International Journal of Research in Medical Sciences
Oruobu-Nwogu A et al. Int J Res Med Sci. 2022 Sep;10(9):1865-1871
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20222260

Original Research Article

Analgesic effects of caudal dexmedetomidine versus midazolam combined with bupivacaine on postoperative pain following paediatric infraumbilical surgeries

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Received: 05 July 2022
Revised: 30 July 2022
Accepted: 02 August 2022

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ABSTRACT

Background: There is continued search for an ideal adjuvant necessitated by the limited duration of singleshot caudal block. The study aimed to compare the analgesic effects of caudal 1.5 µg/kg dexmedetomidine versus 50 µg/kg midazolam combined with 0.20% bupivacaine in children.
Methods: Following ethical approval and parental consent, 66 American Society of Anesthesiologists (ASA) class I or II children aged 1-6 years were randomized into three groups (A, B, and C) of 22 each. All patients had laryngeal mask airway (LMA) general anaesthesia induced with propofol and maintained with isoflurane in 100% oxygen. Group A received 1 ml/kg 0.20% bupivacaine and 1.5 µg/kg dexmedetomidine (1 ml), B received 1 ml/kg 0.20% bupivacaine plus 50 µg/kg midazolam (1 ml) while C received 1 ml/kg 0.20% bupivacaine and 0.9% normal saline (1 ml), via the caudal space. Pain was assessed using the face, leg, arm, cry, consolability (FLACC) scale. The time to first analgesic request, (TTFAR) was defined as the period from caudal injection to pain score of ≥4. Analgesic was given when FLACC score was ≥4.
Results: All 66 children completed the study. The TTFAR was longest in group A (14.4±2.36), followed by group B (12.0±3.69), and shortest in group C (5.6±1.45), p=0.01, with greatest 24 hours analgesic consumption in group C, p=0.01.
Conclusions: Caudal dexmedetomidine or midazolam combined with bupivacaine significantly prolonged the analgesic duration, with superiority of dexmedetomidine over midazolam group in analgesic profile.

Keywords: Bupivacaine, Caudal, Dexmedetomidine, Midazolam, Postoperative pain

INTRODUCTION

Achieving sufficient duration of postoperative analgesia through a technique with high safety margin without causing systemic upset is a desirable goal for Anaesthesiologists. Of the various techniques employed to achieve paediatric postoperative analgesia, caudal block still remains one of the most common; it is easy to perform, effective, safe and can be combined with general anaesthesia for intraoperative and postoperative analgesia in paediatric patients undergoing infraumbilical surgeries.[1,2] Being a regional technique singleshot caudal block circumvents untoward effects such as sedation, respiratory depression, nausea, vomiting, pruritus and dependence from opioids used in general anaesthesia, however, it has the disadvantage of a relatively short duration.[1,2] Also, the utilization of caudal catheter for continued administration of local anaesthetic agent raises concerns about infection.[3] These limitations have necessitated the search for an ideal adjuvant. Dexmedetomidine, a highly selective α_2 agonist with sedative, analgesic and sympatholytic properties, has documented safety and efficacy as caudal adjuvant used in the dose range of 1-2 µg/kg.[4] Preservative free

midazolam prolongs the duration of action of local anaesthetic agents when administered as a caudal additive; a dose of 50 µg/kg is optimal for upper abdominal surgeries.[1] Given the paucity of literature directly comparing caudal dexmedetomidine with midazolam, this study, therefore, was designed to compare the analgesic efficacy of adjuvant 1.5 µg/kg dexmedetomidine versus 50 µg/kg midazolam, combined with 0.20% bupivacaine for caudal block in children.

METHODS

After ethical clearance from the University of Port Harcourt Teaching Hospital (ethical clearance reference: UPTH/ADM/90/S.II/VOL.XI/461) for a prospective, randomized, double blind, placebo controlled study and written informed consent from the parents, 66 paediatric patients, aged 1-6 years, with ASA classification I or II scheduled for infraumbilical surgeries, were randomized into three groups A, B and C, of 22 each. All 66 subjects completed the study which was conducted from July, 2018, to June, 2019, in the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria.

