

Dexmedetomidine versus Magnesium as Adjuvants to Bupivacaine-Induced Caudal Block in Children: A Randomized, Double-Blinded, Placebo-Controlled, Trial

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Abstract

Citation: Refaee HH, Abo Elela AH, Hanna MG, Ahmed Ali MA, El Khateeb AM. Dexmedetomidine versus Magnesium as Adjuvants to Bupivacaine-Induced Caudal Block in Children: A Randomized, Double-Blinded, Placebo-Controlled, Trial. Open Access Maced J Med Sci. <https://doi.org/10.3889/oamjms.2019.024>

Keywords: Caudal block; Children; Magnesium; Dexmedetomidine

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Received: 08-Nov-2018; **Revised:** 14-Dec-2018; **Accepted:** 15-Dec-2018; **Online first:** 12-Jan-2019

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

BACKGROUND: Caudal block remains fundamental in pediatric anaesthetic practice. It is very useful in a wide range of surgical procedures and has proved to have a remarkable safety record. But one of the major limitations of the single-injection technique is the relatively short duration of postoperative analgesia. Prolongation of caudal analgesia using single-shot technique has been achieved by the addition of various adjuvant.

AIM: This work aims to compare magnesium and dexmedetomidine as adjuvants to bupivacaine-induced caudal block in children undergoing lower limb orthopaedic surgery.

STUDY DESIGN: Randomized, double-blind trial.

SETTINGS: Pediatric OR of a tertiary care centre.

METHODS: A double-blinded, randomised controlled trial included 36 children, aged between 1 and 7 years, scheduled for lower limb orthopaedic surgery. Patients received general anaesthesia in addition to the caudal block. Patients were divided into three groups: Dexmedetomidine group (n = 12): received 0.5 mL/Kg bupivacaine + 2 mcg/Kg dexmedetomidine, Magnesium group (n = 12): received 0.5 mL/Kg bupivacaine + 50 mg magnesium, and control group (n = 12): received 0.5 mL/Kg bupivacaine + normal saline. Patients were compared according to the duration of analgesia, pain scores, sedation scores, mean arterial pressure, and heart rate.

RESULTS: Both magnesium group and dexmedetomidine group showed better analgesic profile (duration of analgesia and pain scores) compared to the control group without significant difference between the two former groups. Dexmedetomidine group showed higher sedation score, lower mean arterial pressure and lower heart rate compared to other groups.

CONCLUSIONS: Both magnesium (50 mg) and dexmedetomidine (2 mcg/Kg) improved the analgesic profile of bupivacaine-induced caudal block in children. Dexmedetomidine administration was accompanied with higher sedation score and negative hemodynamic profile.

Introduction

Caudal block remains fundamental in pediatric anaesthetic practice. Single-injection technique for the caudal block is usually limited by short duration of postoperative analgesia [1]. Addition of adjuvants to local anaesthetics could prolong the duration of the caudal block.

Dexmedetomidine (Dex) is a highly selective

α_2 -adrenoreceptor agonist with various uses in anaesthesia and intensive care units [2], [3]. Dex offers a unique pharmacological profile because it is a sedative, sympatholytic, analgesic with minimal respiratory depression. Dex had shown good results when used as an adjuvant to caudal block [4]. Although dexmedetomidine is a highly promising adjuvant to local anaesthetics, its use is limited by the negative hemodynamic profile and the high cost.

Magnesium (Mg) is another drug which has analgesic and antinociceptive effects. In a recent

systematic review, Kawakami et al. had reported that Mg improved the analgesic profile of caudal block in children [5]. To the best of our knowledge, no data is available for comparison of Dex and Mg as adjuvants to bupivacaine-induced caudal block in children.

We conducted this study to compare the analgesic and hemodynamic effects of dexmedetomidine and magnesium sulphate when added to bupivacaine in the caudal block in children.

Methods

This double-blinded, randomised, controlled trial was conducted in Cairo University hospital after approval of the research ethics committee. Written informed consent was obtained from the patient's parents or guardians.

