	%
Age		
Newborn (<1 month)	3	9
1 month to 1 year	13	37
2 to 6 years	6	17
7 to 12 years	7	20
13 to 18 years	6	17
Presenting Signs & Symptoms		
Difficulty of breathing	9	25.7
Fever	6	17.1
Bleeding (Melena/Hematochezia)	6	17.1
Seizure	5	14.3
Vomiting	3	8.6
Loose bowel movement	2	5.7
Headache	2	5.7
Others	2	5.7
Abdominal pain	1	2.9
Comorbidities	20	57
Leukemia & solid organ tumors	7	35
Chronic liver disease	4	20
Epilepsy	3	15
Prematurity	2	10
Renal disease	2	10
Others (malnutrition, MSUD)	2	10
Classification of severity		
Asymptomatic	0	0
Mild	6	17.1
Moderate	15	42.9
Severe	3	8.6
Critical	11	31.4
Outcome		
Died	10	28.6
Recovered	25	71.4

22 of 35 patients demonstrated pneumonia on chest radiograph (63%), while 12 of 35 (34%) had normal chest findings, and only one patient had a finding of cardiomegaly (3%) (Table 3). Among those with pneumonia, ground glass or hazy opacities was the most common finding at 46%, followed by reticular or linear opacities at 32%, and reticulonodular appearance at 14%. One of 22 patients showed reticular opacities with concomitant bilateral pleural effusion, and only one patient showed a single consolidation pneumonia. 90% of pneumonia was found on the inner lung zones (central) with bilateral involvement (20 of 22), with only one finding of perihilar dominance and unilateral lung. Below are actual chest x-ray images showing the different radiographic findings (see figures 1 to 4).

Table 3. RADIOGRAPHIC FINDINGS OF COVID-19 CONFIRMED PATIENTS

Radiographic Findings	N = 35	%
Normal CXR	12	34.3
Cardiomegaly	1	2.8
Pneumonia	22	62.9
Pattern of lung opacities	N = 22	
Ground glass or hazy opacities	10	45.5
Linear or reticular opacities	7	31.8
Reticulonodular opacities	3	13.6
Reticular opacities with pleural effusion	1	4.5
Consolidation	1	4.5
Distribution	N = 22	
Perihilar dominant	1	4.5
Left lower lung involvement	1	4.5
Bilateral inner lungs	20	90.0

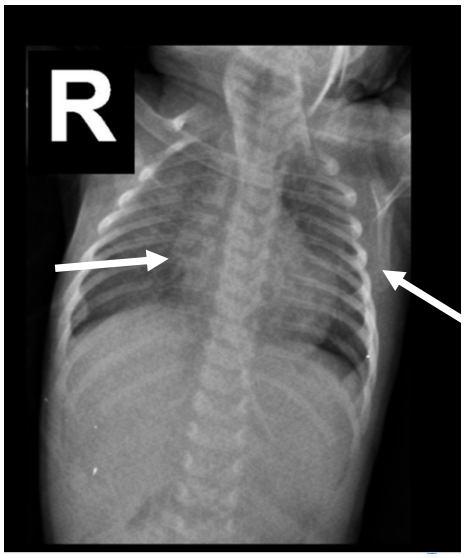

Figure 1. Pneumonia with ground glass opacities in the right lung and left upper lung (white arrows) in a 1 month old girl with a consideration of maple syrup urine disorder

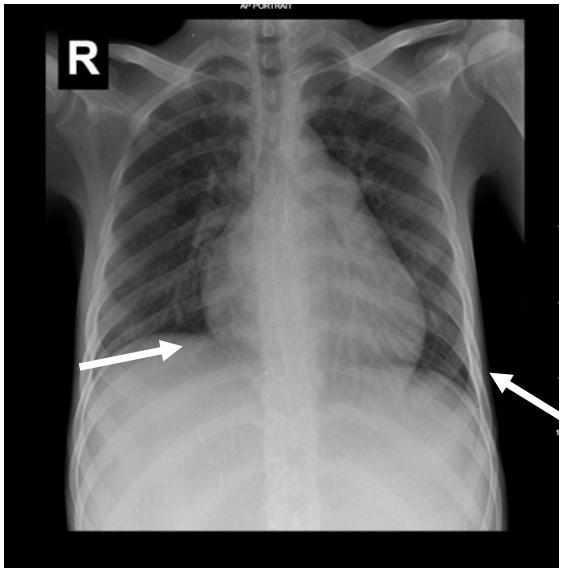

Figure 2. Pneumonia on bilateral inner lung zones showing reticular or linear opacities (white arrows) in a 16-year old male with chronic myelogenous leukemia

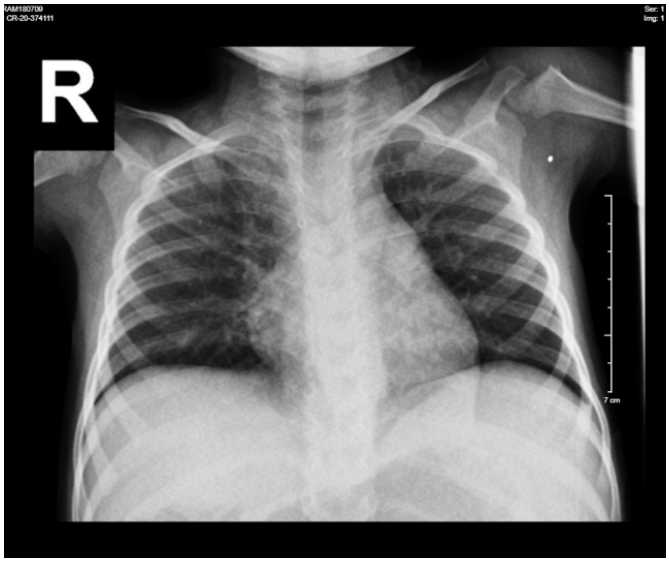

Figure 3. Pneumonia showing reticulonodular opacities (white arrows) in the bilateral inner lung zone distribution in a 3-year old boy with portal hypertension

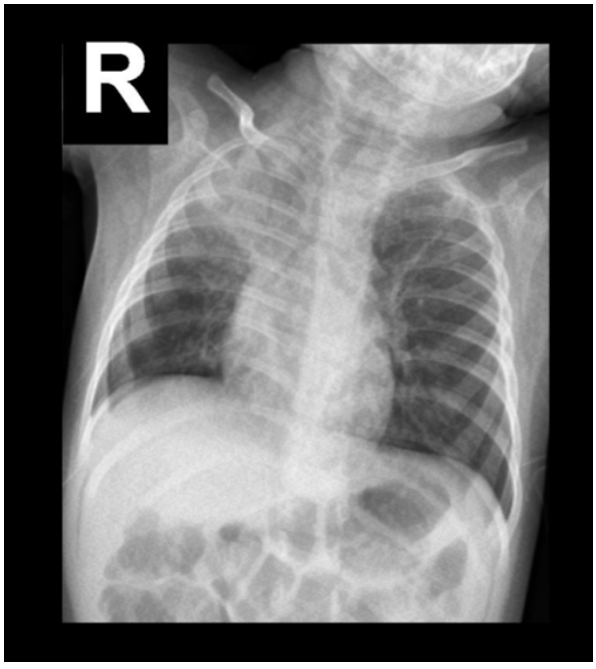

Figure 4. Pneumonia showing consolidation on the right upper lobe in a 6-month old boy with concomitant intussusception

Table 4 reveals the signs and symptoms of all the study subjects with their subsequent chest x-ray results. Only difficulty of breathing (p=.0001) had a significant association with having pneumonia on chest x-ray.

Table 4. ASSOCIATION OF SYMPTOMS AND CHEST X-RAY RESULTS

	Normal	Others	Pneumonia	p value
Signs and Symptoms				
Difficulty of breathing	8 (8.7)	4 (44.4)	53 (33.5)	0.0001*
Fever	25 (27.2)	1 (11.1)	25 (15.8)	0.0730ns
Seizure	15 (16.3)	1 (11.1)	21 (13.3)	0.8392ns
LBM	6 (6.5)	1 (11.1)	4 (2.5)	0.1137 ns
Bleeding	11 (12.0)	1 (11.1)	12 (7.6)	0.4113 ns
Abdominal related pain	3 (3.3)	0 (0.0)	10 (6.3)	0.6150 ns
Cough	2 (2.2)	0 (0.0)	7 (4.4)	0.6324 ns
Vomiting	6 (6.5)	0 (0.0)	7 (4.4)	0.7240 ns
Headache	1 (1.1)	0 (0.0)	3 (1.9)	1.0000 ns
Weakness	4 (4.3)	0 (0.0)	2 (1.3)	0.3516 ns
Edema	1 (1.1)	0 (0.0)	7 (4.4)	0.4477 ns
Poor Activity	3 (3.3)	0 (0.0)	1 (0.6)	0.2562 ns
Others	8 (8.7)	1 (11.1)	6 (3.8)	0.1725 ns

***significant,** ns not significant*

At presentation, each patient underwent both chest radiograph and RT-PCR testing. 158 of 259 patients (61%) had pneumonia on their chest x-ray, however, 136 (of 158, 86%) turned to be negative for RT-PCR. The sensitivity or the probability that the chest x-ray shows pneumonia when the RT-PCR result is positive is 62.86% (95% CI 44.92% to 78.53%), while the specificity or the probability that the chest x-ray is either normal or showed other findings when the RT-PCR is negative is only 39.29% (95% CI 32.85% to 46.01%). Overall accuracy is only 42.47% (95% CI 36.34% to 48.74%) while resulting area under the curve is only 0.51 (95% CI 0.45 to 0.57) with p value of 0.8379, denoting that

a chest x-ray cannot significantly discriminate positive from negative RT-PCR results. The probability that patients with pneumonia on CXR truly have COVID-19 (positive predictive value) is computed at 13.92% (95% CI 10.94% to 17.57%) and the probability that patients with normal CXR truly do not have COVID-19 (negative predictive value) is at 87.13% (95% CI 81.03% to 91.48%). Additionally, resulting positive and negative likelihood ratio are 1.04 (95% CI 0.79 to 1.36) and 0.95 (95% CI 0.60 t 1.50) respectively. See table 5.

Table 5. DIAGNOSTIC ACCURACY OF CHEST X-RAY RESULTS IN PREDICTING POSITIVE SARS-COV2 RT-PCR RESULTS

CXR results	Positive RT-PCR	Negative RT-PCR
Pneumonia	22 (62.9%)	136 (60.7%)
Others/Normal results	13 (37.1%)	88 (39.3%)
Total	35	224
	Values	95% CI
Sensitivity	62.86	44.92 to 78.53
Specificity	39.29	32.85 to 46.01
Accuracy	42.47	36.34 to 48.74
Positive Predictive Value	13.92	10.94 to 17.57
Negative Predictive Value	87.13	81.03 to 91.48
Positive Likelihood ratio	1.04	0.79 to 1.36
Negative Likelihood ratio	0.95	0.60 to 1.50
Area under the curve	0.51	0.45 to 0.57
p value	0.8379^{ns}	

^{ns} *not significant*

Univariate logistic results show that none of the variables, such as age, sex, comorbidities, signs and symptoms and chest x-ray results significantly predict positive RT-PCR results. Bleeding (p=.0919) turned out to have some potential to predict RT-PCR positivity (Table

6). Specifically, resulting odds ratio of 2.37 (95% CI 0.9 to 6.5) for bleeding symptoms suggest that having this symptom at admission slightly increases the chances of a positive RT-PCR. On chest x-ray findings, having pneumonia resulted to an odds ratio higher than one (1.07, 95% CI (0.5 to 2.3), which indicates that it can slightly increase the chances of positive RT-PCR results. Chest x-ray, together with the variables that have a p value of <0.20 were run on a multivariate logistic regression. Results show the top five signs and symptoms, and those who presented with these symptoms on admission, with a finding of pneumonia on CXR did not have any significant potential to affect COVID-19 positivity.

Table 6. DETERMINING PREDICTORS OF POSITIVE SARS-COV2 RT-PCR RESULTS

	SARS COV		Univariate			Multivariate		
	Positive	Negative	OR	95% CI	p value	OR	95% CI	p value
Age (years)	5.8 ± 5.9, (4.0)	6.0 ± 6.0, (4.0)	0.99	0.9 to 1.1	0.8567[ns]	-	-	-
Sex								
Male	21 (60.0)	118 (52.7)	1.35	0.7 to 2.8	0.4203 [ns]	-	-	-
Female	14 (40.0)	106 (47.3)	-	-	-			
Comorbidities								
With	20 (57.1)	141 (63.2)	0.78	0.4 to 1.6	0.4903 [ns]	-	-	-
None	15 (42.9)	82 (36.8)	-	-	-			
Signs and Symptoms								
Difficulty of breathing	9 (25.7)	56 (25)	1.04	0.5 to 2.3	0.9278 [ns]	-	-	-
Fever	6 (17.1)	46 (20.5)	0.8	0.3 to 2.0	0.6418 [ns]	-	-	-
Bleeding	6 (17.1)	18 (8.0)	2.37	0.9 to 6.5	0.0919 [ns]	2.55	1.0 to 55.2	0.0694[ns]
Seizure	5 (14.3)	32 (14.3)	1.00	0.4 to 2.8	1.0000 [ns]	-	-	-
Vomiting	3 (8.6)	10 (4.5)	2.01	0.5 to 7.7	0.3094 [ns]	-	-	-
Chest X-Ray Findings								
Normal	13 (37.1)	88 (39.3)	-	-	-			
Pneumonia	22 (62.9)	136 (60.7)	1.10	0.5 to 2.3	0.8090 [ns]	1.12	0.5 to 2.4	0.7655 [ns]

***significant,** *ns not significant*

DISCUSSION

This study reports the diagnostic accuracy of a chest x-ray as a screening tool in triaging pediatric patients during the COVID-19 pandemic. A chest x-ray is often the first imaging study used to evaluate a pediatric patient with signs and symptoms of respiratory distress, such as cough and fast breathing. Chest radiography, at least in adults, is less sensitive than a computed tomography scan in identifying COVID-19 pneumonia. However, we avoid CT scan as an initial imaging study in children due to increased radiation sensitivity and cost effectivity.[9] A CT scan is recommended when there are already findings in the CXR of a pediatric patient and with progressive clinical deterioration.

CXR alone has limited sensitivity (62.86%) and poor specificity (39.29%), with an overall accuracy of 42.5% in diagnosing COVID-19 in the pediatric population. This is consistent with other studies in the adult population were sensitivity ranged from 51.9% to 94.4% and specificity ranged from 40.4% to 88.9%.[10] This is in comparison to the gold standard, which is the SARS-CoV2 RT-PCR nasopharyngeal and oropharyngeal swab, where the sensitivity is between 71% to 98% and the specificity at 95%.[11] Of the 35 patients (of 259, 13%) who tested positive for COVID-19 with RT-PCR, 22 patients (63%) showed pneumonia on chest radiograph. The main feature of ground glass or hazy opacities on chest radiography in pediatric COVID-19-related pneumonia is consistent with previously published articles in both the adult and pediatric population, although, the distribution of lung opacities in adults are usually peripheral in location. In a study by Palabiyik, F.,[12] ground glass opacities were seen in 41% of pediatric patients, 5% with consolidation and 36% with a combination of both. Serrano et al also found central ground glass opacities in 85.7% of pediatric COVID-19 patients.[13] The Philippine Academy of Pediatric Pulmonologists describe typical pediatric chest findings for COVID-19 as: bilateral peripheral and/or subpleural ground-glass opacities and/or consolidation, while indeterminate findings are nonspecific and consist of unilateral or bilateral peripheral and central GGO and/or consolidation or bilateral peribronchial opacities, or diffuse GGO and/or

consolidation. Atypical findings, being uncommon, are described as unilateral lobar or segmental consolidation, central unilateral or bilateral GGO and/or consolidation, single round consolidation, presence of pleural effusion and/or lymphadenopathies.[14] Only one of 22 patients presented with consolidation on the right upper lobe of the lungs, and one of 22 patients showed pneumonia with bilateral pleural effusion. This study found that distribution is mostly central, rather than peripheral, in contrast to adults, which is consistent with atypical findings of pediatric COVID-19 in terms of distribution of radiographic lesions. Duan et al observed the same, that children often have a combination of peripheral and central distribution of pneumonia.[15] Serrano et al also concluded that peribronchial opacities were the most common finding in pediatric x-rays and may be a nonspecific response of the bronchus to any viral infection. Moreover, peripheral distribution in children may not be as common as in adults.[13] Among the COVID-19 positive patients, 34% still had normal chest x-ray findings. In a study by Foust et al., he noted pediatric chest radiography may show normal findings, along with the other typical findings. [9] This is consistent with the fact that imaging may not yet show any findings at the onset of the illness, especially without respiratory symptoms, even though the RT-PCR is positive.[15]

In children, symptoms of COVID-19 are often nonspecific, although fever and cough remain the most common symptoms worldwide. Other symptoms such as flu-like illness (nasal obstruction, runny nose), gastrointestinal symptoms, sore throat, myalgia, fatigue are variably common as well. Most may even be asymptomatic, and most children have been infected unknowingly. Of the 259 subjects, the three most common signs and symptoms at presentation were difficulty of breathing, fever and seizure. Among those who eventually became positive for COVID-19, difficulty of breathing, fever and bleeding were the top three. This study revealed that a patient presenting with difficulty of breathing may be more likely to have pneumonia on his/her chest x-ray, whichever gender, age or whether or not he/she had

comorbidities. Those who also presented with bleeding symptoms were more likely to be COVID-19 positive on swab test.

CONCLUSION

COVID-19 continues to be a pandemic to this time and the gold standard for diagnosis remains to be the SARS-CoV2 RT-PCR. A chest x-ray has limited sensitivity and specificity in its diagnosis in the general population; however, it is a reliable adjunctive tool for triaging patients who present at the emergency room. The most common finding in pediatric COVID-19 patients with pneumonia is ground glass or hazy opacities with central distribution and bilateral involvement, which is often accompanied by fever, difficulty of breathing, and bleeding. Once these are met at the presentation of a patient, COVID-19 is highly suspected and triaging may be easier. Overall, history taking and accurate clinical assessment remain vital in the care of pediatric patients during this pandemic, and with the benefit of a chest x-ray, this may provide the clinician with a prompt assessment and a more accurate disposition of patients.