Sample size determination

Sample size (N) was determined using power analysis formula5 for comparison of means:

$$N = \frac{(Z_\alpha + Z_\beta)^2 \times (SD_1{}^2 + SD_2{}^2)}{(\mu_1 - \mu_2)^2}$$

Where Z_α=1.28 with power of 90% for this study; Z_β=1.96 at 5% significance level.

In a similar study, the standard deviation of the group that had plain bupivacaine alone was 0.98.[6] Based on the null hypothesis, the standard deviations for the dexmedetomidine and midazolam groups, it was assumed, were not different. So, $SD_1 = SD_2 = 0.98$.

$\mu_1 - \mu_2$ was the expected difference in hours of the duration of effective analgesia between the groups, and for this study, it was 1 hour.

Substituting,

$$n = \frac{(1.28 + 1.96)^2 \times (0.982^2 + 0.982^2)}{(1.0)^2}$$

= 20.16, approximately 20 per group.

Adding 10% for attrition, each group requires 22 subjects. Therefore, a total of 66 patients were recruited for the study.

Simple randomization and blinding were ensured through picking of opaque envelopes and recruitment of research assistants, with the lead researcher blinded to the subjects' group allocations and study drug preparation. The parents of the subjects were made to pick one out of 66 opaque envelopes from a bag on the morning of surgery under the supervision of a research assistant and a nurse. Each of these envelopes concealed an alphabet (A, B, or C) in it with an equal number of 22 of each alphabet in the bag. The envelope picked was excluded from the rest and the patient allocated to that group designated by the alphabet picked.

A different registrar anaesthetist (second research assistant), blinded to the outcome of the caudal blocks, prepared the study caudal agents according to the group and weight specifications. Records were kept using a different code for each subject's group and caudal drug against hospital number, to enable quick access to every child involved in the study, in the event of any adverse effect. All patients had preoperative evaluation and preparation the day before surgery; the parents stopped solid food 6 hours, breast milk 4 hours but gave clear fluid up to 2 hours prior to the time for surgery. Children aged 1-6 years scheduled for elective infraumbilical surgeries, in ASA class I or II and whose parents gave consent comprised the inclusion criteria while parental refusal to participate in the study, positive history of bleeding diathesis or allergy to study agents, infection at caudal region, ASA class >II, age >6 years, day-case and emergency surgeries constituted the exclusion criteria. The FLACC scale was used for postoperative pain assessment.[7] Preoperative sedatives and analgesics were avoided; rather, balloons, toys or cartoon videos were used to reduce separation anxiety. On the morning of surgery, a multiparameter monitor (Dash 4000®) was attached to obtain and record patient's heart rate, blood pressure, SpO_2 and peripheral temperature.

All caudal blocks were performed under general anaesthesia induced with i.v. propofol 3 mg/kg and fentanyl 1 µg/kg, and maintained with 1 to 1.5% isoflurane in 100% oxygen via mapleson F breathing system and LMA. Observing asepsis, the caudal space was accessed using size 22-gauge intravenous cannula (MEDIFLON, GLOBAL MEDIKIT, INDIA). Each subject received a caudal injection of 1 ml/kg of the respective study solution in the left lateral position, comprising plain bupivacaine 0.20% and the group specific adjuvant [group A received 1.5 µg/kg dexmedetomidine hydrochloride (Jiangsu Hengrui Medicine), group B 50 µ/kg preservative free midazolam hydrochloride (Pfizer Medicals), and 0.9% normal saline for group C]. Subjects received Lactated Ringer's solution intraoperatively and 5% dextrose saline postoperatively guided by the 4-2-1 rule.

