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

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ABSTRACT

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

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

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

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

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

INTRODUCTION

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

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

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

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

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

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

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

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

OBJECTIVES OF THE STUDY

General Objective

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

Specific Objectives

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

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

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

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

METHODOLOGY

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

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

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

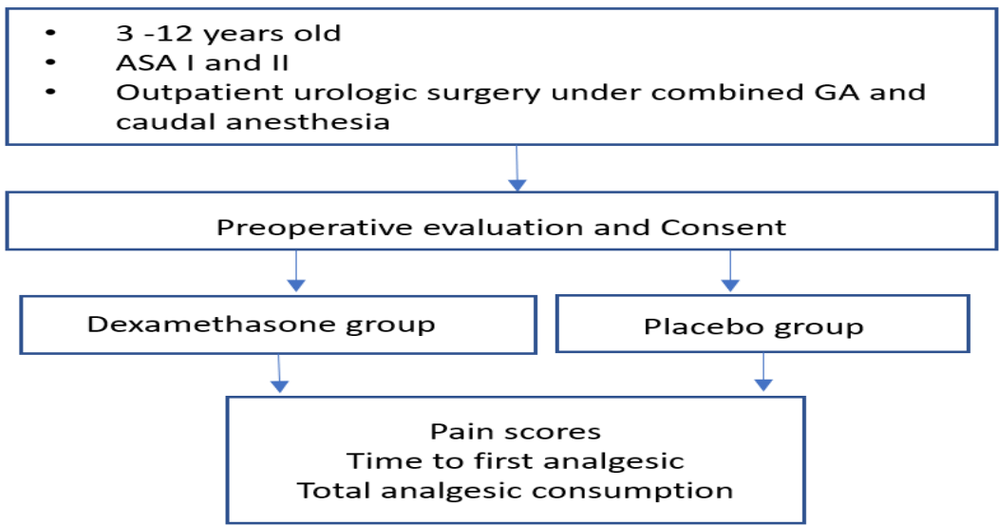
Subjects were randomly assigned to either Dexamethasone (D) group or Placebo (P) group using computer-generated random numbers. Randomization was done by an anesthesiologist who is not participating in the study. Treatment assignment were placed in sealed envelopes and were opened by another anesthesiologist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

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

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

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

Figure 1. Methodology Algorithm



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

The investigator monitored the following data:

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

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

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

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

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

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

RESULTS

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

Table 1. Demographics and Intraoperative Characteristics

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

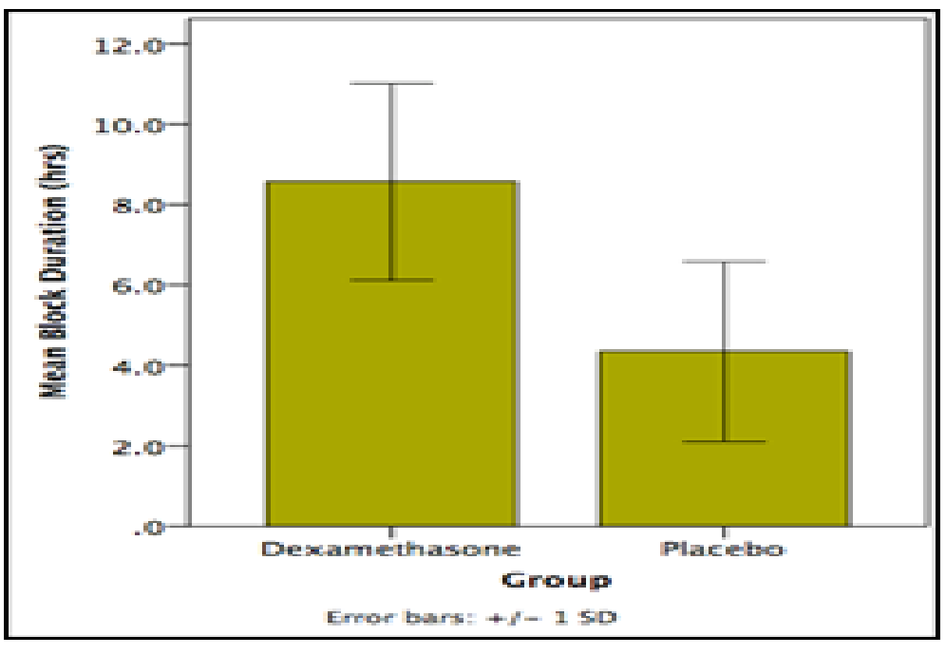
Values expressed as mean ± SD.