Thirty-six patients aged between 1-7 years, ASA I-II scheduled for infra-umbilical orthopaedic surgeries were included in the study. Patients were randomly assigned into 3 groups using an online randomisation program (<http://www.randomizer.org>). Concealment was achieved using opaque envelopes. Exclusion criteria include allergy to the study drugs, suspected coagulopathy, local infection, history of developmental delay, neuromuscular disorders, skeletal deformities, and magnesium therapy. Patients in whom caudal block failed were excluded from our study.

On arrival to the preparing room, patients were sedated by midazolam (0.2 mg/kg IM). On arrival to the operating room, patients were monitored using five-lead electrocardiography (ECG), automated non-invasive blood pressure monitor (NIBP), pulse oximetry and temperature probe.

Inhalational induction of anaesthesia was achieved by sevoflurane in 100% oxygen, and an appropriate-sized cannula was inserted. The endotracheal tube was inserted.

Patients were randomly assigned into 3 groups:

a. Group D (n = 12): received caudal block bupivacaine (0.25%) at dose of 1 mL/Kg plus dexmedetomidine (2 µg/kg diluted into 0.5 mL) mL/Kg.

b. Group M (n = 12): received caudal block with bupivacaine (0.25%) at a dose of 1 mL/Kg plus magnesium sulphate (50 mg in 0.5 mL)

c. Group C (n = 12): received caudal block with bupivacaine 0.25% diluted in normal saline at a dose of 1 ml/kg plus 0.5 mL normal saline.

At the end of the operation, sevoflurane was discontinued. The endotracheal tube was removed, and patients were discharged in the post-anaesthesia

care unit. Rescue analgesia in the form of oral paracetamol (10-15 mg/kg/dose) was taken and had to be repeated every 6 hours if needed (the time at which FLACC score 4 or more).

The patients were transferred to the ward after spending two hours in the recovery room after the surgery.

Duration of analgesia (defined as the time of caudal block was performed to the time at which FLACC score 4 or more)

Hemodynamic measures: mean arterial blood pressure (MAP) (mmHg) and heart rate (bpm): were measured at the baseline (before induction of anaesthesia), after induction of anaesthesia, and every 5 minutes till the end of the operation. We analysed three readings: baseline reading, post-caudal block reading, and the average of all other intra-operative readings.

Pain score (FLACC score) [6] (ranging from 0 to 10): was assessed at the end of surgery and 1, 2, 6, 8, and 12 hours postoperatively,

Ramsay score [7]: (ranging from 1 to 8) was recorded after PACU arrival

Total (12-hours) postoperative paracetamol requirements were recorded

Complications secondary to test drugs (postoperative nausea, vomiting, bradycardia (HR < 80 BPM) and hypotension (SBP < 70 mmHg + age in years * 2) were also reported.

Our primary outcome was the duration of analgesia. The previous study showed a mean duration of analgesia 286.4 ± 47.8 minutes in children who received bupivacaine in caudal block [8]. We calculated our sample size to detect a difference of 20% (58 ± 47.8 minutes) between study groups. A minimum number of 9 patients per group were calculated to have a study power of 80% and an alpha error of 0.05. The number was increased to 12 patients per group to compensate for dropouts.

Data were statistically described regarding mean \pm standard deviation (\pm SD), median and range, or frequencies (number of cases) and percentages as deemed appropriate. Comparison of numerical variables was made using one-way analysis of variance (ANOVA) test with post-hoc multiple 2-group comparisons in normally distributed data, and Kruskal-Wallis test with post-hoc multiple 2-group comparisons in skewed data. For comparing categorical data, Chi-square (χ^2) test was performed. The exact test was used instead when the expected frequency is less than 5. A p value less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

Forty-four patients were screened for eligibility. Six patients were excluded, and 36 patients were available for final analysis (Figure 1).