The following parameters were non-invasively monitored intra-operatively: (1) heart rate/pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) every 2 minutes post caudal block for the first 16 minutes, thereafter, every 5 minutes till the end of surgery, (2) peripheral arterial

haemoglobin oxygen saturation (SpO_2), to ensure a value >95%, and (3) continuous peripheral temperature, to maintain normothermia (36.5-37.4ºC), and intraoperative blood loss (by swab count). A sustained increase in heart rate and mean arterial blood pressure within 15 minutes of skin incision in excess of 15% of preincision values was regarded as inadequate analgesia due to failed caudal block; such child was to be given fentanyl 2 µg/kg and excluded from the study. A decrease in SBP or HR ≥30% of baseline values was defined as hypotension and bradycardia respectively, and were to be treated with fluid bolus, atropine or ephedrine as necessary. At the end of surgery, patients were transferred to the recovery room where SpO_2, respiratory rate (RR), HR, SBP, DBP, MAP and temperature were assessed every 15 minutes for two hours. FLACC score was assessed at 30 minutes 2, 4, 6, and 12 hours. At a FLACC score of ≥4, intravenous fentanyl 1 µg/kg was given, oral acetaminophen 15 mg/kg was also administered and repeated 6 hourly to provide analgesia. Any incidence of adverse effects was evaluated, promptly treated and recorded.

Data collection and analysis

Data were entered into Excel spreadsheet and exported to the Statistical Package for Social Sciences (SPSS) version 20.0 (Armonk, NY: IBM Corp.) for statistical analysis. Statistical significance was set at $p<0.05$.

RESULTS

The patients' demographics, ASA classifications, base line mean values in SBP, DBP, MAP, PR, RR, SpO_2 and temperature, and mean duration of surgery in the groups were comparable (Table 1).

Table 1: Demographic characteristics, ASA, baseline vital signs and mean duration of surgery.

Variables	Group A (n=22)	Group B (n=22)	Group C (n=22)	P value
Age (years)	2.9±1.06	2.9± 1.41	2.8±1.08	0.95
Weight (kg)	17.2±4.47	17.8±5.21	16.8±3.76	0.73
SBP (mmHg)	112.8±10.51	116.0±7.98	115.2±8.32	0.47
DBP (mmHg)	70.4±8.32	69.9±7.40	71.1±7.52	0.90
MAP (mmHg)	82.8±6.49	82.5±5.60	83.4±5.80	0.89
PR	102.3±10.05	104.9±11.52	105.7±10.23	0.54
SP02	99.9±0.21	99.9±0.29	99.8±0.53	0.25
Temp. (°C)	36.9±0.25	36.9±0.13	37.0±0.23	0.16
ASA I	20 (90.9)	19 (86.4)	19 (86.4)	0.89
ASA II	2 (9.1)	3 (13.6)	3 (13.6)	0.99
Mean duration of surgery in minutes	50.82±33.20	51.18±34.71	50.95±30.89	

Data are expressed as mean±SD or as number (%)

Table 2: Distribution of surgeries across the three groups.

Surgeries	Group A (n=22)	Group B (n=22)	Group C (n=22)
Herniotomy	11 (50.0%)	12 (54.5%)	10 (45.5%)
Orchidopexy	9 (40.9%)	6 (27.3%)	9 (40.9%)
Hypospadias repair	2 (9.1%)	4 (18.2%)	3 (13.6%)

Data are expressed as number (%)

From the distribution of surgeries done across the three groups (Table 2), in group A 11 patients (50.0%) had herniotomy, 9 patients (40.9%) had orchidopexy and 2 patients (9.1%) had hypospadias repair. In group B, 12 patients (54.5%) had herniotomy, 6 patients (27.3%) had orchidopexy and 4 patients (18.2%) had hypospadias repair. In group C, 10 patients (45.5%) had herniotomy, 9 patients (40.9%) had orchidopexy and 3 patients (13.6%) had hypospadias repair.

