Regular Article

The Effect of 1 μg/kg Dexmedetomidine Combined with High-Volume/ Low-Concentration Caudal Ropivacaine in Children Undergoing Ambulatory Orchiopexy

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When local anesthetics are used, the administration of dexmedetomidine (DEX) can prolong analgesic duration. However, the effect of caudal DEX on high volume/low concentration (HVLC) local anesthetics has not been studied. We investigated the analgesic effect of DEX added to a HVLC of ropivacaine for caudal block in children. Eighty children (the American Society of Anesthesiologists (ASA) status I; age, 1–6 years) undergoing ambulatory orchiopexy were enrolled in the study. Children were randomly assigned to undergo a caudal block with 1.5 mL/kg of 0.15% ropivacaine and either 1 μg/kg of DEX (DEX group, *n*=40) or the same amount of saline (Control group, *n*=40) under general anesthesia. The results showed that the time to first analgesic request was significantly longer in the DEX group than in the control group. The sevoflurane requirement for anesthesia and frequency of emergence agitation (EA) were also significantly lower in the DEX group. There was no difference in adverse events between the two groups. In conclusion, a dose of 1 μg/kg of caudal DEX prolonged the first analgesic request time, although the immediate postoperative pain scores were comparable in both groups. Furthermore, caudal DEX significantly reduced the sevoflurane requirement and the frequency of EA.

Key words dexmedetomidine; caudal block; child; orchiopexy

Caudal block is common method for postoperative analgesia in children undergoing infra-umbilical surgery. One major limitation of caudal block is a relatively short analgesic duration owing to the single-injection. Thus, adjuvants such as ketamine, clonidine, or opioids are frequently added to the local anesthetics in order to improve analgesic efficacy and duration.[1,2] The effectiveness of local anesthetics using in caudal block is dependent upon the dose, volume, and concentration of the local anesthetic solution, but high-concentration local anesthetics can increase the incidence of motor weakness, delayed micturition, or urinary retention. In children undergoing ambulatory surgery, such adverse effects can prolong the discharge time and may result in inadvertent admission. Recently, high-volume/low-concentration (HVLC) regimens for caudal blocks in children (1.5 mL/kg of 0.1–0.2% local anesthetics) have gained popularity following a report by Silvani *et al.* that demonstrated that a HVLC regimen provides a longer analgesic duration with less adverse effects than conventional dose/concentration.[3–8] However, the analgesic duration is still limited in caudal block with single-injection.

Dexmedetomidine (DEX) is a highly selective α_2 adrenoceptor agonist with an $\alpha 2/\alpha 1$ selectivity ratio of 1600 : 1, and is eight times more potent than clonidine.[9] DEX is successfully used as an adjuvant in caudal blocks for children in order to reduce pain without inducing any significant respiratory and hemodynamic effects. Several studies have reported that in children, caudal DEX (1–2 μg/kg) with 0.25% bupivacaine (1 mL/kg) prolongs postoperative analgesic duration by 2.5–3 fold compared with a bupivacaine alone.[10–13] However, there is no report that examines the effect of DEX in combination with HVLC local anesthetics.

We designed this randomized and double blind study to assess the analgesic effects of 1 μg/kg caudal DEX on HVLC ropivacaine (0.15%, 1.5 mL/kg) when administered together in children undergoing orchiopexy.

METHODS

This study was approved by the Institutional Review Board of Severance Hospital (4-2011-0111) and registered at www.Clinicaltrials.gov (NCT02163980). After obtaining written informed consent from the parents, 80 children (the American Society of Anesthesiologists (ASA) status I, age 1–6 years) undergoing ambulatory unilateral orchiopexy were enrolled in the study. The exclusion criteria were developmental delay or mental retardation, neuromuscular or psychiatric disorders, coagulopathy, allergy to the study drugs, or infection at the site of the caudal block.

The patients were allocated into the DEX group (*n*=40) or the Control group (*n*=40) using a computer-generated randomization method conducted in the pre-anesthesia room. The drug solutions of 1.5 mL/kg of 0.15% ropivacaine with either 1 μg/kg dexmedetomidine (Precedex, Hospira Inc., Lake Forest, IL, U.S.A.) or the same amount of saline were prepared in syringes and coded as A or B by nurses who were not participating in the study. The drug solution was delivered to the anesthesia provider prior to the caudal puncture. All anesthetic practitioners and postoperative investigators were blinded to the medication groups.

The children were transferred to the operating room while accompanied by one of their parents. After the application of hemodynamic and bispectral index (BIS) monitors, anesthesia

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was induced using 6–7% sevoflurane administered *via* a face-mask, and intravenous (i.v.) access was secured. Endotracheal intubation was performed without a neuromuscular blocker. The patients were placed in the lateral decubitus position and a caudal block was performed using a 22G caudal needle. Successful needle placement was confirmed with ultrasound, and the prepared drug solution was injected slowly. Anesthesia was maintained with sevoflurane in oxygen. The inspired sevoflurane concentration was adjusted to maintain a BIS score of 45–55 and a mean arterial blood pressure (MAP) within 20% of the baseline values.

The MAP, heart rate (HR) and end-tidal sevoflurane (Et-Sevo) concentration were recorded every 5 min until the completion of surgery. We planned to administer ephedrine or atropine as needed if the MAP or HR decreased by >20% of the baseline value. No additional analgesics or antiemetics were given during the surgery.