This study had several limitations. First is that the patients were not followed through to their hospital course, and serial chest radiographs and repeat SARS-CoV2 RT-PCR swabs were not monitored and correlated to the patients' clinical outcomes. Second, since our subjects involved pediatric patients, reported signs and symptoms among the younger age group are based on the parents' reports alone, which may lead to inaccurate recording of symptoms at the onset. Third, the official CXR results were not verified by another radiologist. Therefore, recommendations include follow through of the clinical course of the patients, together with the serial imaging and swab procedures, to assess the sensitivity and specificity of chest x-ray through time and throughout the course of the COVID-19 illness, coinvestigation with another radiologist/s to review the chest x-ray results in consensus to validate findings and classify according to a severity grading system, and lastly, comparison of the accuracy between the use of CXR, chest CT and chest ultrasound may also be done in future studies.

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A META-ANALYSIS ON THE EFFECTIVENESS OF POSTOPERATIVE ANALGESIA WITH INTRATHECAL NALBUPHINE VERSUS INTRATHECAL FENTANYL AS NEURAXIAL ADJUVANTS IN CESAREAN SECTION

AILEEN P. BALATBAT, JOY ANN R. LIM

ABSTRACT

Background: Inadequately treated postoperative pain can contribute significantly to morbidity in women undergoing cesarean section. Recent studies showed that nalbuphine and fentanyl has promising result as neuraxial adjuvants in terms of postoperative analgesia and with lower incidents of adverse effect when use in cesarean section.

Objective: To compare postoperative analgesia with intrathecal nalbuphine versus intrathecal fentanyl as neuraxial adjuvants in cesarean section.

Methods: A meta-analysis following the PRISMA guidelines was performed. Articles were searched through the Cochrane Library, PubMed.Gov and Pubmed Central, Google Scholar, HERDIN, WPRIM and ProQuest Guideline Central using different search strategies such as keywords and MeSH term. 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.

Results: A total of four trials, involving 425 full term pregnant women were compared. The pooled mean difference showed significantly longer duration of postoperative analgesia (MD=21.12 minutes, 95%CI=11.13,31.11, I^2=73%), pooled risk ratio showed lesser risk for pruritus (RR=0.09, 95%CI=0.02,0.50, I^2 = 0%) and postoperative nausea and vomiting (RR=0.38, 95%CI= 0.19,0.78, I^2 = 11%) who received intrathecal nalbuphine compared to intrathecal fentanyl.

Conclusions: The results of this meta-analysis demonstrates that the use of intrathecal nalbuphine appears to have longer duration of postoperative analgesia and lesser incidence of PONV and pruritus than fentanyl. However, due to the presence of heterogeneity it warrants that the results should be treated with caution especially with the possibility of publication bias.

Recommendations: Better literature search through inclusion of high-quality studies from relevant databases and strict adherence on the uniformity of the dosage and methods used are very crucial to achieve the target clinical outcomes and minimize the publication bias.

Keywords: *Cesarean section; Nalbuphine; Fentanyl; Meta-analysis*

INTRODUCTION

In most cesarean section, spinal anesthesia is the preferred anesthetic due to its simplicity and safety. Its advantages include a conscious mother during delivery, minimal anesthetic exposure to the neonate, and avoiding the possible complications that may be caused by general anesthesia.(1) The main limitation, however, of spinal anesthesia is its short duration of action. It does not provide prolonged postoperative analgesia when it is only performed with local anesthetics. Inadequately treated postoperative pain can contribute significantly to morbidity of surgical patients, resulting in the delay of patients' recovery, functional capacity and ultimately additional hospital stay. Adding adjuvant drugs to intrathecal local anesthetics improves quality and duration of spinal blockade, and prolongs postoperative analgesia. It is also possible to reduce dose of local anesthetics, as well as total amount of systemic postoperative analgesics. It has been almost 40 years since neuraxial opioids first underwent rigorous clinical study for use in humans.(2). Preservative-free morphine is perhaps the most popular adjuvant administered via intrathecal or epidural route in many countries. It provides proven and significantly prolonged postoperative analgesia with a reduction in postoperative analgesic requirement. However, the estimated incidents of the adverse effects such as, pruritus, nausea, vomiting and respiratory depression are significantly high. Recent studies showed that the use of neuraxial opioids such as nalbuphine and fentanyl have a promising result in terms of postoperative analgesia and with lesser side effects when used in cesarean section. The findings of this study will give additional evidence-based information which can support and guide the administration of neuraxial opioids for pregnant patients to ensure an ideal balance of risks and benefits.

Nalbuphine is a mixed synthetic agonist antagonist which attenuates the μ-opioid effects and enhances the κ-opioid effects (3). Reports show that nalbuphine has no established neurotoxicity.(4) In a study conducted by Mukherjee et al. (2011), it was seen that intrathecal nalbuphine 0.4 mg used as an adjuvant

in subarachnoid block prolongs postoperative analgesia without increased side-effects.[5] Another study reported that intrathecal nalbuphine 0.8 mg can provide good intraoperative and early postoperative analgesia without significant side effects of postoperative nausea and vomiting (PONV) or pruritus.[6] In a more recent study, adding 1 mg nalbuphine to 12.5 mg hyperbaric bupivacaine is an effective postoperative analgesia with non-significant adverse effects in patients undergoing elective cesarean section. The rapid onset of sensory and motor block (1.95±.44 min) with slow regression of sensory block and time to Bromage I (211.6± 13.2 min) was seen in patients who received nalbuphine. Also, the analgesic time was noted to be 263.7± 16.3 with a high sedation score (1.78± 0.63).[7] On the other hand, fentanyl improves duration of sensory anesthesia and postoperative analgesia without causing significant side effects.[8],[9] In one study consisting of healthy parturients (n=70) with singleton pregnancy scheduled for elective cesarean section, it was found out that the duration of sensory block was prolonged in group which received adjuvant fentanyl (p-value < 0.05) with bupivacaine as compared to the group which received subarachnoid block with 0.5% bupivacaine alone. Also, effective analgesia (134 ± 5.6 minutes versus 164 ± 9, p-value =0.00) were also prolonged in the fentanyl group. It was then concluded that addition of fentanyl to intrathecal bupivacaine during cesarean section increases the duration of postoperative analgesia without increasing risk for maternal or neonatal complications.[10] In another study, women scheduled for cesarean section (n= 40) received either 0.5% bupivacaine or isobaric bupivacaine with fentanyl added. Results showed that peak sensory level was lower and motor block was less intense in the bupivacaine-fentanyl group. On the other hand, patients from standardized bupivacaine groups were more likely to require treatment for hypotension (75% versus 15%) and had more persistent hypotension (4.6 versus. 1.0 hypotensive measurements per patient) than patients in the bupivacaine-fentanyl group. Also, more emetic effects were reported in the bupivacaine group than the bupivacaine-fentanyl

group. It was concluded that bupivacaine plus fentanyl can provide better spinal anesthesia for CS with less hypotension and vasopressor requirements.[11] However, as of this writing there has been no pooled data on the comparison of intrathecal nalbuphine versus intrathecal fentanyl as neuraxial adjuvants in cesarean section published. This study aims to compare the effectiveness of postoperative analgesia with intrathecal nalbuphine versus intrathecal fentanyl as neuraxial adjuvants to cesarean section.

METHODOLOGY

This meta-analysis conducted the following guidelines of Cochrane Handbook and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Guidelines. All studies with a target population of female adult patients (at least 18years old, ASA Physical Status I and II, term pregnancy) who underwent elective cesarean section under spinal anesthesia were included. However, studies whose participants were less than 18 years old, preterm pregnancy, with known fetal abnormality, cardiovascular and cerebrovascular disease, renal disease, allergy to study medication and refused to participate were not included in the analysis. The primary intervention dose used was of 0.8 mg to 1 mg of intrathecal nalbuphine combined with 2ml 0.5% hyperbaric bupivacaine or 2ml 0.75% isobaric ropivacaine given during induction of spinal anesthesia. The comparator dose used was 20 mcg to 25 mcg intrathecal fentanyl combined with 2 ml 0.5% hyperbaric bupivacaine or 2ml of 0.75% isobaric ropivacaine. Both groups did not receive any other intervention that interfered in the outcome of the study. The primary outcomes were duration of analgesia in minutes and total analgesic requirement. Secondary outcomes were onset of sensory block, onset of motor block, incidence of maternal side effects (postoperative nausea and vomiting (PONV), pruritus and hypotension) and fetal side effects (Apgar score)

Randomized controlled trials comparing the effectiveness of post-operative intrathecal nalbuphine versus intrathecal fentanyl in cesarean section were included. Non-comparative clinical trials, outcomes research or real-world data,

animal experiments, and reviews were not included. Duplicate studies or those that were republished, observational studies, case reports or series, and other types of publications were removed. Two review authors independently screened the abstracts and titles of yielded studies with reference to the specified eligibility criteria (see Annex A). No disagreements happened between the reviewers. Assessment for risk of bias was preformed using the Review Manager program, and version 2 of the Cochrane risk-of-bias tool for randomized trials tool (RoB 2.0). Each included article was independently 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. Discrepancies in the included studies were resolved by reexamination of the original articles and through discussion. Investigator and co-investigator performed data extraction. Extracted data on study design, patient population, facility location, comparator, intervention, and all outcomes measured were tabulated (Table 2). A literature search from various search engines and electronic databases such as PubMed, Cochrane CENTRAL, Google Scholar, Proquest, Guideline Central, WPRIM, and local websites such as Herdin Plus were done. Included studies were also searched for relevant citations. The database medRvix was searched. Grey literature was searched to identify studies not indexed in the databases listed above. Anesthesia consultants were asked for possible reference articles or unpublished studies. Reference and citation lists of the eligible studies have been reviewed also to further look for relevant articles. 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. The meta-analysis was performed using the Reviewer

Manager Software, version 5. (Cochrane Collaboration, UK). All data were analyzed using a random-effects model due to clinical or methodological heterogeneity. Mean difference for mean duration of analgesia between the groups was used. Relative risk for nausea, vomiting, pruritus and hypotension 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 1,128 references. Most articles were excluded due to different study designs, population, and other outcomes used. Twelve full text articles were reviewed for eligibility. Out of the twelve, six full text articles were excluded due to different surgical procedures, two were excluded due to incomplete data. A total of four (4) studies were then included in the analysis. A flowchart of study selection is summarized in Figure 1 below.

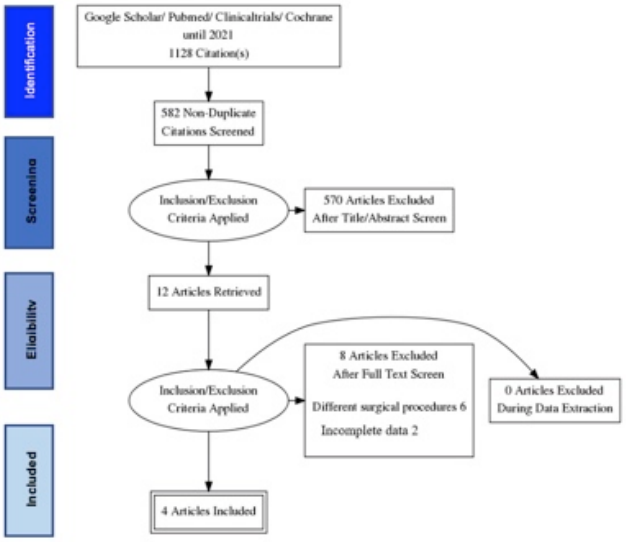

Figure 1. PRISMA diagram for study screening and selection

This meta-analysis included 4 randomized controlled trials (RCT), comparing the effect of postoperative analgesia of intrathecal nalbuphine versus intrathecal fentanyl as neuraxial adjuvants in caesarean section. Population, intervention, control and other details of the study are included in Table 2.

This study encompasses data for 425 women, wherein 165 of them were randomized to nalbuphine, while 165 were randomized to fentanyl and the remaining 95 fall into placebo arm. The population of these trials range from 60 (Gomaa et al) to 150 (Bindra et al) full term pregnant women scheduled for elective caesarean section.

Table 2. Characteristics of Studies Included in the Meta-Analysis

STUDY ID Author, Year, Location	Study Title	Population	Method/Design	Group Sample Sizes	Comparator	Intervention	Placebo arm	Study Outcomes
A Mohamed, etal 2021 Egypt (Department of Anesthesia, Surgical ICU and Pain Management, Cairo University	A comparison between intrathecal nalbuphine and fentanyl for intraoperative pain management during uterine exteriorization in cesarean section: a randomized	Inclusion: Full term parturients, ASA I and II, aged 20-45 years, weight 60-100 kgs, height 160-180 cm, for elective cesraean section under spinal anesthesia Exclusion: ASA III and IV, coagulopathies, uncooperative, allergy to local anesthetics, cardiac disorder, cns illness, preterm, small birthweight	Randomized controlled trial	Nalbuphine = 45 Fentanyl = 45 Normal saline = 45	0.5% hyperbaric bupivacaine + nalbuphine 800 mcg (Volume of 0.5% hyperbaric bupivacaine was determined by patient's weight and height table 1.3 ml -2.2 ml)	0.5% hyperbaric bupivacaine + fentanyl 25 mcg (Volume of 0.5% hyperbaric bupivacaine was determined by patient's weight and height table 1.3ml -2.2 ml)	0.5% hyperbaric bupivacaine + 0.5 ml normal saline (Volume of 0.5% hyperbaric bupivacaine was determined by patient's weight and height table)	Duration of effective analgesia, VAS for visceral abdominal, total fentanyl used as rescue analgesia, number of patients required rescue fentanyl, onset of sensory and motor block, hypotension,brady cardia, pruritus, nausea, vomiting shivering, APGAR score
B Ahmed 2019 Egypt (Department of Anesthesia and Surgical Intensive Care, Zagazig University)	Intrathecal nalbuphine versus fentanyl as an adjuvant to bupivacaine in spinal anesthesia for elective cesarean section: a randomized double blind study	Inclusion: full term singleton parturients, ASA I and II, aged 20-40 years, for elective cesarean section under spinal anesthesia Exclusion: Aged <20 or >40 years, contraindications to spinal anesthesia, morbid obesity, emergency cs, complicated pregnancy, intrauterine fetal compromise	Randomized double blind study	Nalbuphine = 40 Fentanyl = 40	12.5 mg of 0.5% hyperbaric bupivacaine + fentanyl 25 mcg	12.5 mg of 0.5% hyperbaric bupivacaine + nalbuphine 800 mcg	None	Duration of postoperative analgesia and consumed analgesic dose post op, onset of sensory and motor block, incidence of pruritus, shivering, PONV, sedation, hypotension, bradycardia and neonatal APGAR score
C Bindra, etal. 2018 Punjab, India (Department of Anesthesia and Critical Care, GMC, Paitala)	Postoperative Analgesia with Intrathecal Nalbuphine versus Intrathecal Fentanyl in Cesarean Section: A Double-Blind Randomized Comparative Study	Inclusion: Full term parturients, ASA I and II, aged 20-45 years, normal coagulation profile, for elective cesarean section under spinal anesthesia Exclusion: Contraindication for spinal anesthesia	Randomized double-blind, controlled study	Nalbuphine = 50 Fentanyl = 50 Normal saline = 50	2 ml 0.5% hyperbaric bupivacaine (10mg) + 0.4 ml fentanyl (20 mcg)	2 ml 0.5% hyperbaric bupivacaine (10mg) + 0.4 ml nalbuphine (0.8mg)	2ml 0.5% hyperbaric bupivacaine + 0.4 ml normal saline	Duration of effective analgesia, number of rescue analgesics, onset of sensory and motor block
D Gomaa, etal. 2014 Egypt (Kasr Al Ainy Hospital, Cairo University, Ahmed Maher Hospital, Cairo University)	A comparison between post-operative analgesia after intrathecal nalbuphine with bupivacaine and intrathecal fentanyl with bupivacaine after cesarean section	Inclusion: Full term parturients. ASA I and II, Aged 20-45 years, weight 60-90 kgs, height 160-180 cm, normal coagulation profile, for elective cesarean section under spinal anesthesia Exclusion: ASA III and IV, patient refusal, infection at the injection site, coagulopathy, anticoagulant medications, pre existing neurological disease, uncooperative patients, cardiac or respiratory system failure, allergy to local anesthetics	Double Blind Randomized Comparative Study	Nalbuphine = 30 Fentanyl = 30	2 ml 0.5% hyperbaric bupivacaine + 0.5 ml fentanyl (25 mcg)	2ml 0.5% hyperbaric bupivacaine +0.5 ml nalbuphine (0.8 mg)	None	Duration of analgesia, sensory and motor block, effective analgesic time, incidence of hypotension, nausea, vomiting, pruritus, shivering, and fetal APGAR score

Risk of bias of the selected articles was judged based on Risk of bias tool (ROB 2.0) and Review Manager 5.0 bias assessment tool. Two out of the four included studies in this paper had minimal risk of bias while the other two studies had high risk of bias based on five different domains as summarized in Figure 2. Sensitivity analysis performed for the primary outcome by excluding the studies with high risk of bias did not affect the conclusion.