The TTFAR for groups A, B and C were 14.4±2.36 hours, 12.0±3.69 hours and 5.64±1.45 hours respectively. The values were significantly different between groups A and B (p=0.02), A and C (p=0.001) and groups B and C (p=0.001). The corresponding mean total postoperative fentanyl consumptions in 24 hours were 17.17±4.47 µg, 17.83±5.20 µg and 18.80±3.80 µg for groups A, B and C, while the mean total postoperative acetaminophen consumption in 24 hours was 102.67±89.62 mg, 118.59±98.71 mg and 248.60±80.43 mg for groups A, B and C respectively. Post-hoc analysis revealed that there was also statistically significant difference in acetaminophen consumption between groups A and C (p=0.001) and between B and C (p=0.001), but not between groups A and B, p=0.76 (Table 3).

Table 3: Time to first analgesic request and total 24 hours analgesic consumption in each of the groups.

Item	Group A (n=22)	Group B (n=22)	Group C (n=22)	Post-hoc P value
Mean analgesic duration (hours)	14.4±2.36	12.0±3.69	5.64±1.45	*0.02[1], *0.001[2], *0.001[3]
Total 24 hrs. fentanyl (µg)	17.17±4.47	17.83±5.20	18.80±3.80	1.00[1], 0.192, 0.05[3]

Continued.

Item	Group A (n=22)	Group B (n=22)	Group C (n=22)	Post-hoc P value
Total 24 hours acetaminophen (mg)	102.6±89.62	118.59±98.71	248±80.43	0.76[1], *0.001[2], *0.001[3]

Data are expressed as mean±SD. Posthoc Bonferroni test: [1]Group A and Group B, [2]Group A and Group C, [3]Group B and Group C. *Statistically significant.

Postoperatively, the mean FLACC pain scores at 30 minutes, 2, 4, 6 and 12 hours are shown in Table 4; the corresponding p values across the three groups, p=0.13, 0.00, 0.00, 0.00 and 0.03, show statistically significant difference in the scores at 2, 4, 6 and 12 hours.

Table 4: Postoperative pain assessment using FLACC score at different time points.

Pain assessment (FLACC)	Group A (n=22)	Group B (n=22)	Group C (n=22)	P value
30 minutes	0.1±0.35	0.3±0.48	0.4±0.50	0.13
2 hours	0.3±0.48	0.5±0.51	1.4±0.85	0.00*
4 hours	0.5±0.67	1.0±0.79	4.0±0.95	0.00*
6 hours	0.6±0.59	1.9±1.21	3.6±0.79	0.00*
12 hours	0.6±1.40	1.3±1.62	2.0±1.09	0.03*

*Statistically significant

Only 1 subject (4.5%) in group B experienced fever and vomiting, p=0.36, (Table 5).

Table 5: Postoperative complications among groups in the study.

Compli-cations	Group A N (%) n=22	Group B N (%) n=22	Group C N (%) n=22	P value
Vomiting				
Yes	0 (0.0)	1 (4.5)	0 (0.0)	0.36
No	22 (100.0)	21 (95.5)	22 (100.0)	
Fever				
Yes	0 (0.0)	1 (4.5)	0 (0.0)	0.36
No	22 (100.0)	21 (95.5)	22 (100.0)	

DISCUSSION

The time to first analgesic request (TTFAR) was significantly more prolonged in the bupivacaine plus dexmedetomidine group (group A) and bupivacaine plus midazolam group (group B) than in the bupivacaine alone group (group C), with associated higher postoperative analgesic consumption by the patients in group C than in groups A and B. Furthermore, in comparison with group B, a significantly longer TTFAR was found in group A. However, the incidence of adverse effects was comparably minimal in all the three groups.