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

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

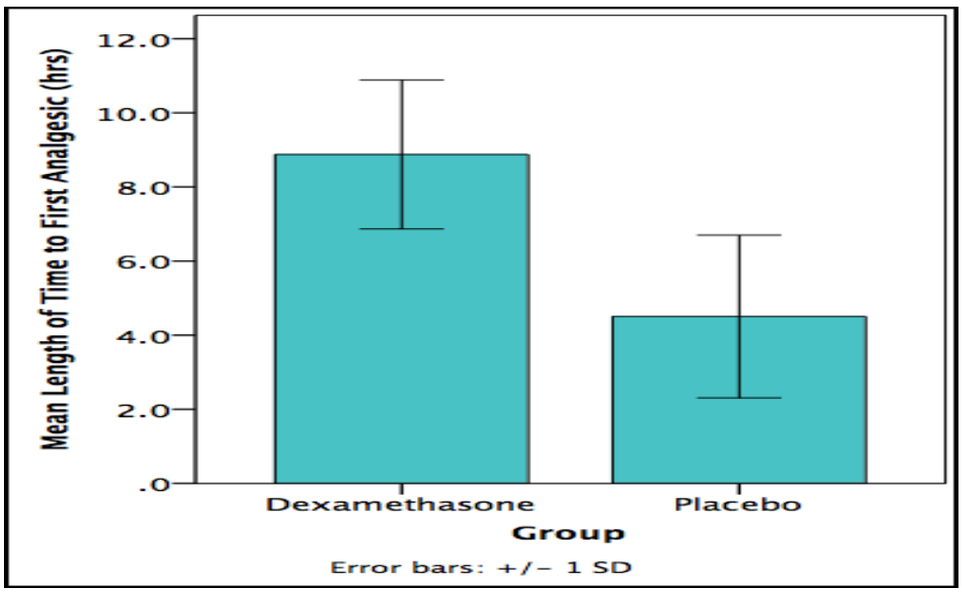
Values expressed as mean ± SD.

Figure 3. Mean Block Duration



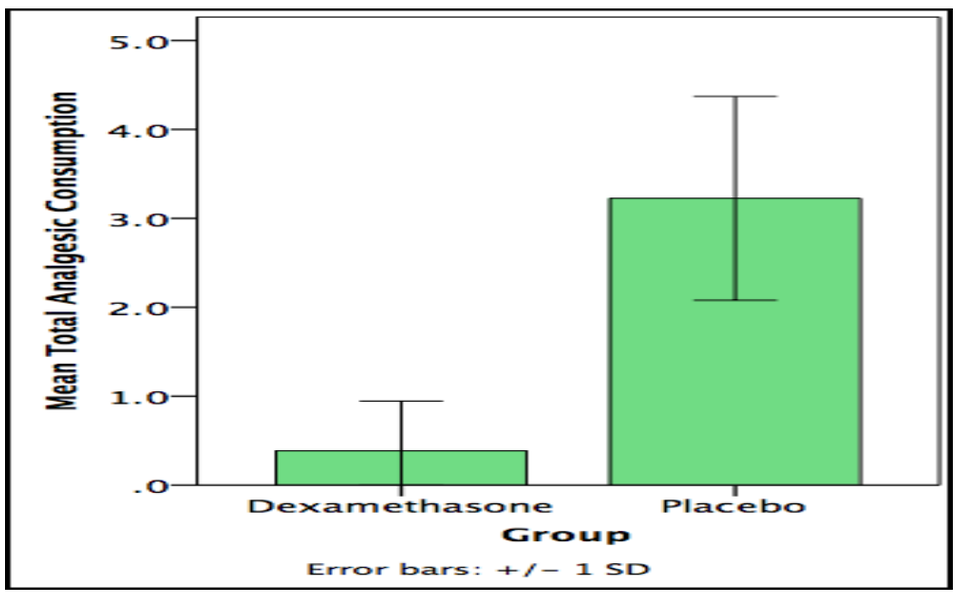
There was no failure of caudal blocks noted in any of the patients. It is evident that the mean duration of analgesia (block duration) of patients treated with dexamethasone is significantly higher (p<0.001) than the placebo group. This shows that the duration of analgesia of patients treated with dexamethasone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

Figure 4. Mean Length of Time to First Analgesic



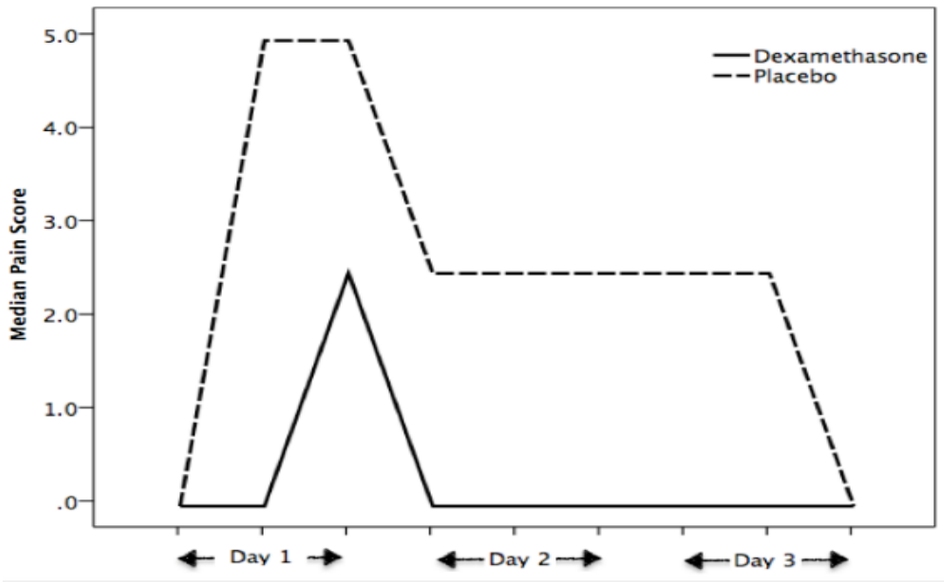
None of the children in both groups needed rescue Paracetamol in the PACU. Thirty-one (31) patients in the placebo group, while 11 patients treated with dexamethasone had been given Paracetamol. It was evident that among the patients, the mean length of time to first rescue analgesic of patients treated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

Figure 5. Mean Total Analgesic Consumption



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

Figure 6. Median Pain Scores



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

DISCUSSION

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

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

CONCLUSION AND RECOMMENDATIONS

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

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

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