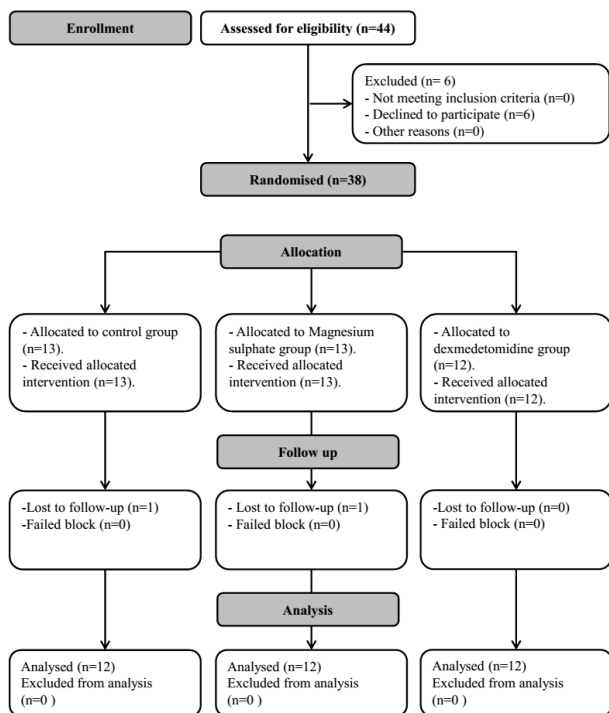


Figure 1: Consort chart for patient enrolment

Demographic data were comparable between the three groups (Table 1).

Table 1: Patient characteristics. Data are presented as mean ± standard deviation and frequency (%)

	Group C (n = 12)	Group D (n = 12)	Group M (n = 12)
Age (years)	4.11 ± 1.7	3.9 ± 2.2	3.1 ± 1.4
Weight (kg)	17.3 ± 4.1	16.8 ± 4.9	15.2 ± 4.1
Male gender	8 (67%)	6 (50%)	3 (25%)

Data are presented as mean ± standard deviation and frequency (%).

FLACC score was lower in both Group M and Group D when compared to Group C at all postoperative readings (Table 2).

Table 2: Mean arterial pressure. Data are presented as mean ± standard deviation

	Group C (n = 12)	Group D (n = 12)	Group M (n = 12)
Baseline reading (mmHg)	70 ± 11	63 ± 9	63 ± 10
Post-block reading (mmHg)	63 ± 8	55 ± 9	66 ± 8
Mean intraoperative reading (mmHg)	60 ± 15	48 ± 6*	52 ± 7

*denotes significance compared to group C.

Group D showed lower FLACC score compared to group M at the first postoperative hour; while both groups were comparable in the subsequent readings (Table 3).

Table 3: Heart rate. Data are presented as a mean ± standard deviation

	Group C (n = 12)	Group D (n = 12)	Group M (n = 12)
Baseline reading (mmHg)	136 ± 13	136 ± 20	138 ± 16
Post-block reading (mmHg)	124 ± 11	118 ± 10	119 ± 13
Mean intraoperative reading (mmHg)	115 ± 13	103 ± 7*	111 ± 10

*denotes significance compared to group C.

Ramsay score was comparable between group D and group M; while it was higher in both groups compared to group C (Table 4).

Table 4: FLACC score. Data are presented as median (range)

	Group C (n = 12)	Group D (n = 12)	Group M (n = 12)
One-hour postoperative	1.5 (1-3)	*0 (0-1)	*1 (0-2)
Two-hour postoperative	2 (2-4)	*1 (0-2)	*2 (1-2)
Six-hour postoperative	4 (2-6)	*2 (0-4)	*2 (1-4)
Eight-hour postoperative	5 (4-6)	*4 (1-5)	*4 (2-6)
Twelve-hour postoperative	6 (5-6)	*4 (4-4)	*4 (4-6)

FLACC: face, legs, activity, cry, insolubility scale; *denotes significance compared to group C; † denotes significance compared to group M.