Without the addition of adjuvants, the use of a local anaesthetic is limited by its duration of action and dose dependent side effects.[8] In this study, group C had the shortest duration of analgesia and a pain score of ≥4 was achieved earliest compared to groups A and B. The observed significantly most prolonged TTFAR in group A compared to the other groups agrees with the findings made by El-Hennawy et al and Dipak et al that the addition of dexmedetomidine to bupivacaine in caudal anaesthesia significantly prolongs postoperative TTFAR, inferring the occurrence of analgesic synergism between dexmedetomidine and bupivacaine.[9,10] There is documented evidence of intensification of local anaesthetic conduction block in neurons and causation of local vasoconstriction by dexmedetomidine Xiang et al also reported comparable analgesic duration in their study using a lower dose of caudal dexmedetomidine.[11,12] However, the observation by Xiang et al could not preclude the effects of ketamine.[12] For the avoidance of confounding variable Ketamine was not administered to subjects in this study.

A dose of 1 ml/kg of bupivacaine 0.20% was administered in this study. Though this is lower than that in the study by Goyal et al who used 1 ml/kg of bupivacaine 0.25%, the postoperative analgesic durations are comparable.[7] Apparently, the higher dose of bupivacaine compensated for a lower dose (1.0 µg/kg) of dexmedetomidine as used by Goyal et al.[7] Findings by Sharpe et al show that a volume of plain bupivacaine as low as 0.5 ml/kg would not achieve adequate anaesthesia, indicating that an optimal concentration and adequate volume of bupivacaine are prerequisites to achieving surgical analgesia in paediatric caudal block.[13] Buttressing this fact, the decreased efficacy of a low volume (0.5 ml/kg) compared to an average volume (0.7 5ml/kg) of same concentration (0.25%) of bupivacaine in paediatric caudal block was also documented by Akpoduado et al.[14] The empirical report by Verghese et al is that a caudal block with larger volume (1 ml/kg) of dilute (0.20%) bupivacaine is more effective than a smaller volume (0.80 ml/kg) of a more concentrated (0.25%) solution.[15]

Caudal adjuvant dexmedetomidine 1.5 µg/kg was combined with bupivacaine 0.20% in this study. Al-Zaben et al documented that 2 µg/kg dexmedetomidine resulted in greater adverse effects without increasing analgesic benefits.[16] Variations in the TTFAR following caudal bupivacaine plus dexmedetomidine administration have reported by several researchers. Elfawal et al recorded for their dexmedetomidine group 8.2±0.22 hours compared to 14.4±2.36 hours in the present study.[17]

The difference can be understood from their use of smaller volume of 0.25% levobupivacaine, a finding similarly corroborated by Lakshmi et al.[18] Again, Xu et al reported a shorter TTFAR using 1 µg/kg dexmedetomidine added to ropivacaine for caudal anaesthesia, supporting that a combination of caudal 1.5 µg/kg dexmedetomidine and 0.20% bupivacaine gives a relatively desirable superior analgesic profile.[19]

Midazolam 50 µg/kg as caudal adjuvant could be considered as optimal deducing from the documentation by de Beer et al, Kumar et al and Gulec et al alike, using similar caudal midazolam dose of 50 µg/kg, reported comparatively longer analgesic durations of 16.8±3.9 hours and 21.15±1.20 hours respectively.[1,20,21] Undoubtedly, the observation by Kumar et al is attributable to the use of 70% nitrous oxide and a higher dose (1 ml/kg 0.25%) of bupivacaine combined with 50 µg/kg midazolam.[20]

In the case of Gulec et al the prolonged sedation recorded in their bupivacaine plus midazolam group could underpin their observation of a much longer analgesic duration, as sedation could easily be swapped for analgesia in nonverbal children.[21] In the present study, however, nitrous oxide was not utilized. Adetoye et al recorded only 7.97±0.90 hours of analgesia while studying caudal midazolam 50 µg/kg plus 1 ml/kg of 0.125% of bupivacaine, supporting Joshi et al that with a subanaesthetic bupivacaine concentration (0.125%) the addition of adjuvants may not achieve sufficient duration of postoperative analgesia in caudal block.[22,23] Abodesira et al administering caudal 0.5 ml/kg ropivacaine combined with midazolam 50 µg/kg reported a shorter TTFAR (5.20 hours), further supporting Verghese et al.[15,24] To note, Musa et al using 1 ml/kg of 0.25% caudal bupivacaine plus 50 µg/kg midazolam observed as long as 18.28±2.10 hours of postoperative TTFAR, showing a positive correlation between prolonged analgesia and a higher dose of bupivacaine.[25] In group C of the present study the TTFAR was 5.64±1.45 hours, and that corroborates Amlan et al.[8]