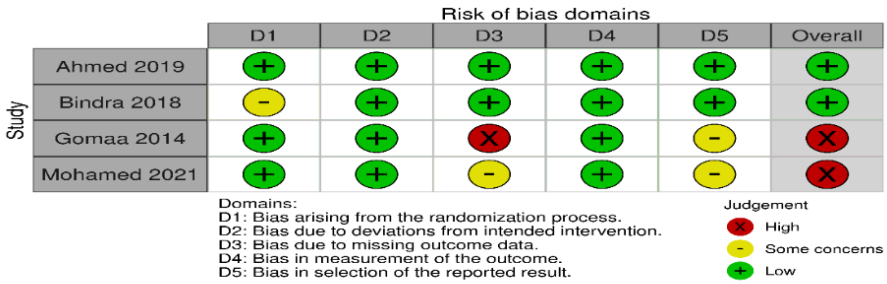

Figure 2. Risk of bias summary of included studies

Comparison of Outcomes

Primary Outcome: *Effect on the duration of postoperative analgesia*

Mean duration of effective analgesia (in minutes) for both intervention group and comparator were primarily pooled in this study, in which the overall effect estimate was calculated as the mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects model. Figure 3 indicates that patients who had **intrathecal nalbuphine as neuraxial adjuvant during cesarean section had significantly longer duration of analgesia** compared to fentanyl group (MD=21.12 minutes, 95%CI=11.13,31.11, p-value<0.0001). Intrathecal nalbuphine used as a neuraxial adjuvant in cesarean section can prolong the duration of postoperative analgesia by an average of 21.12 minutes compared to intrathecal fentanyl. The level of heterogeneity using I^2 was 73% (moderate) although the forest plot showed that all included studies leaned more towards nalbuphine than fentanyl group. (Figure 3)

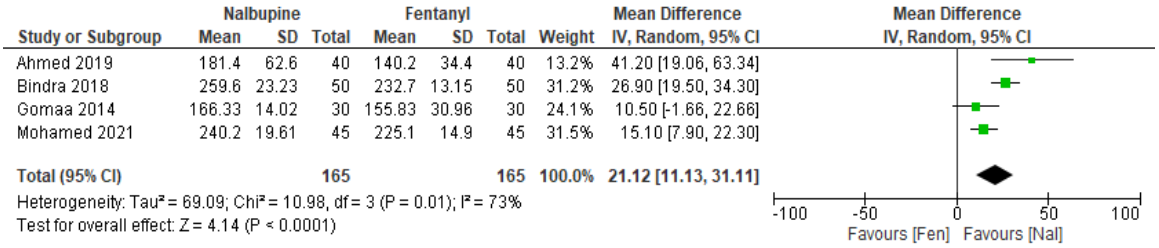

Figure 3. Meta-analysis on the effect on duration of postoperative analgesia

A sensitivity analysis omitting 1 study at a time was done to check for possible causes of heterogeneity by: 1) bupivacaine hyperbaric spinal dose 2) fentanyl dose and 3) high risk of bias. Ahmed's trial used a higher spinal dose of bupivacaine hyperbaric (12.5 mg), Bindra's used a different fentanyl dose (20 mcg), and Gomaa's trial and Mohamed trial due to 3) high risk of bias. Ahmed's trial, Bindra's trial, Gomaa's trial and Mohamed's trial were removed from the sensitivity analysis as shown in Figure 4,5,6 and 7 in which none of the individual studies eliminated the heterogeneity.

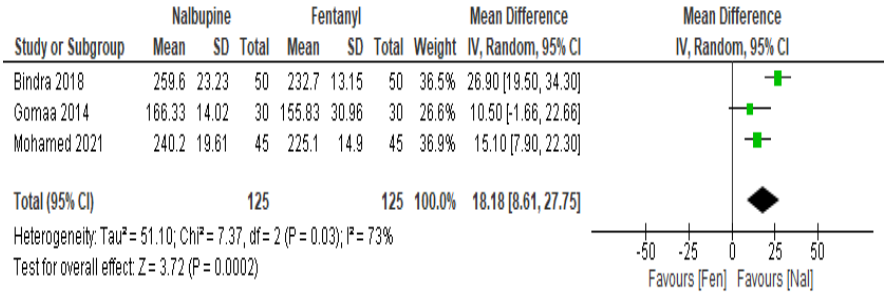

Figure 4. Sensitivity analysis on the effect on duration of postoperative analgesia excluding Ahmed's trial

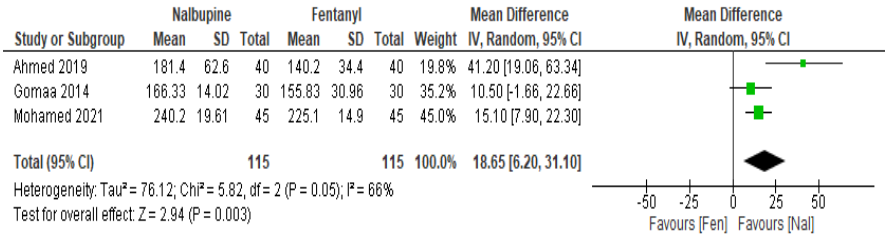

Figure 5. Sensitivity analysis on the effect on duration of postoperative analgesia excluding Bindra's trial

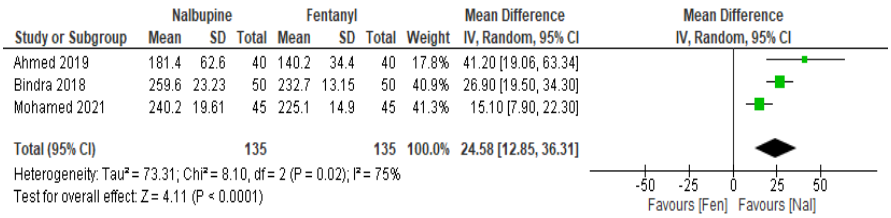

Figure 6. Sensitivity analysis on the effect on duration of postoperative analgesia excluding Gomaa's trial

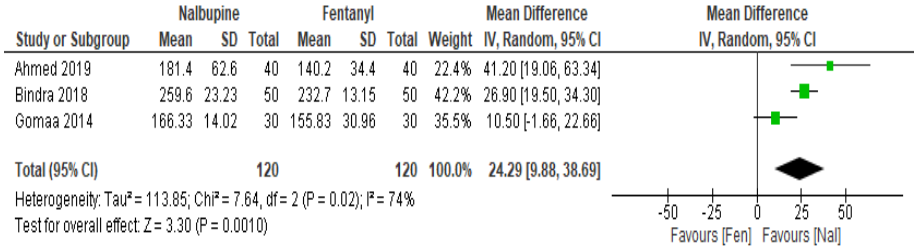

Figure 7. Sensitivity analysis on the effect on duration of postoperative analgesia excluding Mohamed's trial

Secondary Outcome 1: *Effect on time for the onset of sensory block*

Mean onset of sensory block for both intervention group and comparator group were primarily pooled. The overall effect estimate was calculated as the mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects method. All the included studies reported the mean time for onset of sensory block among patients who received intrathecal nalbuphine and intrathecal fentanyl during cesarean section. As shown in Figure 8, the overall the pooled mean difference between the two groups was comparable. (MD=0.22minutes,95%CI—0.03,0.46,pvalue=0.08). The studies demonstrated high heterogeneity (I^2=98%). Sensitivity analysis was performed to detect the possible cause of heterogeneity. When the study by Goma was identified as an outlier due to high risk of bias, the heterogeneity on the effect on the onset of sensory block between the nalbuphine group versus fentanyl group was removed (MD= 0.29 minutes 95%CI 0.27,0.31, p value <0.001, I^2=0%) and none of the remaining studies eliminate the heterogeneity.

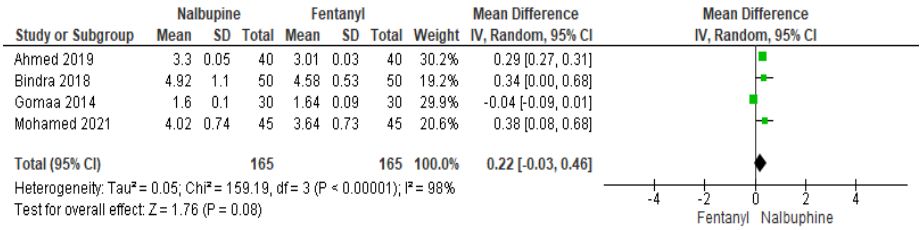

Figure 8. Meta-analysis on the effect on time for onset of sensory block

Secondary Outcome 2: *Effect on time for the onset of motor block*

Mean onset of motor block for both nalbuphine group and fentanyl group was primarily pooled in this study. The overall effect estimate was calculated as the mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects method in Review Manager 5.3. All the included studies reported the mean time for onset of motor block among patients who received intrathecal nalbuphine and intrathecal fentanyl during cesarean section. Overall, the pooled mean difference showed no significant difference between the two groups (MD=0.30, 95%CI -0.05,0.65, p value = 0.09). The studies demonstrated high heterogeneity (I^2=85%). Sensitivity analysis was also performed to detect the possible cause of heterogeneity. When Ahmed's trial was identified as an outlier due to different spinal dose of bupivacaine hyperbaric (12.5 mg) used, the heterogeneity on the effect on the onset of sensory block between the nalbuphine group versus fentanyl group was reduced (MD = 0.16 minutes 95%CI -0.03,0.35, p value = 0.09, I^2 = 38%) and none of the remaining individual studies eliminated the large heterogeneity.

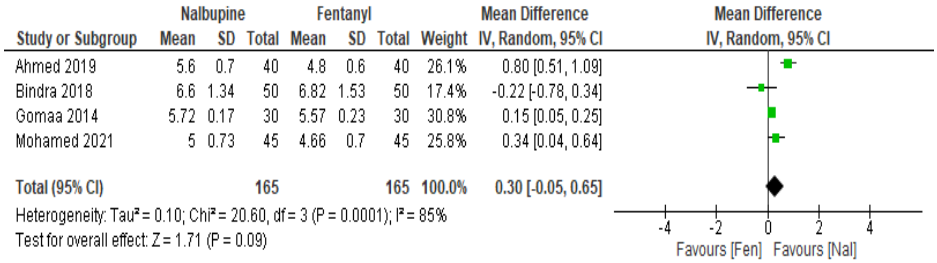

Figure 9. Meta-analysis on the effect on time for onset of motor block

Secondary Outcome 3: *Effect on the APGAR scores*

Three studies reported the effect on 1- minute APGAR scores between the nalbuphine and fentanyl group. The effect on the 1- minute APGAR scores for both intervention group and comparator group was primarily pooled. The overall effect estimate was calculated as mean difference with 95% confidence interval. Pooled summary estimates were derived using the random effects method in Review Manager 5.3. The pooled mean difference between the two groups was comparable as shown in Figure 10.

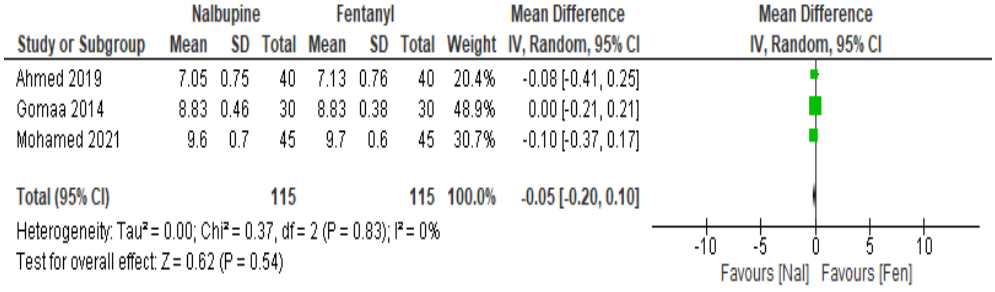

Figure 10. Meta analysis on the effect on postoperative hypotension

Secondary Outcome 4: *Effect on the postoperative hypotension*

Three studies measured the risk of postoperative hypotension as their outcome.

Relative risk for incidence of postoperative hypotension and random effects method was used to estimate the pooled effect with 95% confidence interval. Pooled risk ratio as presented in Figure 11 showed no significant difference between the two groups in terms of risk of postoperative hypotension (RR=0.78,95%CI=0.38,1.60, p value = 0.50).

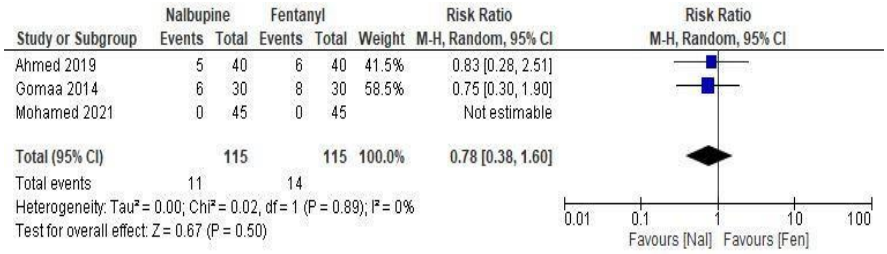

Figure 11. Meta analysis on the effect on postoperative hypotension

Secondary Outcome 5: *Effect on the postoperative nausea and vomiting* Three out of four studies measured the risk of postoperative nausea and vomiting as one of their outcomes. The relative risk for incidence of postoperative nausea and vomiting and random effects method was used to estimate the 95% confidence interval. Pooled data as presented in Figure 12 showed that the use of intrathecal **nalbuphine reduced the risk of PONV by 62%** compared to fentanyl (RR=0.38,95%CI= 0.19,0.78, p value = 0.008 I^2 = 11%).

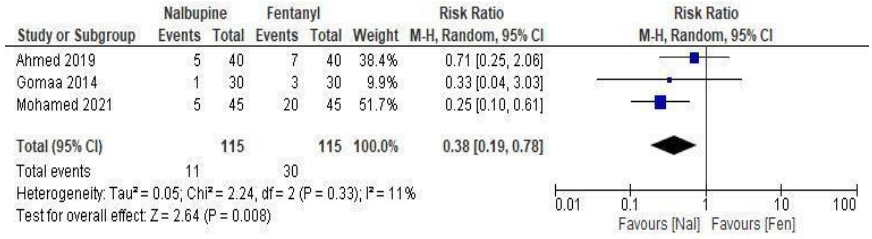

Figure 12. Meta-analysis on the effect on postoperative nausea and vomiting Secondary

Outcome 6: *Effect on postoperative pruritus*

Only three studies included the risk for postoperative pruritus between the two groups. The relative risk for incidence of postoperative pruritus and random effects method was used to estimate the 95% confidence interval. Pooled risk ratio as shown in Figure 13 showed that **nalbuphine group decreased the risk of pruritus by 91%** compared to the fentanyl group (RR=0.09, 95%CI=0.02, 0.50, p value = 0.006 I^2 = 0%). Funnel plot to address any publication bias was not done as there were <10 studies for each outcome.

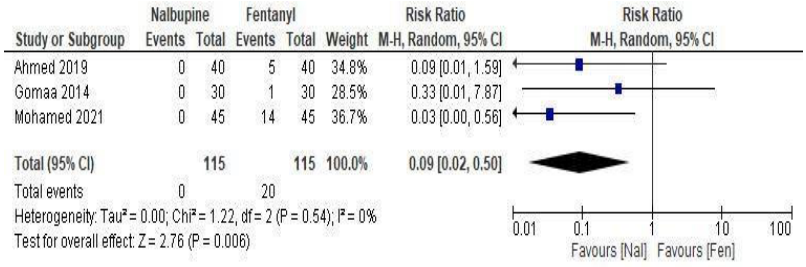

Figure 13. Meta-analysis on the effect on postoperative pruritus. Additional Analysis

DISCUSSION

After pooling the results of the study, pregnant women who were given intrathecal nalbuphine had longer a duration of postoperative analgesia compared to the fentanyl group. A longer duration of postoperative analgesia for even just 21.12 minutes will be beneficial to patients and anesthesiologists which can lead to possible lesser analgesic requirement, early postop recovery, lesser hospital stay and a satisfactorily childbirth experience. This result can be comparable to to the systematic review and meta-analysis by Yu et al [12] about the effect of nalbuphine as an adjuvant to local anesthetics in spinal anesthesia and concluded that the use of intrathecal nalbuphine can prolong the duration of analgesia (MD=118.11; 95%CI = 71.34-164.89, p<0.0001) without increasing the incidence of adverse reactions in comparison to control group (normal saline). Analysis on the

duration of postoperative analgesia of intrathecal nalbuphine versus intrathecal fentanyl in this review showed moderate heterogeneity (I^2=73%) however. the forest plot showed that majority leaned more towards nalbuphine than fentanyl. The following factors can contribute to the heterogeneity of the review. 1) different fentanyl dose (20 mcg) in Bindra et al study 2) higher spinal dose of hyperbaric bupivacaine (12.5mg) as seen in Ahmed's trial and 3) high risk of bias in Gomaa's and Mohamed's trial. Sensitivity analysis was conducted omitting one study at a time but the pooled result remained heterogenous. The presence of heterogeneity involving this outcome reduce the robustness of the result and it warrants that the result should be treated with caution. Initially, the pooled data on the effect on time for onset of sensory block showed that there was no difference between the nalbuphine group and fentanyl group (MD=0.22 minutes, 95%CI— 0.03,0.46, p value = 0.08 I^2=98%). When sensitivity analysis was conducted omitting 1 study at a time, the significant heterogeneity was eliminated after excluding the study by Gomaa et al due to high risk of bias, [13] in which the original finding was substantially changed and there was a statistical difference in the results (MD= 0.29 minutes, 95%CI 0.27,0.31, p value <0.001, I^2=0%). However, a difference of 0.07 minutes on the onset of sensory block has no clinical significance. In a study by Yu et al [12] it showed that nalbuphine group had no difference when compared to control group on the effect on onset of sensory block and supports the initial findings of this outcome. Pooled results on the effect on time for onset of motor block demonstrated that nalbuphine group were comparable to fentanyl group (MD=0.30 minutes, 95%CI -0.05,0.65, p value = 0.09 I^2=85%). After sensitivity analysis was done in which Ahmed study was excluded due to a higher spinal dose of bupivacaine hyperbaric used (12.5mg) it removed the heterogeneity. Nevertheless, the pooled results remained unchanged from the original finding (MD = 0.16 minutes (95%CI -0,03,0.35, p value = 0.09 I2=38%). Pooled results also showed that nalbuphine group reduced the risk of PONV by 62% compared to fentanyl group (RR=0.38, 95%CI= 0.19,0.78, p value = 0.008,

I^2= 11%). Similarly, the risk of pruritus was also reduced by 91% among the nalbuphine group compared to the fentanyl group (RR=0.09, 95%CI=0.02, 0.50, p value = 0.006 I^2=0%). With regards to this results, Yu's review [12] showed that the risk of pruritus (RR=0.23, 95% CI = 0.10-0.53, p<0.01) was lower in nalbuphine than the potent opioid group. In lieu of these results, Uppal et al study [14] concluded that the addition of intrathecal fentanyl was associated with higher incidence of pruritus (RR=5.89, 95%CI=2.07-16.79; p<.001; I2=0%). However, in contrast with the results of this meta-analysis, Uppal's review [14] also concluded that the risk of PONV (RR=0.41; 95%CI, 0.24-0.70; p<.001;I2 35%) was lesser in fentanyl compared to potent opioid group. Pruritus and PONV had the highest prevalence among the adverse effects of lipophilic opioids. Based on literatures and pooled data from multiple randomized trials it showed that fentanyl being a mu agonist usually have a mu receptor-based side effects like nausea, vomiting and pruritus and on the contrary, nalbuphine a mixed agonist-antagonist opioid provides analgesic effects and exhibits lesser mu adverse effects like nausea, vomiting and pruritus due to its kappa agonistic action [15] and supports the findings of this review.