Time of 1st rescue analgesia was longer in the group M, and group D compared to group C without significant difference between the two former groups (7.83 ± 1.19 hours, 7.75 ± 1.35 hours, and 4.92 ± 1.16 respectively) (Table 5).

Table 5: Postoperative data. Data are presented as mean ± standard deviation, median (range), and frequency (%)

	Group C (n = 12)	Group D (n = 12)	Group M (n = 12)
Ramsay score	2 (2-2)	4 (4-5) ††	4 (2-5)*
Time to rescue analgesia (hours)	4.9 ± 1.2	7.8 ± 1.4*	7.8 ± 1.2*
Number of rescue analgesic boluses (1 bolus / 2 boluses)	4/8	12/0*	12/0*

*denotes significance compared to group C. † denotes significance compared to group M.

Hemodynamic measures (MAP and heart rate) were comparable between the three groups at the baseline and post-block reading. Post-hoc analysis showed no difference between Group M and the other two groups in the intraoperative hemodynamic readings; while Group D had lower mean intraoperative readings compared to group C (MAP: 60.33 ± 14.9 vs 47.58 ± 5.6, p = 0.029), and (114.83 ± 13.5 vs 102.92 ± 7.2, p = 0.012)(Table 2 and 3).

Discussion

We reported that both dexmedetomidine and magnesium improved the analgesic properties of the caudal block when added to bupivacaine. No difference was observed between both drugs according to the duration of analgesia and pain score at most of the postoperative reading; however, dexmedetomidine was associated with lower intraoperative MAP and heart rate. Dexmedetomidine had been frequently reported as one of the most promising additives in neuraxial as well as peripheral nerve blocks [2], [9]. In a recent review, Trifa et al. had

suggested that there is sufficient evidence to recommend adding dexmedetomidine to local anaesthetics in the caudal block in children [4]. Dexmedetomidine is an alpha-2 adrenoreceptor agonist with unique pharmacological properties overall response to α_2 adrenoreceptors agonists is related to the stimulation of α_2 adrenoreceptors located in the CNS and spinal cord. These receptors are involved in the sympatholysis, sedation, and antinociception effects of α_2 adrenoreceptors [10]. Although dexmedetomidine is a potent adjuvant to local anaesthetics, its use had some limitations such as high cost and negative hemodynamic profile.

Magnesium is another drug with various clinical uses. Magnesium is a non-competitive NMDA receptor antagonist that promotes intracellular signalling culminating in long-term synaptic plasticity and the 'wind-up' phenomenon. Blocking the channel inhibits the development and maintenance of central sensitisation [5]. Thus, magnesium is characterised by useful analgesic effects when used as an adjuvant to local anaesthetics. In a recent systematic review and meta-analysis, Kawakami et al. had [5] reported that magnesium might improve the analgesic properties of the ropivacaine-induced caudal block in children. Kawakami et al. had [5] recommended more randomised controlled trials to affirm their findings. No study to the best of our knowledge had investigated magnesium as an adjuvant to bupivacaine in the caudal block in children. We reported that using dexmedetomidine was associated with negative cardiovascular profile compared to magnesium; this finding is in line with most of the available data for using dexmedetomidine in neuraxial and peripheral nerve blocks [3], [9], [11]. Systemic absorption of dexmedetomidine had been well reported after extra-vascular injection [12]. This systemic absorption is associated with linear dose-dependent plasma level [13].

Pain management in children is essential and challenging. Caudal analgesia is the commonest regional block performed in the pediatric population. To the best of our knowledge, this is the first trial which compares magnesium and dexmedetomidine in the caudal block. It is also the first study to investigate both drugs as adjuvants to bupivacaine. Our findings suggest that the use of both magnesium and dexmedetomidine was associated with similar analgesic properties. This favours the use magnesium as a reasonable choice in the caudal block which is efficient, economic, and safe.