An intergroup evaluation of the postoperative analgesic duration revealed a statistically significant difference between group A and B, between group A and C, and between group B and C. This significant superiority in analgesic profile of group A over B is attributable to a greater intrinsic analgesic property possessed by dexmedetomidine than may be present in midazolam. Berkker and Sturaitis have documented the effectiveness of dexmedetomidine in reducing transmission of substance-P mediated nociceptive signals in spinal cord.[26] Another reason for the greater analgesic duration observed in group A relative to group B would be the dissimilar binding affinities exhibited by the two drugs toward their respective receptors. While the affinity of midazolam toward GABA receptors is reported as only twice that of diazepam, the documented affinity of dexmedetomidine toward α_2 adrenoceptors is 8 times that of clonidine.[27,28]

Significantly higher FLACC scores were recorded from 2 hours postoperatively in Group C, denoting sooner waning analgesic effect of caudal bupivacaine without adjuvant. Agreeably, a significant difference in 24 hours acetaminophen consumption was observed between groups A and C, and also between B and C; however, such was not recorded in 24 hours fentanyl consumption across the groups in this study. This indicates that repeated assessment of pain and repeated dosing of analgesic over a longer duration might be better reflective of actual analgesic consumption than a single pain assessment and analgesic dose. The reduced total analgesic consumption observed in Group A further agrees with the finding by Salama et al.[29] Though Baris et al in their study found no difference in analgesic requirement across the groups, they admitted the advantage in bupivacaine with adjuvant combination over bupivacaine alone during caudal block for more painful surgeries.[30]

This study recorded 4.5% incidence of vomiting and fever which occurred 5 hours postoperatively in one patient in Group B only. The patient responded well to sponging with tepid water, acetaminophen and antimalarial treatment. Himabindu et al in a similar study reported higher (18%) incidence of vomiting, most likely a consequence of the nitrous oxide used.[31]

There are some limitations of the study. The doses of the two adjuvants chosen for comparison in the study might not be equipotent; a dose-response curve for each adjunct was not determined and the doses selected were based on previous studies with the assumption that such doses were optimal. During the first four hours of the postoperative period, the FLACC scale could be considered a weak tool for postoperative pain evaluation given the fact that the children could still have residual neuromuscular blockade from the caudal; consequently, the 'L' (leg) component of the FLACC scale could be misevaluated

CONCLUSION

The addition of dexmedetomidine or midazolam to bupivacaine significantly prolongs the duration of postoperative analgesia and consequently the time to first request for analgesic; furthermore, the dexmedetomidine plus bupivacaine combination comparatively shows superior analgesic profile to midazolam and bupivacaine mixture, without significant adverse effects or derangement in haemodynamic parameters.

ACKNOWLEDGEMENTS

The authors hereby acknowledge Professor. Philemon Okoro, Dr, Isesoma Gbobo, Dr. Nnamdi Enwezor, Dr. Ijeoma Onyeka Orji, Matron Ibiene Owenedaba and

Chief Nursing officer Onome Blue-Jack of The University of Port Harcourt Teaching Hospital, for the immense support and cooperation given during the period of this research.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of the University of Port Harcourt Teaching Hospital, Nigeria (Clearance Reference: UPTH/ADM/90/S.II/VOL.XI/461)

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Cite this article as: Oruobu-Nwogu A, Aggo AT, Johnson UU. Analgesic effects of caudal dexmedetomidine versus midazolam combined with bupivacaine on postoperative pain following paediatric infraumbilical surgeries. Int J Res Med Sci 2022;10:1865-71.