Pooled results on the effect on the 1-minute APGAR scores between intrathecal nalbuphine and intrathecal fentanyl based on pooled mean difference showed that there was no significant difference between the 2 groups (MD -0.05, 95%CI= -0.20, 0.10, p value = 0.54). It should, however, be noted that none of the studies included in this meta-analysis were powered to demonstrate differences in the neonatal outcomes assessed. Similarly, none of the studies had sufficient power to detect the risk of postoperative hypotension between the two groups (RR=0.78, 95%CI=0.38,1.60, p value = 0.50).

This review also included the effect on the total analgesic requirement between nalbuphine group and fentanyl group. Ahmed et al, [16] compared the consumed total ketorolac dose (mg/patient over 24 hours) (Nalbuphine (N=40) SD= 39.8 + 14.2, Fentanyl (N=40) SD = 49.5 +14.5 p value =

0.003) and total pethidine dose (mg/patient over 24 hours) (Nalbuphine (N=40) SD=39.8 + 14.2, Fentanyl (N=40) SD=49.5 +14.5 p value= 0.005) between the two groups. While, Bindra et al [3] compared the administered intramuscular diclofenac (75mg) as rescue analgesic and the total number of rescue analgesics postoperatively in 24 hours between the two groups. (Nalbuphine (N=50) SD=1.54+ 0.705, Fentanyl (N=50) SD=2.06 +0.682 p value = <0.001). Lastly, Mohamed et al [15] compared the total fentanyl used as rescue dose (Nalbuphine (N=45) SD=5.6 95%CI 1-10.2, Fentanyl (N=45) SD=3.3 95%CI 0.4-7 p value = 0.49) and the number of patients required rescue fentanyl between the nalbuphine (Nalbuphine(N=45) SD=5 (11.1%), Fentanyl (N=45) SD=3 (6.7%) p value = 0.45). However, due to the inconsistency on how this outcome was reported in the 3 studies since 1) there was nonuniformity of pain medications used as rescue analgesics and 2) different methods were used in comparing the total analgesic requirement between the two groups, hence meta-analysis cannot be performed on the said outcome.

CONCLUSION AND RECOMMENDATION

The results of this meta-analysis demonstrates that the use of intrathecal nalbuphine appears to have a better outcome in increasing the duration of postoperative analgesia and with lesser incidence of PONV and pruritus than fentanyl. However, due to the presence of heterogeneity it warrants that the results should be treated with caution especially with the possibility of publication bias. It is heterogenous due to the nonuniformity of the dosage and method used together with the inclusion of high risk of bias studies. It has a low power to determine the significant publication bias since there are only four studies included in this review. Better literature search through inclusion of high-quality studies from relevant databases and strict adherence on the uniformity of the dosage and methods used are very crucial to achieve the target clinical outcomes and minimize the publication bias.

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FACTORS AFFECTING THE CLINICAL OUTCOME OF PEDIATRIC ANTI- N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS, A SINGLE CENTER STUDY

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ABSTRACT

Background: Anti-N-Methyl-D-Aspartate receptor (anti-NMDAR) Encephalitis is the most common type of autoimmune encephalitis that affects children, adolescents and young adults. Since its discovery in 2007, there is still a paucity of data on the disease and factors affecting its outcome.

Objectives: To describe the clinical characteristics of children and adolescents with anti-NMDAR encephalitis and to analyze factors that may affect its outcome.

Methods: Forty-three patient records of diagnosed anti-NMDAR Encephalitis were included. The outcome was evaluated using the modified Rankin Scale (mRS), and Clinical Assessment Scale for autoimmune Encephalitis (CASE).

Results: Ages ranged from 2 years to 18 years old, majority in the 12-18 years age range. Sixty percent were female. First line treatment using immunotherapy was given to all patients: 37% as monotherapy and 84% combination therapy (MPT only 23%, IVIg only 4%, MPT + IVIg or TPE 21-26%, and MPT + IVIg + TPE 16%). Clinical outcomes on discharge and on follow-up were assessed using the mRS and CASE. On discharge the proportion of the patients who had mild impairment (mRS<2, CASE<9) was more than 50%. On median duration follow-up of 31 weeks (range 24-40 weeks), 96.8% had significant improvement (mRS<2, CASE<9). Among the possible factors that were assessed to affect outcome, only severity of the illness at the start of the treatment influenced clinical outcome.

Conclusion: Early diagnosis and initiation of treatment before the progression of the disease will promote faster recovery and more optimal clinical outcome. CASE may be used as an additional tool in assessing response to treatment.

Keywords: Anti-NMDAR encephalitis, autoimmune

INTRODUCTION

Autoimmune encephalitis (AE) is a clinical spectrum of neuropsychiatric symptoms such as deficits of memory, cognition, psychosis, seizures, abnormal movements, or coma. The most common type is the anti-N-methyl-D-aspartate (NMDA) receptor encephalitis surpassing viral encephalitis. [2] Anti-N-Methyl-D-Aspartate receptor (anti-NMDAR) encephalitis affects predominantly young adults, adolescents, and children as young as 22 months of age. A female preponderance has been observed (Female:Male:4:1).[1,3,6,7,8] Prodromal symptoms such as headache, fever, or a viral-like illness, can precede the neuropsychiatric symptoms in about 1/3 of cases.[4] The disease course is variable in the pediatric age group, and is severe especially if diagnosed late, requiring prolonged hospitalization and intensive treatment. Studies have shown that early initiation of treatment often leads to better outcome, but even in those patients with delayed diagnosis and treatment, immunotherapy could still result in significant clinical improvement. [12,13] At present, the modified Rankin Scale (mRS) has been used to assess the outcome of patients with autoimmune encephalitis, including anti-NMDAR encephalitis both in adults and children. It is, however, a non-specific tool that assesses the functional outcome and degree of disability of the patients. A more specific assessment tool that assesses more impairment can provide a better profile of the clinical outcome.

In 2019, Lim et al, presented a new and more specific Clinical Assessment Scale for autoimmune encephalitis (CASE) consisting of nine (9) items (seizure, memory dysfunction, psychiatric symptoms, consciousness, language problems, dyskinesia/dystonia, gait instability, and ataxia, brainstem dysfunction, and weakness) which was further validated in a multicenter validation cohort study.[16] Using this tool, Shim (2020) investigated the clinical features and long-term outcomes of 32 children with anti-NMDAR encephalitis aged 7 months - 17 years old, and compared the results with the mRS scores. While

the mRS scores showed good functional outcome in the majority of the patients, the results of the CASE assessment tool showed that these patients continued to have significant impairments in the cognitive and memory abilities. In the present study, the clinical features, and outcomes of 43 pediatric anti-NMDAR encephalitis patients were evaluated using both the mRS and CASE.

General Objective

To determine the clinical outcomes of pediatric patients diagnosed with Anti-NMDAR Encephalitis admitted at Philippine Children's Medical Center from 2018-2020, and the factors that affect these clinical outcomes.

Specific Objectives

1. Describe the baseline characteristics of the patients based on:
    a. Demographics
        i. Age at onset of illness
        ii. Gender
        iii. Geographic Location
        iv. Duration of illness before the diagnosis
        v. Duration of illness before the initiation of treatment
    b. Clinical Profile
        i. Symptomatology: Prodrome, Initial symptoms, Symptoms from the time of admission until discharge
        ii. Diagnostics
            1. Electroencephalogram (EEG)
            2. Cerebrospinal Fluid (CSF) Analysis
            3. Neuroimaging (Cranial Computed Tomography (CT) Scan and Magnetic

Resonance Imaging (MRI)

4. Tumor work-up

2. Classify the patients based on the severity of the symptoms using CASE and mRS prior to initiation of treatment.
3. Determine the response to treatment either with Monotherapy (Methylprednisolone (MPT) or Intravenous Immunoglobulin (IVIg); and Combination therapy (MPT + IVIg, MPT + TPE, MPT + IVIg + TPE) upon discharge and on follow-up (within 6 months) using CASE and mRS.
4. Determine if age, severity of illness based on mRS and CASE, and duration of illness prior to initiation of treatment will affect their response to treatment.
5. Identify the adverse effects or events during and after treatment.

METHODOLOGY

This was a retrospective cohort Study of patients confirmed with anti-NMDAR Encephalitis admitted at Philippine Children's Medical Center from January 2018 until December 2020. A minimum of 40 patients diagnosed with anti-NMDAR encephalitis was required to have an 80% chance of determining, as significant at the 5% level, the changes in response to treatment according to age at onset, severity of illness, type of treatment and duration of illness before treatment based on assumed large effect sizes.

Inclusion

- *All patients with a clinical diagnosis of definite anti-NMDAR Encephalitis*
- *Admitted and given immunotherapy: Monotherapy with MPT or IVIg; or Combination therapy with (MPT + IVIg, MPT + TPE, MPT + IVIg + TPE)*
- *Age 1 to 18 years old*

Exclusion

- *Patients with anti-NMDAR encephalitis admitted for another medical condition/systemic illness*

- *Patients with anti-NMDAR encephalitis who did not receive treatment*

This study reviewed both in-patient and out-patient records of all patients diagnosed with Anti-NMDAr Encephalitis from January 2018 until December 2020. Forty-eight charts were retrieved and 43 were included based on the inclusion criteria. Three of the excluded subjects did not receive any treatment and went home against medical advice, and two were seen as out-patient only.

A standardized three-part data collection tool was used. Part I consisted of the general and clinical data of the patients including the mRS scores. Part II was the assessment of severity of symptoms using the CASE, and Part III included the adverse effects of treatment. This study determined the factors affecting the outcomes based on age, severity and type of treatment, using the CASE and mRS. Outcome of patients was described as GOOD (mRS 0-2 or CASE score of 0-9) or POOR (mRS 3-5 or CASE score of 10 or more). Recovery from illness was described as follows: Full Recovery (mRS 0 or CASE Score of 0); Substantial improvement (mRS 1-2 or CASE 1-9); Limited Recovery (mRS 3-5 or CASE 10 – 18). mRS of 6 or CASE of 20 indicated death from the illness. Summary statistics were reported as mean and standard deviation (SD) or standard error (SE) for continuous data with normal distribution or as median (range) for quantitative variables with skewed distribution and as count (percent) for qualitative measures. Shapiro-Wilks test was used to determine whether continuous variables deviate from a normal (Gaussian) distribution. McNemar test was used to compare proportion of patients according to symptoms across periods of assessment. Analysis of variance of repeated measures was used to estimate how treatment response based on total CASE score changed according to type of treatment, age at onset, severity of illness and duration of illness before treatment. Kruskal Wallis test was used to compare treatment response based on mRS scores. Friedman test was used to compare treatment response based on mRS scores across

periods of assessment. Mann Whitney U test was used to compare mRS scores between severity of illness (mRS) and duration of illness before treatment. Chi-square test or Fisher's exact test was used to compare proportions. Pairwise comparisons of proportions were based on Bonferroni adjusted *p*-values. Kaplan-Meier analysis was performed to estimate mean time to achieving good treatment response and full recovery. Log rank test was used to compare time across treatments. Bivariate cox proportional hazards regression analysis was performed to assess possible effects of age at onset, severity and duration of symptoms prior to initiation of treatment on treatment response. Multivariate models were derived where possible. Crude and adjusted hazards ratio and 95% confidence interval were reported. One-way analysis of variance was used to compare duration of illness at follow-up across treatment. Statistical significance was based on p-value ≤ 0.05. STATA version 15 (Stata Corp LLC, College Station, TX, US) was used in data processing and analysis.

RESULTS

Forty-three patients were included in this study. Table 1 shows the baseline characteristics of patients. The majority were female (60.5%) in adolescence (55.8%), with a duration of illness of 1-3 months (58%) before initiation of treatment. Prodromal symptoms were seen in 39.5%, [headache (20.9%), fever (11.6%) and respiratory illness (14%)]. Tumor workups were all negative. Brain imaging was abnormal in 7%. CSF analysis was abnormal in 11 patients (25%) which included lymphocytic pleocytosis and elevated CSF protein levels. Thirty-two EEG studies were available for review. Eighty seven percent were abnormal [generalized slowing (46.4%), continuous delta slowing (53.5%) focal slowing (75%), epileptiform discharges (7.14%) and delta brush (7.14%)].

Table 1. Baseline characteristics of patients n=43

Characteristic	No. of Patients (Percent)
Age in years	
Early childhood (2 years to 5 years old)	8 (18.6%)
Middle childhood (6 years to 11 years old)	11 (25.6%)
Adolescence (12 years to 18 years old)	24 (55.8%)
Gender	
Male	17 (39.5%)
Female	26 (60.5%)
Location	
Within Metro Manila	17 (39.5%)
Outside Metro Manila	26 (60.5%)
Duration of illness prior to admission (in months)	
<1	37 (86.0%)
1-3	6 (14.0%)
Duration of illness before treatment (in months)	
<1	18 (41.9%)
1-3	25 (58.1%)
Prodrome	
At least one symptom	17 (39.5%)
Fever	5 (11.6%)
Headache	9 (20.9%)
Respiratory	6 (14.0%)
Ultrasound (Abdominal,Pelvic,Testicular)	
Normal	41 (95.3%)
Abnormal	2 (4.7%)
Cranial MRI/CT scan	
Normal	40 (93.0%)
Abnormal	3 (7.0%)
CSF White blood cell count	
Normal (≤ 5 cells/hpf)	39 (90.7%)
Elevated (> 5 cells/hpf)	4 (9.3%)
CSF protein level in mg/L	
≤450	36 (83.7%)
>450	7 (16.3%)
Electroencephalogram (n=32)	
Normal	4 (12.5%)
Abnormal EEG*	28 (87.5%)
Generalized background slowing	13(46.4%)
Continuous delta slowing	15 (53.5%)
Intermittent Focal slowing	21 (75%)
Frontal	9 (32.14%)
Frontotemporal	9 (32.14%)
Midtemporal	4 (14.28%)
Temporal	4 (14.28%)
Occipital	2 (7.14%)
Frontocentral	6 (21.42%)
Centroparietal	3 (10.71%)
Focal epileptiform activity	2 (7.14%)
Delta brush	2 (7.14%)

Characteristic	No. of Patients (Percent)
Electromyography (n=5)	
Normal	2 (40%)
Abnormal	3 (60%)
Treatment regimen	
Monotherapy	16 (37%)
MPT	14 (23%)
IVIg	2 (4.65%)
Combination	
MPT + IVIg	10 (26%)
MPT + TPE	9 (21%)
MPT+ IVIg +TPE	8 (16%)

Data are n (%) on 43 pediatric patients with anti-NMDAR encephalitis.

CT: computed tomography, MRI: magnetic resonance imaging, CSF: cerebrospinal fluid

Table 2. Treatment regimen given to Filipino children with anti-NMDAR encephalitis (n=43)

Treatment regimen	Number of patients (n=43)
Monotherapy	16 (37%)
MPT	14 (23%)
IVIg	2 (4.65%)
Combination	
MPT + IVIg	10 (26%)
MPT + TPE	9 (21%)
MPT+ IVIg +TPE	8 (16%)

Initial symptoms reported at the time of admission (Figure 1) included seizures (51.2%), cognitive and behavioral impairments (37.2%), sleep disorders (9.3%), movement disorders (4.7%) and language problems (2.3%). Post-treatment, there was a significant decrease in the number of patients with seizures (9.3% vs. 67.4%), movement disorder (53.5% vs. 72.1%) and language deficits (65.1% vs. 90.7%). A further decrease in the proportion of patients with movement disorders was observed upon discharge (11.9% vs. 52.4%, n=42). On follow-up (range: 20-40 weeks, median 31 weeks), cognitive and behavioral impairments were still present in 41.9% of patients. One patient did not show any functional improvement.

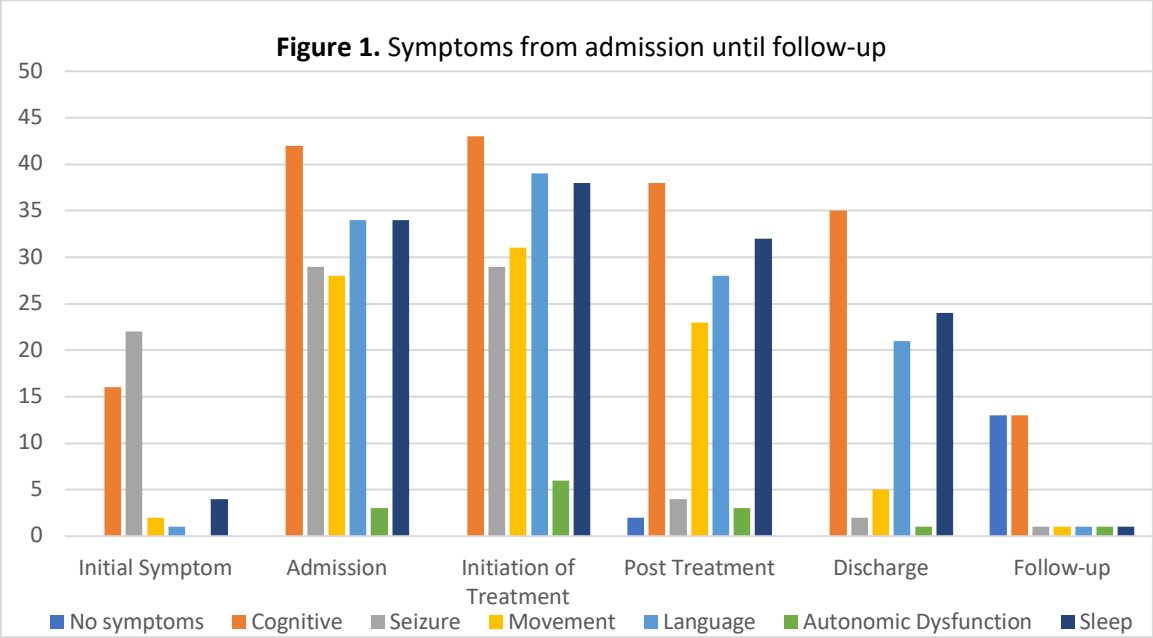

Fig 1. Distribution of patients based on the severity of symptoms using mRS and CASE

Figure 2 presents the severity of symptoms based on mRS and CASE scores prior to initiation of treatment. Based on mRS 79.1% had moderate and 20.9% had severe symptoms. Using the total CASE scores, symptoms were either mild (14%), moderate (58.1%) or severe (27.9%).