Our study has the advantage of being a well-powered, double-blinded, randomized controlled trial. However, it had some limitations: 1- It is a single centre study. 2- We used a single dose for each drug. 3- We performed as a single shot caudal block; thus, we could not extrapolate our findings in continuous blocks. We recommend future studies to evaluate the optimum doses and to investigate both drugs in continuous blocks.

In conclusion, both magnesium (50 mg) and dexmedetomidine (2 mcg/Kg) improved the analgesic profile of bupivacaine-induced caudal block in children. Dexmedetomidine administration was accompanied with higher sedation score and negative hemodynamic profile.

References

1. Ansermino M, Basu R, Vandebeek C, Montgomery C. Nonopioid additives to local anaesthetics for caudal blockade in children: a systematic review. *Paediatr Anaesth*. 2003; 13:561–573. <https://doi.org/10.1046/j.1460-9592.2003.01048.x> PMID:12950855
2. Marhofer P, Brummett CM. Safety and efficiency of dexmedetomidine as adjuvant to local anesthetics. *Curr Opin Anaesthesiol*. 2016; 29:632–637. <https://doi.org/10.1097/ACO.0000000000000364> PMID:27258154
3. Farag E, Argalious M, Abd-Elsayed A, Ebrahim Z, Doyle DJ. The use of dexmedetomidine in anesthesia and intensive care: a review. *Curr Pharm Des*. 2012; 18:6257–6265. <https://doi.org/10.2174/138161212803832272> PMID:22762468
4. Trifa M, Tumin D, Tobias JD. Dexmedetomidine as an adjunct for caudal anesthesia and analgesia in children. *Minerva anesthesiologica*. 2018; 84(7):836-47. PMID:29479931
5. Kawakami H, Mihara T, Nakamura N, Ka K, Goto T. Effect of magnesium added to local anesthetics for caudal anesthesia on postoperative pain in pediatric surgical patients: A systematic review and meta-analysis with Trial Sequential Analysis. *PLoS One*. 2018; 13:e0190354. <https://doi.org/10.1371/journal.pone.0190354> PMID:29293586 PMCID:PMC5749796
6. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs*. 1997; 23:293–297. PMID:9220806
7. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J*. 1974; 2:656–659. <https://doi.org/10.1136/bmj.2.5920.656> PMID:4835444 PMCID:PMC1613102
8. Fyनेface-Ogan S, Mato CN, Tobin M. A comparative study between caudal bupivacaine and bupivacaine co-administered with neostigmine for postoperative analgesia in children. *Niger Postgrad Med J*. 2014; 21:51–56. PMID:24887252
9. Wu H-H, Wang H-T, Jin J-J, Cui G-B, Zhou K-C, Chen Y, Chen GZ, Dong YL, Wang W. Does dexmedetomidine as a neuraxial adjuvant facilitate better anesthesia and analgesia? A systematic review and meta-analysis. *PLoS One*. 2014; 9:e93114. <https://doi.org/10.1371/journal.pone.0093114> PMID:24671181 PMCID:PMC3966844
10. Lönnqvist P-A. Alpha-2 adrenoreceptor agonists as adjuncts to Peripheral Nerve Blocks in Children--is there a mechanism of action and should we use them? *Paediatr Anaesth*. 2012; 22:421–424. <https://doi.org/10.1111/j.1460-9592.2012.03821.x> PMID:22486904
11. Abdulatif M, Fawzy M, Nassar H, Hasanin A, Ollaek M, Mohamed H. The effects of perineural dexmedetomidine on the pharmacodynamic profile of femoral nerve block: a dose-finding randomised, controlled, double-blind study. *Anaesthesia*. 2016; 71:1177–1185. <https://doi.org/10.1111/anae.13603> PMID:27611039
12. Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. *Br J Clin Pharmacol*. 2003; 56:691–693. <https://doi.org/10.1046/j.1365-2125.2003.01944.x> PMID:14616431 PMCID:PMC1884292
13. Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology*. 1993; 78:813–820. <https://doi.org/10.1097/0000542-199305000-00002> PMID:8098190