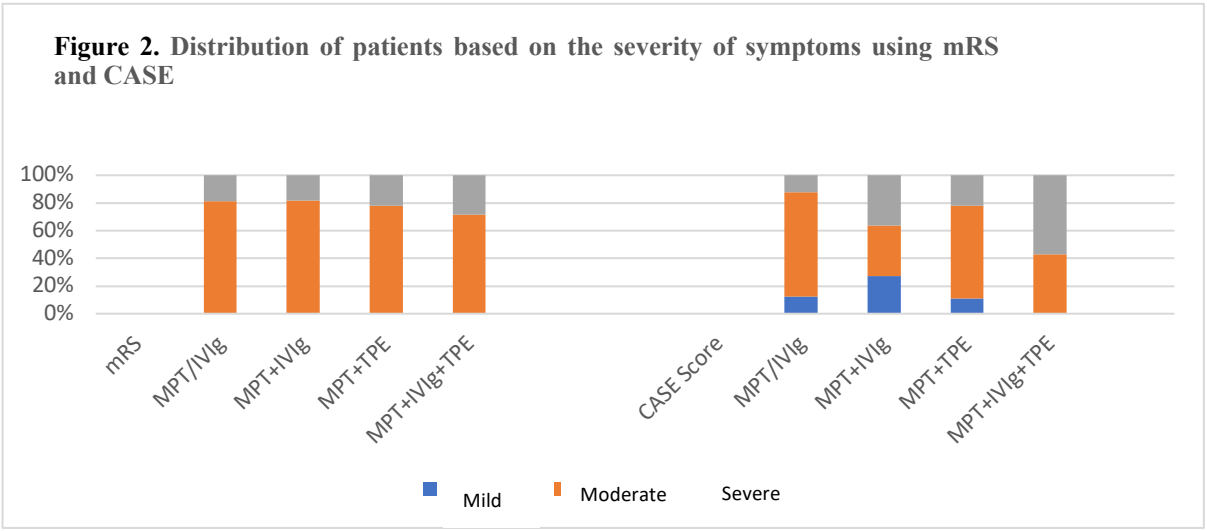

Fig 2. Response to treatment according to type of treatment and period of assessment

Overall, there was a difference in the mRS and CASE scores from initiation of treatment until follow-up. However, the scores at each period of assessment were comparable across the treatment groups (Figure 3).

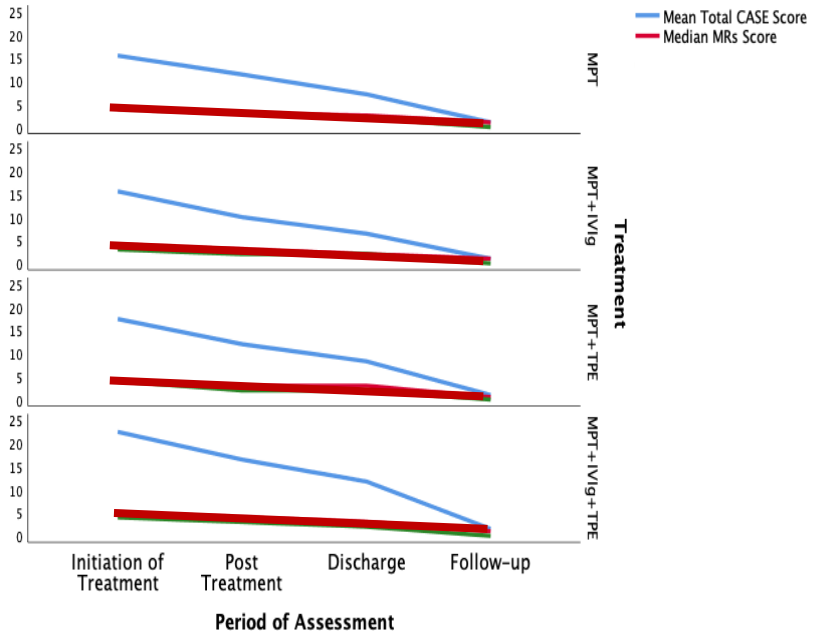

Figure 3. Total CASE and mRS scores from initiation of treatment to follow-up

The response to treatment on discharge (Table 3) and follow-up (Table 4) was analyzed using the mRS, and CASE score.

Table 3. Response to treatment as measured by mRS score, CASE on discharge

		Severity			Time to Mild Symptoms (in weeks)		
Treatment	No. of Patients	Mild	Moderate	Severe	Mean	SE	95% CI
mRS							
Monotherapy + MPT/IVG	15	8 (53.3%)	7 (46.7%)	-	6.375	0.614	5.171 to 7.579
MPT + IVIg	11	8 (72.7%)	3 (27.3%)	-	6.916	0.573	5.793 to 8.040
MPT + TPE	9	4 (44.4%)	5 (55.6%)	-	7.356	0.486	6.403 to 8.309
MPT + IVIg + TPE	7	3 (42.9%)	3 (42.9%)	1 (14.3%)	10.918	1.894	7.206 to 14.631
Total	42	23 (54.8%)	18 (42.9%)	1 (2.4%)	9.076	0.797	7.514 to 14.631
CASE Score							
Monotherapy + MPT/IVG	15	11 (73.3%)	4 (26.7%)	-	5.670	0.545	4.601 to 6.739
MPT + IVIg	11	8 (72.7%)	3 (27.3%)	-	6.879	0.594	5.714 to 8.043
MPT + TPE	9	6 (66.7%)	3 (33.3%)	-	7.265	0.544	6.198 to 8.331
MPT + IVIg + TPE	7	4 (57.1%)	2 (28.6%)	1 (14.3%)	10.612	1.796	7.093 to 14.132
Total	42	29 (69.0%)	12 (28.6%)	1 (2.4%)	7.845	0.676	6.519 to 9.170

MRS data are n (%), mean time, standard error and 95% confidence interval on 42 pediatric patients with anti-NMDAR encephalitis. One patient expired post MPT treatment. CASE Data are n (%), mean, standard error and 95% confidence interval on 42 pediatric patients with anti-NMDAR encephalitis. One patient expired post MPT treatment.

Table 4. Response to treatment as measured by mRS score, CASE **on follow-up**

Treatment		Severity			Time to No or Mild Symptoms (in weeks)		
	No. of Patients	No Symptom	Mild	Severe	Mean	SE	95% CI
MRS							
Monotherapy + MPT/IVG	9	4 (44.4%)	5 (55.6%)	-	31.825	0.675	30.502 to 33.148
MPT + IVIg	8	1 (12.5%)	7 (87.5%)	-	33.286	0.722	31.871 to 34.701
MPT + TPE	7	3 (42.9%)	4 (57.1%)	-	34.143	0.296	33.563 to 34.723
MPT + IVIg + TPE	7	3 (42.9%)	3 (42.9%)	1 (14.3%)	35.755	1.493	32.830 to 36.681
Total	31	11 (35.5%)	19 (61.3%)	1 (3.2%)	33.613	0.498	32.636 to 34.589
CASE Score							
Monotherapy + MPT/IVG	9	2 (22.2%)	7 (77.8%)		32.219	0.864	32.525 to 35.913
MPT + IVIg	8	3 (37.5%)	5 (62.5%)		24.564	0.870	32.860 to 36.269
MPT + TPE	7	2 (28.6%)	5 (71.4%)		34.449	0.330	33.803 to 35.095
MPT + IVIg + TPE	7	1 (14.3%)	6 (85.7%)		40.000	1.608	36.848 to 43.152
Total	31	8 (25.8%)	23 (74.2%)		38.609	0.944	36.759 to 40.458

MRS and CASE Score Data are n (%), mean time, standard error and 95% confidence interval on 31 pediatric patients with anti-NMDAR encephalitis.

The mean time to determine improvement to mild symptoms was 9.076 weeks (SE=0.797, 95% CI: 7.514 to 10.631) using mRS scores and 7.825 weeks using the CASE score. Using mRS 54.8% (95% CI: 38.7% to 70.2%) improved with mild symptoms (mRS 0-2) and 45.2% (95% CI=29.8^ to 61.3%) with moderate to severe symptoms (mRS 3-5) at the time of discharge. Using the CASE score, 69% (95% CI: 52.9% to 82.4%) had mild symptoms (good response) and 31% (95% CI=17.6% to 47.1%) had moderate to severe symptoms (poor response) on discharge. None had full recovery on discharge. Comparing these data to the pre-treatment severity of symptoms, most of the patients improved from either severe to moderate symptoms to mild and moderate

symptoms, with 1 exception. Comparison across treatment modalities, however, showed insufficient evidence of significant differences in severity (mRS p=0.469) (CASE p=0.905) and time to good outcome or mild symptoms (mRS p=0.252) (CASE p=0.114).

Only 31 patients were seen on follow-up. Follow-up ranged from 20-40 weeks (median 31 weeks). The mRS (0-2) on follow-up was 96.8% (95% CI: 83.3% to 99.9%) indicating good response to treatment; 61.3% had mild symptoms and 35.5% had no symptoms (full recovery). The mean time to full recovery was 33.6 weeks (SE=0.498, 95% CI: 32.636 to 34.589). The patients who had mild symptoms on follow-up received either monotherapy (55.6%), and combination therapy (44.4%). Based on the CASE score all patients had favorable response to treatment. There were 25.8% (95% CI: 11.9% to 44.6%) who had full recovery (no symptoms) and 74.2% (95% CI: 55.4% to 88.1%) had mild symptoms, with a mean time to full recovery of 38.6 weeks (SE=0.944, 95% CI: 36.759 to 40.458). Comparison across treatment, however, showed insufficient evidence of significant differences in severity of symptoms (mRS p=0.452) (CASE p=0.856) and time to full recovery across treatment modalities (CASE p=0.664) on follow-up.

Factors associated with response to treatment on discharge and follow-up using the mRS are shown in Table 5 and 6 respectively. There was a significant crude association between severity of symptoms prior to treatment and achieving a good treatment response, as patients with moderate symptoms prior to treatment achieved good treatment response faster than those with severe symptoms (crude HR=11.488, 95% CI: 1.504 to 87.751, p=0.019). However, there was insufficient evidence that age at onset, severity and duration of illness prior to treatment had significant effects on achieving full recovery at follow-up.

Table 5. Response to treatment on discharge using mRS

Factor	Patients with Good Response	Patients with Poor Response	Crude HR (95% CI	*p*-value
Treatment				
Monotherapy + MPT/IVG	8 (34.8%)	7 (36.8%)	2.868 (0.741, 11.096)	0.127
MPT + IVIg	8 (34.8%)	3 (15.8%)	2.206 (0.583, 8.349)	0.244
MPT + TPE	4 (17.4%)	5 (26.3%)	1.119 (0.250, 5.018)	0.883
MPT + IVIg + TPE	3 (14.0%)	4 (21.1%)	1	
Age at onset in years				
Early childhood	4 (17.4%)	4 (21.1%)	1.146 (0.364, 3.612)	0.816
Middle childhood	8 (34.8%)	3 (15.8%)	1.371 (0.547, 3.433)	0.501
Early adolescent	11 (47.8%)	12 (63.2%)	1	
Severity of illness before treatment (mRS)				
Moderate	**22 (95.7%)***	**12 (63.2%)**	**11.488 (1.504, 87.751)**	**0.019§**
Severe	**1 (4.3%)***	**7 (36.8%)**	**1**	
Duration of illness before treatment in months				
<1	9 (39.1%)	8 (42.1%)	1.111 (0.479, 2.576)	0.806
1-3	14 (60.9%)	11 (57.9%)	1	

Data are n (%), hazard ratio and 95% confidence interval on 42 pediatric patients with anti-NMDAR encephalitis. * P<0.05 vs. patients with poor response, § P<0.05 vs. reference category

Table 6. Response to treatment at follow-up using mRS

Factor	Patients with Full Recovery	Patients without Full Recovery	Crude HR (95% CI)	*p*-value
Treatment				
Monotherapy + MPT/IVG	4 (36.4%)	5 (25.0%)	3.288 (0.581, 18.614)	0.178
MPT + IVIg	1 (9.1%)	7 (35.0%)	0.535 (048 to 5.917)	0.610
MPT + TPE	3 (27.3%)	4 (20.0%)	1.318 (0.219 to 7.925)	0.763
MPT + IVIg + TPE	3 (27.3%)	4 (20.0%)	1	
Age at onset in years				
Early childhood	2 (18.2%)	3 (15.0%)	1.104 (0.213, 5.716)	0.906
Middle childhood	3 (27.3%)	6 (30.0%)	1.007 (0.239, 4.248)	0.992
Early adolescent	6 (54.5%)	11 (55.0%)	1	
Severity of symptoms before treatment (mRS)				
Moderate	**10 (90.9%)**	**13 (65.0%)**	**7.447 (0.913, 60.702)**	**0.061**
Severe	**1 (9.1%)**	**7 (35.0%)**	**1**	
Duration of illness before treatment in months				
<1	4 (36.4%)	8 (40.0%)	1	
1-3	7 (63.6%)	12 (60.0%)	1.122 (0.327, 3.853)	0.855

Data are n (%), hazard ratio and 95% confidence interval on 31 pediatric patients with anti-NMDAR encephalitis with at least 80 days follow-up.

Factors associated with response to treatment at discharge and follow-up using the CASE score are shown in Table 7 and 8 respectively. The type of treatment and severity of symptoms prior to initiation of treatment had significant crude associations to achieving a good treatment response (no or mild symptoms). That is, patients who received monotherapy with MPT or IVG were more likely to achieve good treatment response faster than those treated with a combination of MPT, IVIg and TPE. Similarly, those with mild or moderate symptoms prior to treatment were more likely to achieve good treatment response faster than those with severe symptoms. Severity of symptoms prior initiation of treatment had a crude association with achieving full recovery. Those with mild symptoms prior to treatment were more likely to recover faster than those with severe symptoms (crude HR=12.907, 95% 1.416 to 117.682, p=0.023)

Table 7. Response to treatment at discharge according to treatment, age at onset of illness, duration, and severity of illness prior to initiation of treatment

Factor	Patients with Good Response	Patients with Poor Response	Model 1	
			Adjusted HR (95% CI)	*p*-value
Treatment				
Monotherapy + MPT/IVG	11 (37.9%)	4 (30.8%)	2.661 (0.700, 10.111)	0.151
MPT + IVIg	8 (27.6%)	3 (23.1%)	2.441 (0.616, 9.678)	0.204
MPT + TPE	6 (20.7%)	3 (23.1%)	1.298 (0.309, 5.449)	0.722
MPT + IVIg + TPE	4 (13.8%)	3 (23.1%)	1	
Age at onset in years				
Early childhood	5 (17.2%)	3 (23.1%)		
Middle childhood	8 (27.6%)	3 (23.1%)		
Early adolescent	16 (55.2%)	7 (53.8%)		
Severity of symptoms before treatment (CASE)				
Mild	**6 (20.7%)**	**-**	**3.680 (1.025, 13.213)**	**0.046§**
Moderate	**18 (62.1%)**	**6 (46.2%)**	**2.878 (0.948, 8.739)**	**0.062§**
Severe	**5 (17.2%)***	**7 (53.8%)**		
Duration of illness before treatment in months				
<1	10 (34.5%)	7 (53.8%)		
1-3	19 (65.5%)	6 (46.2%)		

Data are n (%), hazard ratio and 95% confidence interval on 42 pediatric patients with anti-NMDAR encephalitis. Treatment response was classified as either good (no symptoms or mild) or poor (moderate to severe symptoms). Model 1 is a multivariate model on treatment and age.
* P<0.05 vs. poor response. § P<0.05 vs. reference category

TABLE 8. Response to treatment at follow-up according to treatment, age at onset of illness, duration and severity of illness prior to initiation of treatment

Factor	Patients with Full Recovery	Patients without Full Recovery	Crude HR (95% CI)	*p*-value
Treatment				
Monotherapy + MPT/IVG	2 (25.0%)	7 (30.4%)	3.635 (3.23, 40.965)	0.296
MPT + IVIg	3 (27.5%)	5 (21.7%)	3.101 (0.322, 29.879)	0.328
MPT + TPE	2 (25.0%)	5 (21.7%)	1.798 (0.162, 19.919)	0.622
MPT + IVIg + TPE	11 (12.5%)	6 (26.1%)	1	
Age at onset in years				
Early childhood	1 (12.5%)	4 (17.4%)	0.709 (0.079, 6.368)	0.759
Middle childhood	3 (37.5%)	6 (26.1%)	1.226 (0.271, 5.548)	0.791
Early adolescent	4 (50.0%)	13 (56.5%)	1	
Severity of illness before treatment (CASE)				
Mild	4 (50.0%)*	2 (8.7%)	12.907 (1.416, 117.682)	0.023§
Moderate	3 (37.5%)	11 (47.8%)	3.238 (0.336, 31.248)	0.310
Severe	1 (12.5%)	10 (43.5%)	1	
Duration of illness before treatment in months				
<1	5 (62.5%)	7 (30.4%)	1	
1-3	3 (37.5%)	16 (69.6%)	0.392 (0.093, 1.656)	0.203

Data are n (%), hazard ratio and 95% confidence interval on 31 pediatric patients with anti-NMDAR encephalitis with at least 80 days follow-up.
* P<0.05 vs. patients without full recovery. § P<0.05 vs. reference category

Three patients (7.1%) developed intravenous catheter-related-infection while ongoing treatment. One patient expired post-monotherapy treatment due to severe autonomic dysfunction.

DISCUSSION

This study retrospectively analyzed the clinical and paraclinical factors of the 43 patients diagnosed with anti-NMDAR encephalitis and their response to immunotherapy. Overall, anti-NMDAR encephalitis has been reported across all age groups, mostly affecting female children and young adults.[1,3,4,6] These results were consistent in this study, where 60.5% were females belonging to the early adolescent group. The association of paraneoplastic syndromes in the form of ovarian tumors and anti-NMDAR encephalitis has been established by Zhang et al. [19] However, all tumor workups turned out negative in this study. Although, recommended screening for tumors should be done every 6 months, as the incidence of paraneoplastic syndromes increases with age.

In children, a prodrome or viral illness 1-2 weeks before the onset of neuropsychiatric symptoms has been associated with the seasonal variability of anti-NMDAR encephalitis. Interestingly, this study found that 17 (39.5%) patients who presented with a prodrome had onset of symptoms within the flu season, including 8 (18.6%) with headache, 4 (9.3%) respiratory symptoms, 2 (4.6%) fever, and the remaining three 3 (6.9%) had a combination of either fever and headache or fever and respiratory symptoms. Post-viral association with herpes simplex virus was also seen in some patients.[21] In this study, all patients who had CSF analysis were all negative. In this study, the initial neuropsychiatric symptoms were consistent with those described by Dalmau.[22] These include seizures (51.2%), cognitive and behavioral dysfunction (37.2%), sleep alteration (9.3%), abnormal movement (4.7%)

and language alterations (2.3%). Due to these symptoms, a few were initially treated as cases of new-onset epilepsy, viral encephalitis, and psychiatric disorders causing delays in diagnosis and treatment. During the illness, there was a significant increase in the proportion of patients with symptoms of cognitive dysfunction (97.7% vs. 37.2%), sleep disturbance (79.1% vs. 9.3%), and movement disorder (65.1% vs. 4.7%). This pattern of symptom progression was also described by Dalmau in 2017. [1,22] Consistent with an Italian multicenter study on pediatric patients in 2014 [23-25] this study revealed that seizure was the most common initial presentation during the acute phase of illness of patients regardless of gender and age, usually presenting as generalized onset seizures, and some cases as status epilepticus. Cognitive dysfunction (37.2%) was the second most common initial presentation. A systematic review of anti-NMDAR encephalitis patients in Australia reported high rates of persistent impairments in the executive functioning and episodic memory on discharge. These deficits may be explained by abnormalities in the hippocampus and frontal lobes. This same study found that early treatment was the most important clinical factor favoring good cognitive outcome.[28] Monitoring of cognitive functions in the younger age group can be difficult.

All 43 patients had positive anti-NMDAR antibody test on CSF, other abnormal findings include pleocytosis in 9.3% and elevated protein in 16.3%. In some studies, these abnormal CSF findings are reported in as many as 80% of cases. However, these findings have not been shown to affect the outcome of patients.[25] Ninety percent of the imaging studies done were normal, and a handful had non-specific punctate white matter changes. These findings were consistent with the findings of Titulaer.[4,5] mRS and CASE were used to measure the clinical outcome of patients. A dramatic decrease in

the severity of symptoms from moderate or severe to mild was observed on discharge in the majority of patients, regardless of the treatment given. The results revealed a faster recovery among those who received Methylprednisolone alone, or in combination with IVIg, as these patients were the ones who had the less severe symptoms upon initiation of treatment. The final outcome of 31 patients who followed up for a mean duration of 31 weeks was also reviewed. The clinical outcome review revealed that 11% had full recovery, while 89% had substantial recovery. However, looking at the CASE scores of these patients, despite the good outcome, most still have neurocognitive deficit. Since CASE may have an advantage over mRS in tracking the recovery of each symptom of pediatric anti-NMDAR encephalitis, it could be preferentially used in pediatric anti-NMDAR encephalitis. Among all the factors analyzed, the severity of symptoms at the time of initiation of treatment had the most impact in the outcome of the patients.

Several limitations of the present study should be addressed in future studies. First, since this was a retrospective study, there was limitation in the quality of clinical data that could be assessed. Second, since the CASE score was determined retrospectively based on medical records, its clinical utility and accuracy could not be determined. Third, since formal neurocognitive function testing was not performed on follow-up we are unable to conclude whether CASE scoring can identify pediatric patients at risk for neuropsychological problems.

CONCLUSIONS AND RECOMMENDATIONS

This study provided data about the clinical features and factors affecting the outcomes among 43 pediatric anti-NMDAR encephalitis patients based on mRS and CASE. Although the study results are generally consistent with previous findings, our study suggests that the severity of illness prior to initiation of

treatment played an important role in the prognosis, response to treatment, and outcome. Hence, the importance of early diagnosis and treatment in preventing morbidity and mortality in patients cannot be over emphasized. Despite the overall favorable outcomes, cognitive problems may still persist even on follow-up. CASE as another assessment tool may be used to detect these neurocognitive deficits and help in appropriate management. Finally, an appropriate diagnostic and treatment algorithm should be established to facilitate early diagnosis and management. A prospective design with larger sample size is recommended to make correlations between other clinical factors and outcomes. We suggest a prospective, multi-center design using the CASE scoring system, with formal neurocognitive function testing, to overcome these limitations.

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EFFICACY OF 20% MANNITOL VERSUS 3% HYPERTONIC SALINE IN DECREASING INTRACRANIAL PRESSURE IN THE PEDIATRIC AGE GROUP: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This systematic review aimed to assess the available data on the efficacy of 20% mannitol and 3% hypertonic saline in achieving the primary outcome of decreasing intracranial hypertension in the pediatric age group. Secondary outcomes such as GCS scores, hospital stay, discharge and disabilities were also considered.

Method: Search done through PubMed/MEDLINE, Cochrane Central Registry of Clinical Trials (CENTRAL) and EMBASE yielded 280 studies.

Results: Of 280 studies reviewed, 7 studies with a total of 1,892 pediatric patients met the eligibility criteria: 3 RCTs and 4 retrospective studies. From these, two randomized controlled studies showed statistically significant evidence that 3% hypertonic saline was superior to 20% mannitol in reducing increased intracranial pressure (ICP) while two other studies had results that were insufficient to establish statistical significance. Relative risk of mortality was comparable in both groups. There was a low risk of bias for randomized trials and fair to high quality retrospective studies. Heterogeneity was present as number of outcome measures varied among studies.

Conclusion: This review showed that while both agents effectively decreased intracranial pressure, 3% hypertonic saline showed better results compared with 20% mannitol. Due to the limited number and heterogeneity of studies, a pooled analysis of the effects in ICP could not be done. Larger prospective controlled studies using 20% mannitol and 3% hypertonic saline in the treatment of increased ICP in the pediatric age group are needed to render valid affirmations.

Keywords: Mannitol, Hypertonic Saline, Intracranial Pressure

INTRODUCTION

Increased intracranial pressure (ICP) is one of the most common neurologic emergencies. It is defined as sustained ICP of more than 20mmHg [1] Incidence of increased ICP depends on the primary pathology. Different etiologies such as central nervous system infections, traumatic brain injury, hemorrhage, vascular compromise, neoplasms, hydrocephalus, metabolic and others, lead to expansion of the different compartments within the cranium. This then results to an interplay of pressure, compliance, autoregulation, and overall cerebral perfusion. Persistence of hypertension and compromise of cerebral blood flow leads to complications such as herniation syndromes and focal or global ischemia. [2]

In 2019, a consensus in the stepwise management of intracranial hypertension specifically among patients suffering from severe traumatic brain injury was proposed by Kochanek. In the algorithm, baseline treatment is followed by tiers of treatment. Baseline management are geared towards addressing emergent issues such as maintenance of adequate ventilation, insertion of central line catheters and ICP monitors, initial neuroimaging, analgesia, and sedation, addressing intravascular status, positioning and anti-epileptic drug therapy. First tier of treatment addresses intracranial pressure and cerebral perfusion, primarily by utilizing medical decompressant therapy.[3] Refractory cases are addressed by second tier therapy such as surgical decompression, barbiturate, and hypothermia.

At present, common therapies for medical decompression include osmotic agents such as Mannitol, Hypertonic Saline Solution and Glycerol. Osmotherapy functions by creating an osmotic gradient resulting to decrease in the water content from the interstitium into the intravascular space.[4] A solution of 20% Mannitol, a 6-carbon hexahydric alcohol, has a serum osmolality of 1098mOsm/kg. Since

the early 1900s, its therapeutic effect for decreasing ICP has been observed. [5]

During the recent years, a growing number of studies have been made in assessing the role of hypertonic saline in the control of intracranial hypertension. In 2020, guidelines for the management of cerebral edema were made by a panel constituted by the Neurocritical Care society. While they suggested the use of hypertonic saline over mannitol in traumatic brain injury (TBI) and intracranial hemorrhage, they noted using either mannitol or hypertonic saline for acute ischemic stroke.[6] In the pediatric age group, several studies have reported the use of both mannitol and hypertonic saline in decreasing intracranial pressure medically. However, there are no established guidelines yet on the indication of using one over the other for children.

Intracranial pressure is defined as the pressure within the fixed cranium composed of the brain parenchyma, cerebrospinal fluid, and the intravascular volume. Normal pressure ranges between 5 to 15mmHg [4] Pathologies leading to a change in any of the three components, as stated in the Monroe-Kellie Doctrine, leads to a compensatory alteration in the other compartments. Morbidity and mortality of increased intracranial pressure is associated with the etiology and duration. Persistence and failure of mechanisms later lead to compression of structures, increasing intracranial pressure and subsequent loss of autoregulation and vascular compromise.[1] In children, common etiologies causing increased intracranial pressure include traumatic brain injury, hydrocephalus, intracranial hemorrhage, neoplasms, ischemia, cerebral edema and other metabolic causes.

Hyperosmolar therapy has been used as part of the tiers of treatment in the management of intracranial hypertension. Mannitol is a six-carbon sugar alcohol that functions by the decreasing blood viscosity and increasing

plasma osmolality. This shifts fluid from the extracellular space towards the intravascular compartment resulting to the desired effect of decreasing intracranial pressure.[7] It is available in different concentrations such as 5%, 20% and 25%. The most available and commonly used being the 20 grams in 100mL fluid or the 20% concentration.[8] It is given at a dose of 0.5g/kg to 1g/kg given via rapid infusion. Hypertonic saline has also been utilized as an osmotherapeutic agent. Its use causes increase in the intravascular volume and osmolality which results to shifting of fluids and consequent decrease in intracranial pressure. It is available in different concentrations from 3%, 6%, 12% and 23.4%, with the 3% being the most used. In a study by Sabers et al, their review showed a significant decrease in the intracranial pressure and improved cerebral perfusion pressure with increased concentrations of hypertonic saline.[9] In the same study, hypertonic saline was given via fluid boluses as well as combination of continuous infusion with intermittent boluses. The patients given continuous infusion had better fluid balance when compared to those with rapid boluses.

Primary outcomes measured in the use of these decompressants include improvement of Glasgow coma scale scores, morbidities, mortality, and length of hospital stay. In a randomized control study by Mangat on patients 16 years and older diagnosed with severe TBI, they noted that patients given hypertonic saline had decreased cumulative ICP burden as compared to the 20% mannitol group. However, the mortality rates between the two were not statistically significant.[10] A prospective study by Khanna et al on the use of 3% hypertonic saline via continuous infusion on pediatric patients with severe refractory intracranial hypertension due to traumatic brain injury showed decrease in intracranial pressure and consequent improvement on cerebral perfusion associated with increasing serum sodium and serum osmolality. In the study, continuous infusion

was titrated up over a mean duration of 7.6 days until the desired ICP level of less than 20mmHg was achieved.[11]

In a meta-analysis by Zhang et al, sixty-five reports on the complications of mannitol were assessed. Some of the identified complications included acute renal failure, pulmonary edema, cardiac arrest, bundle branch block, hypertonic hyponatremia, hyperkalemia, hypertension or hypotension as well as subcutaneous infiltration. Hypertonic hyponatremia was noted to be due to the increased solute load and increased urinary sodium loss, while hyperkalemia was linked to changes in bicarbonate concentration and movement of potassium along with water from the extracellular space.[5] A study by Kamel et al (2011), reviewed and analyzed randomized control trials comparing the use of hypertonic saline and mannitol in adult patients with increased intracranial pressure of varying causes such as traumatic brain injury, tumors and intracranial hemorrhage. Upon analyzing five RCTs with a total of 112 patients that met the criteria, their assessment showed greater quantitative ICP reduction with the use of hypertonic saline compared to mannitol [12] with a relative risk of 1.2 (95% CI, 1.05-1.36, $p = 0.007$).

For application in clinical practice, we assessed studies supporting the effectiveness of 20% mannitol compared with 3% hypertonic saline in decreasing intracranial pressure in the pediatric age group. Our general objective was to determine the effectiveness of 20% Mannitol and 3% Hypertonic Saline in the management of children presenting with increased ICP. Our specific objectives were: (1) To review and compare the effective dose for mannitol and hypertonic saline in decreasing ICP. (2) To determine differences in effectiveness of 20% mannitol versus 3% hypertonic saline in achieving the primary outcome of decreasing elevated ICP and achieving ICP levels of <20mmHg in patients with different

pathologies: primary intracranial pathologies and other secondary pathologies. ICP levels are determined using intracranial/ ventricular ICP monitors or utilizing cerebral perfusion and mean arterial pressure. Secondary outcomes such as GCS scores, hospital stay, discharge and disabilities will also be assessed. (3) To determine the common complications related to the use of either 20% mannitol or 3% hypertonic saline seen in the pediatric age group.

MATERIALS AND METHODOLOGY

A systematic review of randomized control trials, retrospective and prospective cohort studies was done. The review included studies consisting of male and female subjects less than 19 years old. Literature search was conducted through PubMed/MEDLINE, the Cochrane Central Registry of Clinical Trials (CENTRAL) and EMBASE. Free text and medical subject heading terms were used to identify studies involving the target population and interventions. Search words included the following: "Mannitol" or "20%Mannitol", "Hypertonic Saline" or "3% Hypertonic Saline", "Increased Intracranial Pressure" and "Pediatrics or Children". Other keywords related to increased intracranial pressure such as "Intracranial hemorrhage, CNS infections, traumatic brain injury, intracranial neoplasms/ tumors, neurosurgical, hydrocephalus" were also assessed. The review included literature with available full text articles written in English from year 1965 to year 2021. It included randomized control trials involving human subjects ages less than 19 years old. It utilized randomized control trials with subjects who exhibited increased intracranial pressure of any cause and were admitted and given 20% mannitol and 3% hypertonic saline. Articles with varying manner of infusion and measurement of ICP were included in the study. Prospective observational studies and retrospective studies were also included. Studies involving patients who were given co-interventions to control ICP but were not directly compared to the interventions

under study were included in this review. References from related review articles and clinical trials were cross checked and included in the review.

Two investigators conducted independent searches to decrease possible risk of bias. After assessing eligibility using the inclusion and exclusion criteria, risk of bias assessment was done. After which, the two independent investigators extracted and collated information using a data form. Primary data included demographic information such as the research design, objectives, the number of subjects. Pertinent data on the different intervention arms, ICP monitoring, pathology causing increased intracranial pressure and the use of mannitol and hypertonic saline were assessed. The dose, manner and timing of delivery were also noted. Primary and secondary outcomes from each study such as decrease in ICP, GCS scores, hospital stay, discharge disability and complications were noted. Evaluation for the quality of studies was done using the Cochrane Collaboration Risk of Bias assessment tool. Parameters included randomization, allocation concealment, sequence generation, completeness of outcome, completeness of follow-up, blinding of outcome assessors, selective outcome reporting and other bias. All studies included for analysis were classified as having low, medium, or high risk of bias. The Newcastle-Ottawa Scale was used for observational studies.

A narrative summary of data was provided when studies have significant differences in methodology. Meta-analysis was performed when at least three studies have similar target patient population, adequate sample size and comparable methodology in the assessment of primary and/or secondary outcomes. The Dersimonian and Laird random-effects model was used to account for heterogeneity among the clinical trials. Higgins' I^2 and Cochran's Q statistic was used to assess heterogeneity of studies. Analysis using fixed effects model

was also performed for comparison. Estimates for mean and SD were estimated when median and interquartile range, range or 95% CI were reported in the studies. Sensitivity analysis was also performed to examine the effects of statistical assumptions. The pooled estimate of the standardized mean difference and 95% confidence interval (CI) were reported for decrease in ICP. Pooled relative risk (RR) with 95% CI were estimated for mortality. Statistical significance was based on p-value ≤0.05. Review Manager (Revman) computer program (Version 5.4.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used in data processing and meta-analysis.

RESULTS

A comprehensive search was done through PubMed/MEDLINE, Cochrane Central Registry of Clinical Trials (CENTRAL) and EMBASE. The initial search of articles was done with the following search items: "mannitol", "hypertonic saline" in relation to "intracranial pressure" and a total of 280 studies was noted. Duplicates between searches, studies not written in English as well as those including non-human subjects were removed. After limiting the search to the studies on the pediatric age group (less than 19 years old), a significant number of articles were excluded since majority of studies were included adult subjects. After further excluding other types of studies as well as articles that did not discuss a comparison between the two interventions, a total of 7 articles were deemed eligible for assessment. (Figure 1).

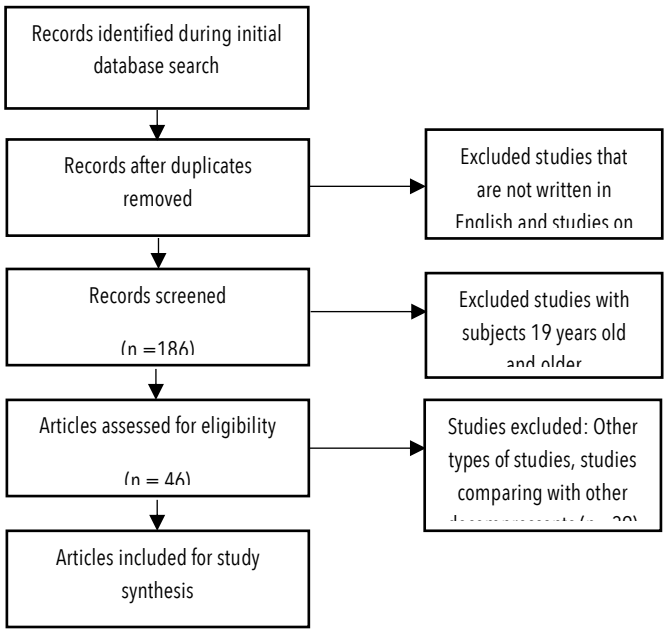

Figure I. Diagram of Study Selection

A prospective randomized control trial done in 2014 comparing the use of 20% Mannitol and 3% Hypertonic Saline among neonates with signs of increased intracranial pressure at the neonatal ICU was not included due to the unavailability of a full text article. A total of seven studies with a total of 1,892 pediatric patients met the eligibility criteria: three RCTs and four retrospective reviews. Study population for the various studies varied from a minimum of 16 subjects to a maximum of 1,632 subjects. The ages of patients ranged from 1 month to <19 years. Characteristics of the studies included in the systematic review are shown in Table I and details of the primary and secondary outcomes are in Table II. Two studies included children presenting with increased intracranial pressure due to traumatic brain injury. The rest of the studies included varying etiologies of increased ICP such as infection (viral and bacterial), hemorrhage, tumors, trauma as well as metabolic causes. Invasive and non-invasive modalities may be done in monitoring increased ICP. Invasive modalities include intraparenchymal catheter and external ventricular drains while some non-invasive measures include transcranial

doppler, optic nerve sheath diameter measurement, tympanic membrane displacement, Visual evoked response, tonometry, pupillometry, neuroimaging with cranial CT or MRI. Currently, the use of an external ventricular drain is considered as the gold standard. In the study, Intracranial monitoring was done in four out of the seven studies. For these studies, an intraparenchymal probe or an intraventricular catheter was used. Other means of monitoring utilized mean arterial pressure calculation and monitoring of various clinical and neuroimaging parameters.

A concentration of 20% Mannitol and 3% Hypertonic Saline was used all the studies assessed. Out of the seven, five studies reported administration of mannitol and hypertonic saline via intravenous boluses. In the study by Rameshkumar et al (2020) [13] an initial bolus of hypertonic saline was given. After which, maintenance doses were given via continuous infusion. Majority of the studies reviewed had dosages within the range of the pediatric dose of 0.25g/kg to 1g/kg for 20% mannitol and 5ml/kg bolus for Hypertonic saline. Three out of seven studies gave equiosmolar doses of mannitol and hypertonic saline. The study by Upadhyay et al [14], utilized a loading dose of 5ml/kg followed by a maintenance dose of 2ml/kg every 6 hours for both mannitol and hypertonic saline. Pre and post infusion ICP values showed significant decrease in the hypertonic saline group specifically during the initial 12 hours of infusion. On the other hand, in the study by Kumar et al [15], equiosmolar doses of mannitol (0.5g/kg or 2.5ml/kg) and hypertonic saline (2.5ml/kg). Mean dose frequency was also specified showing frequency of mannitol delivery at 3.25 doses/day versus hypertonic saline at 4.5 doses/ day. While their study utilized equiosmolar doses and had comparable dose frequency, difference in decrease in ICP was not statistically significant. In the retrospective study by Roumelliotis et at [16],

mannitol dosing (0.6g/kg +/- 0.2) and subsequent osmolality load was higher when compared with hypertonic saline (1.8ml/kg +/- 0.7). For the study, even with higher doses, resultant decrease in ICP was still comparable.

Table 1. Characteristics of studies included in the Systematic Review

Author/ (Year)	Study Design	Age range	Number of patients	Etiologies	ICP monitoring	Formulation /Route		Dose	
						Mannitol	3%HTS	Mannitol	3%HTS
1.Upadhyay et al. (2010)	RCT	2-18 years old	Total N=200 patients Mannitol = 98 3% Hypertonic = 100 Mannitol shifted to 3% = 2	Infection (Meningoencephalitis) Hemorrhagic, Anoxia, Trauma, Space occupying lesion, Infarction	Mean arterial pressure (pre and post drug)	20%/ IV	3% /IV	1g/kg (5ml/kg) bolus then 0.4g/kg (2ml/kg) every 6 hours	Initial (5ml/kg), then 2ml/kg every 6 hours
2.Rameshkumar et al. (2020)	RCT	1-12 years old	Total N= 57 Mannitol =28 3% Hypertonic = 29	Japanese Encephalitis, HSV, Enterovirus, Pneumococcus, Hib, Scrub typhus	Intra-parenchymal catheter (CODMAN, ICP inducer probe), CPP	20%/ IV	3% /IV	0.5g/kg bolus over 20 minutes	10ml/kg loading followed by 0.5-1ml/kg/hr continuous infusion
3. Kumar et al. (2018)	RCT	1-16 years old	Total N=30 Mannitol =16 3% Hypertonic =14	Severe Traumatic Brain Injury	Intraventricular device, Clinical* and Neuroimaging** parameters	20%/ IV	3% /IV	0.5g/kg bolus (1098 mOsm)	2.5ml/kg bolus (1027 mOsm)
4. Vats et al. (1999)	Retrospective Cohort	9 months – 16 years old	Total N=43 Mannitol =18 3% Hypertonic = 25	Closed Head Injury, Intracranial Neoplasm, Fulminant Hepatic Failure, Viral Encephalopathy	Intraparenchymal monitor	20%/ IV	3% /IV	0.5g/kg or 1g/kg bolus	5ml/kg
5. Yildizdas et al. (2005)	Retrospective Study	1y 6mon – 10y 3mon	Total N= 67 Mannitol = 22 3% Hypertonic = 25 Mannitol + 3%HTS = 20	Meningoencephalitis, HIE, Intracranial Hemorrhage, Meningitis, Metabolic Encephalopathy	Clinical* and Neuroimaging** parameters	20%/ IV	3% /IV	0.5g/kg initial then 0.25g/kg bolus	0.5-2ml/kg infusion and 1ml/kg bolus over 15 minutes

6. DeCourcey et al. (2009)	Retrospective Cohort	8y 7mon – 15y 2mon	Total N=1,632 Mannitol = 1,202 3% Hypertonic = 299 Mannitol + 3% HTS = 131	(CEDKA) Cerebral Edema in Diabetic Ketoacidosis; Diabetes with hyperosmolar state, diabetes with coma	Neuroimaging parameters	20%/ IV	3% /IV	Not specified	Not specified
7. Roumeliotis et al. (2016)	Retrospective Study	10-15 years old	Total N=16 Mannitol = 3 3% Hypertonic = 13	Severe Traumatic Brain Injury	Intra-parenchymal catheter or Mean arterial pressure	20%/ IV	3% /IV	0.6g/kg +/- -0.2 bolus	1.8ml+/- 0.7ml; 50% also received continuous infusion 0.5ml/kg /hr

*Clinical Parameters: Clinical: low consciousness less than 8, plus one or more of the ff: unequal, dilated, unreactive pupils, loss of brainstem reflexes (light and oculocephalic) cranial nerve palsies III, VI and cushing's triad

** Neuroimaging Parameters: Effacement of the basal cisterns, thin, slit-like or completely obliterated ventricles, obliterated cortical sulic, shift in the midline, temporal lobe or cerebellar tonsils herniation.

Table 2. Assessment of Primary and Secondary Outcomes

Author	**Primary Outcome (Decrease in ICP)**	**GCS Score (discharge)**		**Length of Stay (days) / Duration of Coma (Hours)**		**Neurodisability/ Mortality (No. of Patients)**		**Complications**
		Mannitol	**3%HTS**	**Mannitol**	**3%HTS**	**Mannitol**	**3%HTS**	
1.Upadhyay et al. (N=200)	Difference: *Mannitol:* 7+/- 3.25 *3% Hypertonic:*11.5+/- 4.48 p <0.001 especially during the initial hours	Not specified	Not specified	Duration of Coma (Hours) *Mannitol:* 98.6 +/- 21.1 Hours *3% Hypertonic:* 77.5+/- 13.05 Hours p value<0.001		Mortality *Mannitol:* Mortality =4 *3% Hypertonic* Mortality =5 p value >0.05		No reported complications
2.Rameshkumar et al. (N=57	Difference: *Mannitol:* -5.4+/-1.7 *3% Hypertonic:*14.3+/- 1.7 p <0.001	GCS 11	GCS 13	PICU Stay (days) *Mannitol:* 19 (12.3-25.7) *3% Hypertonic:* 11 (8.4-13.6) days p value = 0.016		*Mannitol:* None: 17%, Mild 5% Moderate17%, Severe 61% Mortality =10 *3% Hypertonic* None: 39%. Mild: 13% Moderate:17, Severe 31% Mortality =6 Mortality p value= 0.21		Rebound raised ICP: Mannitol: 50%, 3%HTS: 18% Hypotension Acute Kidney Injury

3. Kumar et al. (N=30)	Difference: *Mannitol:* -7.13mmHg (SD 2.9) *3% Hypertonic:* -5.67mmHg (SD 3.9) p value = 0.33	Not specified	Not specified	PICU Stay (days) *Mannitol:* 9.5 (SD 4.3) *3% Hypertonic:* 9.64 (SD 4.4) p value= 0.92 Hospital Stay (days) *Mannitol:* 9.5 (SD 4.3) *3% Hypertonic:* 9.64 (SD 4.4) p value =0.73	Survival without disability *Mannitol:* 13 of 16 *3% Hypertonic:* 12 of 14 p value 0.69 Death of survival in vegetative state *Mannitol:* 3 (23.07%) *3% Hypertonic:* 2 (16.6%)	No reported complications
4. Vats et al. (N=43)	Difference: *Mannitol: 6.6* -8.8mmHg *3% Hypertonic:* 5.9-6.8 mmHg (p< 0.05)	Initial GCS 5 (3-9) Discharge GCS Not specified	Initial GCS 8 (3-9) Discharge GCS Not specified	Not specified	Mortality *Mannitol:* 10 of 18 *3% Hypertonic*: 12 of 25	No reported complications
5. Yildizdas et al. (N=67)	Not specified	Initial GCS 4.4 +/- 1.3 Discharge GCS Not specified	Initial 4.5+/-1.1 Discharge GCS Not specified	Duration of Coma: (hours) *Mannitol:* 123+/-48.2** *3% Hypertonic* 88.6+/- 42.5** Mannitol + 3% HTS: 87.5+/-26.1** p value =0.004	Mortality *Mannitol:* 50% *3% Hypertonic:* 25% Mannitol + 3% HTS: 20% p value =0.003	*Mannitol:* Renal failure *3% HTS:* Hyperchloremic metabolic acidosis *Cause of Mortality:* Septic shock, VAP with ARDS, Progressive Cerebral edema with pulmonary edema
6. DeCourcey et al. (N=1,632)	Not specified	Not specified	Not specified	PICU admission *Mannitol:* 784 (65.2%) *3% Hypertonic:* 269 (90%) *Mannitol + 3%HTS:* 122 (93.1%)	Mortality *Mannitol:* 31/ 1,202 (2.5%) *3% Hypertonic:* 11/299 (3.7%) Mannitol + 3% HTS: 12/131 (9.2%) p <0.001	No reported complications
7. Roumeliotis et al. (N=16)	Mannitol: 21 (17-25); 27 (22-32) p= 0.055 Hypertonic Saline: 23 (19-28); 20 (19-26) p = 0.096	Initial GCS 4 (4-4.5) Discharge GCS Not specified	Initial GCS 6 (6-7) Discharge GCS Not specified	Not specified	Mortality = 5 (31%)	No reported complications

*Converted to hours (from days) ** After 1 bolus

Risk of bias was assessed using the Cochrane Collaboration Risk of Bias assessment tool. Two separate evaluators assessed the included studies and disagreements were discussed. Our study reviewed 3 RCTs. There was low risk of selection bias for majority of the studies

included since the trials were sufficiently randomized. Low or unclear grading was noted due varying presence of blinding for personnel and assessors among different studies.

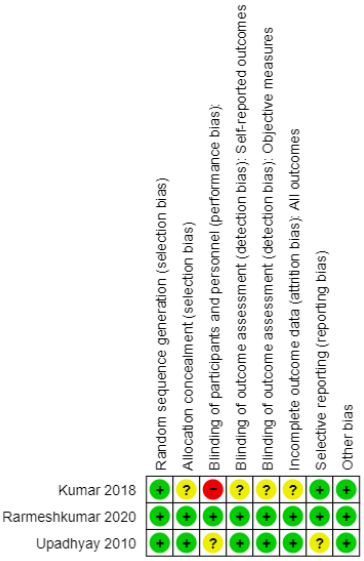

Figure 2. Risk of Bias Summary

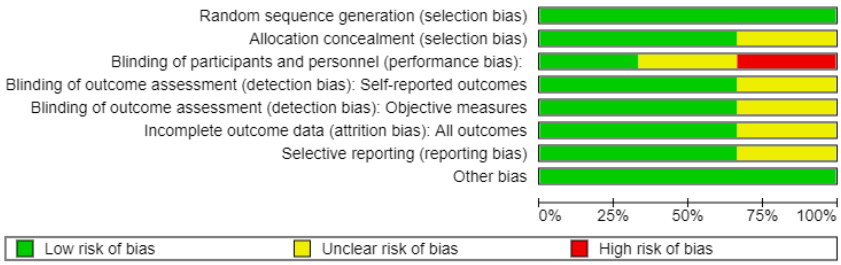

Figure 3. Risk of Bias Graph

For observational studies, the Newcastle-Ottawa Scale was used. The studies had adequate selection, with records showing ascertainment of exposure. The studies also noted proper documentation of evidence of outcomes and sufficient follow-up for outcomes.

Table 3. Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcome
Vats et al. (1999)	★★★★	★	★★
Yildizdas et al. (2005)	★★	★	★★
DeCourcey et al. (2009)	★★★★	★	★★
Roumeliotis et al. (2016)	★★★	★	★★★

Study Outcomes

Two randomized controlled studies showed evidence that 3% hypertonic saline was superior to 20% mannitol in reducing raised intracranial pressure. In the prospective randomized study by in Upadhyay et al. 2010 [14] (n=200), the estimated mean difference (±SE) in ICP from baseline to 48h between the mannitol and HTS groups was significant (male: -4.6±0.06, $p<0.001$; female: -1.5±0.07, $p<0.001$). Similarly, in a recent open-label randomized trial by Rameshkumar et al. in 2020 [13] (n=57), the trend in mean ICP in the first 72 hours was significantly lower (14 ± 2 vs 22 ± 2 mmHg; p=0.009) in the hypertonic saline group. The mean change from baseline to 72 hours was significantly lower (-14.3±1.7 vs -5.4±1.7; $p \leq 0.001$) in the HTS group. Two other studies with smaller sample sizes also showed decrease in ICP but was insufficient to establish statistical significance. This was observed in the open label randomized controlled trial by Kumar et al. in 2018 [15] (n=30), the mean (±SD) reduction in ICP, was −7.13±2.9 in the mannitol group and −5.67±3.9 in HTS group; the difference was not statistically different (p=0.92). In a retrospective study by Roumeliotis et al [16] in 2016 (n=16), both mannitol and HTS were also followed by a decrease in ICP in the following 4-hour period, however, this did not achieve statistical significance (mannitol p= 0.055 and HTS, p=0.096). Due limited number of studies and high heterogeneity, a pooled analysis could not be done.

In a recent retrospective cohort study by Rameshkumar et al (2020), the median m-GCS score upon discharge from the PICU in the HTS group was 13 (IQR=10 to 14) and 11 (IQR=3 to 13) in the mannitol group. Test of independence of distributions between the two groups showed that GCS scores in the saline group were significantly higher than in the mannitol group (p=0.006). Although baselinescores were reported in 3 of 7 studies, no other study reported GCS score upon discharge.

Of 332 cases of increased intracranial pressure treated with either 20% mannitol or 3% hypertonic saline, duration of coma or length of stay in PICU was significantly shorter in the saline group than in the mannitol group (SMD=0.68, 95% CI=0.17 to 1.17, p=0.008).

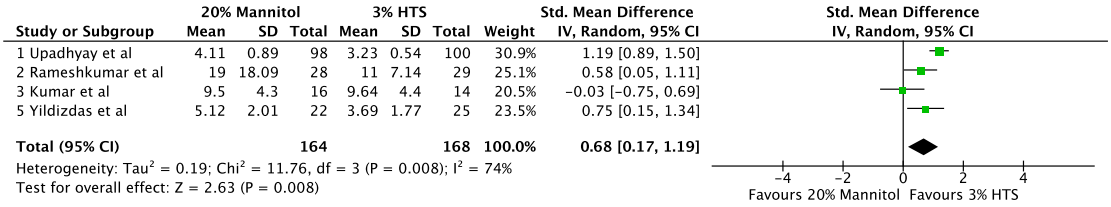

FIGURE 4. Forest plot on the duration of coma or stay in PICU (in days) between 20% Mannitol and 3% Hypertonic saline in children with increased intracranial pressure

Of 1,876 cases of patients with increased intracranial pressure, 285 were randomly treated with either 20% Mannitol or 3% hypertonic saline. Mortality in these groups were comparable. The pooled risk of mortality using 3% hypertonic saline compared to 20% mannitol was 1.36 (95% CI: 0.70 to 2.62, p=0.36). In comparison to a fixed effects model, there was no substantial change in the pooled RR and although the 95% confidence intervals narrowed, mortality rate was still comparable between the two groups (RR=1.31, 95% CI: 0.68 to 2.52, p=0.42). Similar results were observed on the 1,591 cases treated with either 20% Mannitol or 3%

hypertonic saline (RR=1.07, 95% CI: 0.72 to 1.59, p=0.730).

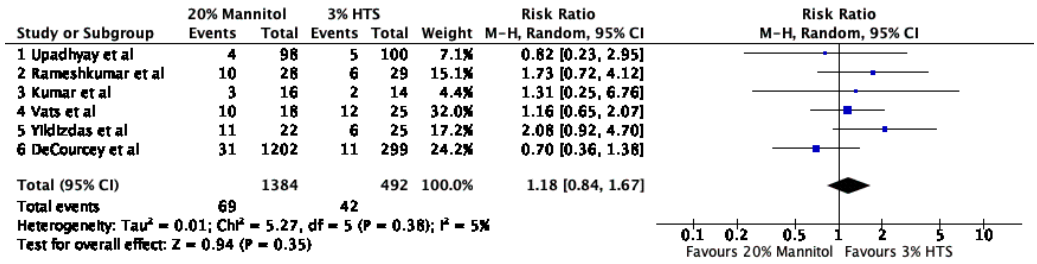

FIGURE 5. Forest plot on relative risk of mortality between 20% Mannitol and 3% Hypertonic saline in children with increased intracranial pressure

No complications were reported in 5 of 7 studies. In an open label randomized trial by Rameshkumar et al. in 2020, there was a significantly higher proportion of patients who developed rebound increase in intracranial pressure in the mannitol group than in the hypertonic saline group (50% vs 18%, RR=0.42, 95% CI=0.19 to 0.92). In the same study, they also reported a lower number of patients experiencing hypotension in the hypertonic saline group as compared to the mannitol group. They also reported the occurrence of acute kidney injury and hemolysis, which was comparable between the two groups. In a retrospective study by Yildizdas et al. [17] in 2006, one patient developed renal failure. Treatment with mannitol was then discontinued. One patient from the hypertonic saline group also developed diabetes insipidus, hence treatment was also discontinued. In the same study, an equal number of patients, two from each group, developed hyperchloremic metabolic acidosis. No serious adverse events were associated with the trial interventions.

DISCUSSION

Osmotherapy plays a vital role in the management of increased intracranial pressure. Being the most available osmotherapeutic agents in our setting, the

study compared 20% mannitol and 3% hypertonic saline. The investigators reviewed available articles and noted that studies on the osmotherapeutic treatment for this neurologic emergency proved to be limited especially in the pediatric age group. Majority of the available studies were done in the adult population with severe traumatic brain injury as the cause for increased ICP.

In terms of reduction in intracranial pressure, there is evidence showing increased benefit of using 3% hypertonic saline over 20% Mannitol. Compared with majority of the previously available studies which focused primarily on traumatic brain injury, the study population assessed in both studies showed varying etiologies causing cytotoxic, vasogenic, interstitial edema or a combination ultimately resulting to increased intracranial pressure. Osmotic diuretics, such as mannitol, alter the starling forces promoting the movement of fluid from the cell reducing intracellular volume and subsequently decreasing intracranial pressure.[18] An intact blood brain barrier enables the maintenance of this gradient. In central nervous system infections such as meningitis, cytokines and other immune cells circulate and affect endothelial cells leading to changes and increased permeability of the blood brain barrier [19]. Similarly, clinical studies on infants with previous hypoxic injury was also noted with increased albumin/ CSF blood ratios suggesting changes in barrier integrity.[20] In the two RCTs assessed, of which majority of the subjects were diagnosed with CNS infections such as viral meningoencephalitis and bacterial meningitis, a better response was seen with the use of hypertonic saline in decreasing intracranial pressure between 48-72 hours. Apart from an infectious cause, a large retrospective study in our review included children diagnosed with cerebral edema due to Diabetic Ketoacidosis. In the study, outcome comparison was made in terms of PICU stay and mortality. Actual decrease in ICP measurement was not

reported. Other etiologies in our review also included patients with hemorrhage, anoxia, infarction, trauma as well as tumors. In terms of effective dose, this study showed that within the therapeutic range, decrease in ICP was seen after administration of 20% mannitol and 3% hypertonic saline. In half of the studies assessed, 20% mannitol and 3% hypertonic saline were both given as bolus and were noted to be of equal dose. Full assessment of appropriate dose titration, manner of infusion and frequency in the various studies however was limited by the differences in available data such as serum osmolality, electrolyte levels, neurologic examination status as well as type of ICP monitoring done. The availability of these laboratory tests and monitoring modalities may also vary among different institutions.

Majority of the studies in the review utilized a bolus infusion for delivering both mannitol and hypertonic saline. Two retrospective studies in the adult population diagnosed with traumatic brain injury compared the method of 3% hypertonic saline infusion and showed varied results. In a 9-year retrospective study by Roquilly et al, 2011 [21], use of continuous controlled infusion showed increase in cerebral perfusion pressure (CPP) and resultant decreased in intracranial pressure. In another retrospective study by Maguigan et al, 2017 [22] more patients given continuous infusion reached the goal serum osmolality compared with bolus administration. However, for their study, there was no statistically significant difference in the CPP and ICP between the two methods of infusion. In the review, the study by Rameshkumar et al (2020) showed use of mannitol delivery in boluses every 4 hours. On the other hand, 3% hypertonic saline was initially given via bolus and was then maintained via continuous infusion. In the study, use of hypertonic saline in this manner resulted in a statistically significant decrease in ICP.

Different complications have been associated with the use of 20% mannitol and 3% hypertonic saline. In the review, hypotension and renal failure was seen in several patients who were previously given mannitol while diabetes insipidus was seen in a patient who was previously given hypertonic saline. In the two studies that reported complications, acute kidney injury, hemolysis and hyperchloremic metabolic acidosis developed in patients under both treatment arms. A retrospective study by Gonda et al in 2013 assessed the level of hypernatremia in prolonged hypertonic saline infusions as well as its complications. In their study including eighty-eight children, they noted that children with sustained serum sodium of >170, compared with those with serum sodium of 150-160 meq/L, had a high occurrence of thrombocytopenia ($p< 0.001$), renal failure ($p< 0.001$) as well as neutropenia and acute respiratory distress syndrome.[23] Comparing this finding with the current review, one RCT study reported complications at serum levels of 141+/- 7 for the mannitol group and 144+/-8 for the hypertonic saline group. In the study by Yildizdaz et al, serum sodium ranged from 144-176meq/L. These support the need for caution in the use of osmotherapy as well as the need for adequate monitoring while titrating to reach adequate osmolality to maximize decompressive effects in children with increased intracranial pressure.

Limitations to the study include the following: (1) few numbers of randomized control trials, comparing the two osmotherapeutic agents in the pediatric age group (2) current available studies have different outcome measures; and (3) there were differences in ICP monitoring and measurements, diagnostics, tools utilized and interventions.

CONCLUSION

This systematic review assessed available literature on the effectiveness of 20% Mannitol and 3% Hypertonic saline in the management of increased ICP in the pediatric

age group. The investigators noted that while both agents showed favorable effects in lowering intracranial pressure caused by varying etiologies, hypertonic saline showed benefit compared with 20% mannitol. While more developed hypotension and rebound increase in ICP with the use of mannitol, both agents reported occurrences of acute kidney injury, hemolysis and hyperchloremic metabolic acidosis. Due to the limited number of articles and heterogeneity of the studies reviewed, no firm conclusions can be made regarding the superiority of one agent over the other. Larger prospective randomized studies in different clinical situations using 20% mannitol and 3% hypertonic saline in the treatment of increased ICP in the pediatric age group are needed to render valid affirmations.

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CALVARIAL TUBERCULOSIS

EFRAIM CULMINAS, LUCY KATHRINA BANTA- BANZALI

ABSTRACT

Skeletal tuberculosis accounts for 1-3% of TB cases, and of these only 0.2-1.3% had calvarial involvement.[1] Calvarial TB is most likely secondary to a primary focus. Diagnosis is confirmed through findings of *Mycobacterium tuberculosis* via microbiological, histopathological or cytopathological methods. This case report presents Primary Calvarial Tuberculosis in a five-year old male presenting with multiple cranial masses and initial diagnosis of Langerhans cell histiocytosis (LCH).

CASE REPORT

A five-year-old male presented with a two-year history of a left frontal head mass. He had a history of head trauma few days prior to the appearance of the mass. The mass was noted to gradually enlarge along with the appearance of multiple masses at the right and left parietal areas. Physical examination showed multiple, soft, fluctuant, non-erythematous, nontender, non-movable masses on the left frontal and both parietal areas of the skull. The rest of his physical and neurologic examination was unremarkable.

A skeletal survey revealed multiple varisized lucent lytic foci with non-sclerotic rims in the skull and a cranial Computed tomography (CT) scan showed multiple osteolytic changes scattered on the calvarium (Figure 1). Imaging findings were consistent with LCH. Two months into the work-up, the patient had cough and undocumented fever. Chest radiography revealed pneumonia with minimal left pleural effusion. Tuberculosis work-up was done and a Mantoux test showed an 11-millimeter induration while sputum Acid Fast Bacilli (AFB) showed negative findings. He was then started on Isoniazid and Rifampicin for three months. The patient has unremarkable past medical, surgical, family, birth, and maternal

history. He had completed his primary series of vaccination including the Bacille Calmette-Guerin (BCG) vaccine. He has no known allergies. His developmental milestones were at par with age.

He then underwent left frontal craniectomy and excision. Intraoperatively, the tumor was soft, yellowish, and thinly circumscribed with cystic fluid within. There was no infiltration to the inner table of the skull. Histopathology reported chronic granulomatous inflammation with multinucleated giant cells and extensive necrosis consistent with calvarial tuberculosis. The CD1a immunohistochemistry staining for LCH was negative. AFB testing of the cystic fluid was also negative. The Estimated Sedimentation Rate (ESR) was noted to be thrice elevated. Patient was subsequently managed as a case of calvarial tuberculosis and was given anti-tuberculosis treatment for 12 months. Three months post craniectomy, the patient already completed the intensive phase of the anti-tuberculosis regimen and is currently on the first month of the continuous phase. There was regression of the cranial masses and there was no evidence of appearance of new lesions.

CASE DISCUSSION

On the background of a normal neurologic examination, metastatic neuroblastoma and calvarial tuberculosis were considered in a patient who presented with bone lytic lesions. Initially, LCH was considered due to his clinical presentation and history that was supported by the imaging findings. Eighty percent of patients with LHC has skeletal system involvement of which 50% involves the skull. Radiologic studies will also reveal punched-out lytic lesions.[3] However this patient had a negative CD1a expression in immunohistochemistry and biopsy showed chronic granulomatous inflammation consistent with calvarial Tuberculosis. The rarity of calvarial tuberculosis put this diagnosis aside until the biopsy results were obtained. Usually this is transmitted via the

hematogenous or lymphatic routes. The spread through a lymphatic route makes this rare as the skull has a generous vascular supply. The primary event is the lodging of the bacilli in the diploic skull bones from an extracalvarial focus. Trauma is postulated to be a predisposing factor. This may be due to direct inoculation[4] or an increased vascularity, decreased resistance, discovery of a latent infection or the attraction of inflammatory cells to the area of trauma.[5,4]

Calvarial tuberculosis has a higher incidence in the young, aged 15-16 years old with predominance in males.[2,6] The most common presentation is a painless, soft fluctuant scalp swelling. This is usually followed by sinus discharge, localized pain, seizures and meningitis.[7] The most common sites of involvement are frontal and parietal bones and is due to the greater amount of cancellous bone with diploe channels at these sites.[2,3,5,6] Raut et al. found that the lesions may appear singly or multiple and has three types: The circumscribed or perforating type, the diffuse type and the least common, the circumscribed sclerotic type.

Our patient is a five-year-old male with a cranial mass who had the same presentation as with other cases of calvarial tuberculosis. Although vaccination was complete and no known exposure to tuberculosis infection were named, the history of head trauma is a strong predisposing factor. His cranial masses also involved frontal and parietal bones and is a perforating type of lesion. Imaging studies help to delineate lesions. A skeletal survey usually detects 80% of lesions and show punched-out defects with both osteolytic and osteoblastic areas. In plain cranial CT imaging, small, circumscribed and punched out, lytic or sclerotic lesions are commonly found in the parietal, frontal or occipital area of the skull. A magnetic resonance imaging (MRI) is highly specific and allow for a conclusive diagnosis as it can delineate subtle parenchymal involvement.

Our patient had lytic lesions in frontal, parietal and occipital area and cranial CT scan demonstrated bone destruction which is noted in 85% of calvarial tuberculosis.[6] Although the patient had no other symptoms such as night sweats, generalized weakness and loss of appetite, he developed fever and cough during his disease. His chest radiograph showed pleural effusion which hinted at a possible primary pulmonary tuberculosis or may represent a reactivation of tuberculosis, as pleural effusions may occur in the absence of a radiologically apparent tuberculosis.[8] A positive Mantoux test and an elevated ESR, as in the case of this patient may give a diagnostic clue to the diagnosis of tuberculosis. Calvarial tuberculosis can be confirmed through the isolation of Mycobacterium bacilli in culture or a positive AFB.[5] The patient's clinicoradiological presentation combined with histopathological evidence of a caseating granuloma is often sufficient to diagnose tuberculosis.[7] Once there is a strong clinical suspicion, the patient can be started on anti-tuberculous treatment and a good response will confirm the diagnosis. Our patient still satisfied the criteria for tuberculosis based on the National Tuberculosis Protocol of the Philippines (NTP). Given the history, physical examination, diagnostic studies, and the histologic confirmation through biopsy, the patient was clinically diagnosed with extrapulmonary tuberculosis.

The management comprises of completion of an anti-Tuberculosis regimen; in some cases, surgical intervention may be necessary. Surgery is indicated for large lesions and if neurological deficits are present.[5] In this case, surgery was vital in the patient's diagnosis as it led to the histologic finding of calvarial tuberculosis. As per NTP guidelines for skeletal tuberculosis, a two-month intensive phase, followed by ten months of the continuation phase is recommended. The patient's progress can be monitored through

serial ESR and cranial CT scans after the intensive phase of anti-Tuberculosis treatment. The prognosis of calvarial tuberculosis is generally good. Currently, the patient has no evidence of new-onset lesions or recurrence of lesions for seven months now since diagnosis. On follow-up patient is generally well, with no significant findings on MRI (Figure 2) and is on the first month of continuous phase anti-tuberculosis treatment.

SUMMARY

Calvarial tuberculosis is a rare form of skeletal tuberculosis, and it is important to diagnose early. This case shows that it is important to consider tuberculosis, which is a common disease in the Philippines but can often be missed due to its varying presentation. A thorough clinical history and physical examination are important as it can provide practical cues to arrive at the right diagnosis and management. Surgery is indicated for obtaining tissue for histological analysis or for removal of bony sequestra. Other surgical indications include cases with large extradural collections causing neurologic deficits or lack of response to treatment. Prognosis is dependent on the provision and compliance of appropriate pharmacotherapy. Hence patient education is vital as tuberculosis has implications to the community.

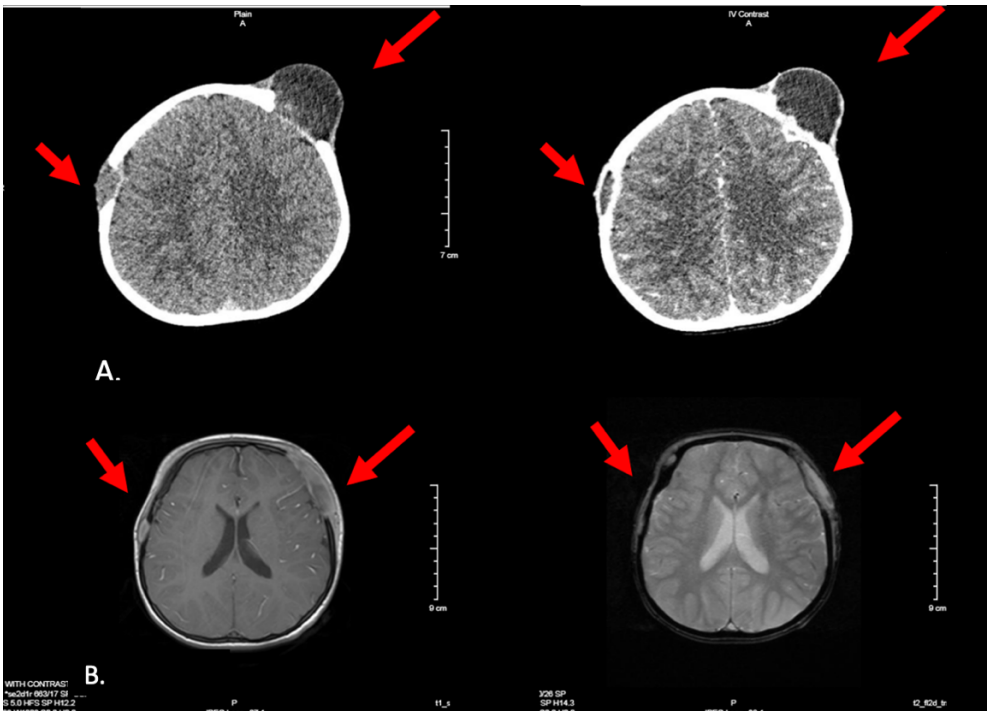

Figure 1. ***A.*** Cranial Computed Tomography (CT) scan preoperatively (without contrast, left. with contrast, right). Multiple osteolytic changes scattered on the calvarium associated with extra-cranial masses through the lytic defects, with most of them exhibiting epidural extensions. An avidly enhancing predominantly solid lesion (arrows) is also evident on the right frontal lobe ang left anterior temporal lobe with associated surrounding vasogenic edema and effacement of adjacent sulci. ***B.*** Cranial MRI post operatively (T1, left. T2, right). Destruction of both inner and outer tables of the skull with multiple soft tissue components extending into the subgaleal region with associated thickening of the dura. Multiple bulging scalp masses were noted at the left posterior frontal convexity, right anterior parietal bone, left posterior temporal to anterior occipital bone.

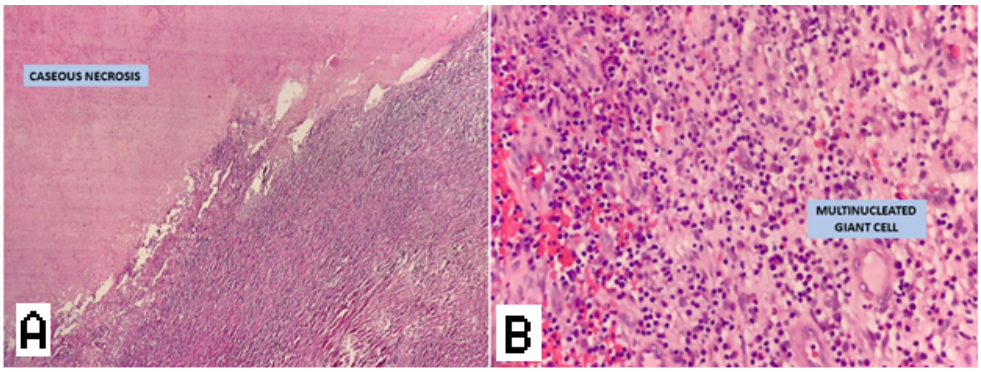

Figure 2. Hematoxylin and Eosin Stain of the calvarial mass (left, frontal) showing A. Caesous Necrosis and B. Granulomatous inflammation with multinucleate.

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