After completing the surgery, the tracheal tube was removed once the children awakened. In an ambulatory post-anesthesia care unit (PACU), an experienced nurse who was blinded the study evaluated the pain scores at arrival, 30 min, 1 h, 2 h, and 3 h using the Face, Legs, Activity, Cry, Consolability scale (FLACC)[14] and the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS).[15] The degree of sedation was assessed at arrival and 30 min of PACU using a three-point objective score[15] (0=eyes open spontaneously, 1=eyes open in response to verbal stimulation, 2=eyes open in response to physical stimulation). Emergence agitation (EA) was also evaluated at arrival and 30 min of PACU using a modified four-point scale by Watcha *et al.*[16] (1=calm, 2=crying, but can be consoled, 3=crying and cannot be consoled, 4=agitated and thrashing around). Children with a score of 3/4 were considered to be having an EA episode. If a child fell asleep, the state was defined as 0. When children showed CHEOPS or FLACC scores ≥4, 0.5 μg/kg of fentanyl was administered. Any other adverse events and the discharge time were also evaluated. While the children were in PACU, they were accompanied by their parents.

Prior to discharge, all parents were instructed on how to assess the pain scores (numerical rating scales from 0 to 10), when to give oral analgesics, and how to record this. They were instructed to give oral acetaminophen if the child's pain score was 4 or greater. Information regarding the analgesia was obtained *via* telephone interview by a blinded investigator at 24 h after surgery.

Statistical Analysis The primary end-point of this current study was to compare the time to the first oral acetaminophen request after discharge between the two groups. On the basis of previous studies,[4,9,11,12,17] we determined that 32 patients would be required in each group with an α level of 0.05 and power of 90% to detect a 10 h difference in time to the first analgesic request between the groups. Forty children were enrolled in each group to allow for a potential 20% drop-out.

Data were analyzed using IBM SPSS Statistics 19™ (SPSS Inc., Chicago, IL, U.S.A.). Normality of distribution was assessed with a q–q plot and the Shapiro–Wilk test. Parametric data was analyzed using the independent *t*-test and repeated ANOVA measures followed by the *post hoc* Dunnett's test. Non-parametric data were compared using the Mann–Whitney *U* test, the Wilcoxon rank-sum test, and the Friedman test,

Table 1. Patient Characteristics and Intraoperative Data

	Control group (n=40)	DEX group (n=40)
Age (months)	21.4 (3–53)	22.6 (2–71)
Body weight (kg)	11.7 (3.4)	12.4 (3.5)
Height (cm)	71.2 (21.1)	82.1 (14.1)
Duration of surgery (min)	40.2 (27.3)	45.2 (28.0)
Awakening time (min)	8.9 (3.7)	8.2 (2.6)
Fluid intake (mL)	73.6 (57.8)	53.7 (58.4)

Data are shown as mean±S.D.

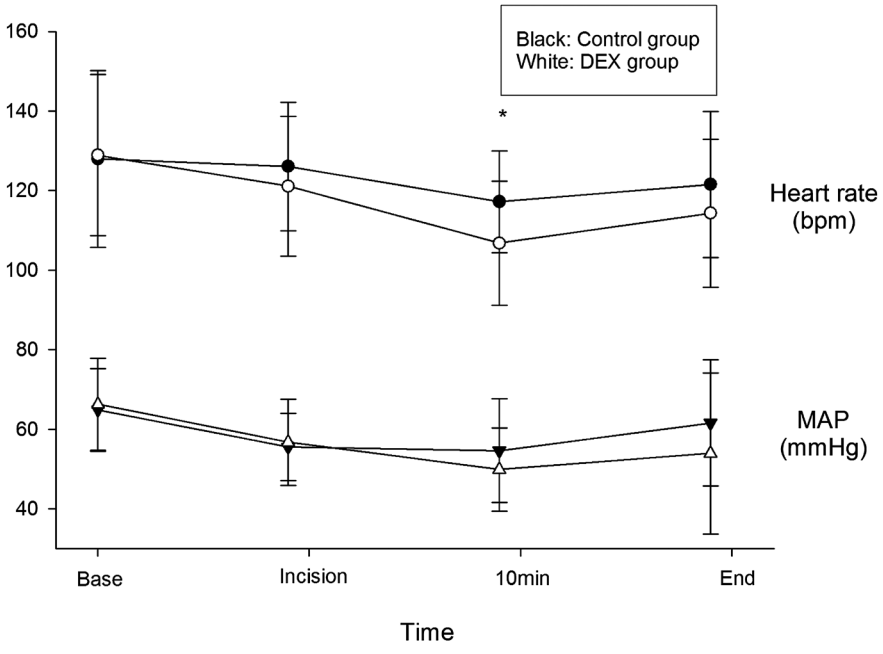

Fig. 1. HR and MAP during Surgery

Base, baseline values before caudal block; Incision, value after surgical incision; 10 min, value 10 min after incision; End, value at the end of surgery. *p<0.05.

with a Bonferroni correction between and within the groups. Frequencies were evaluated using the chi-square and Fisher's exact test. A Kaplan–Meier survival curve was obtained for the time to the first analgesic requirement during the 24 h post discharge. Values are presented as the mean (±standard deviation (S.D.)). A p-value of <0.05 was considered statistically significant.

RESULTS

Eighty male children completed this study (Control group, $n=40$; DEX group, $n=40$). There were no differences in patients' characteristics between the two groups (Table 1).

The HR was significantly reduced at 10 min of surgery in the DEX group compared with the Control group ($p=0.007$), but MAP changes were similar in both groups (Fig. 1). The Et-Sevo concentration was significantly lower in the DEX group compared with the control group during anesthesia (Fig. 2).

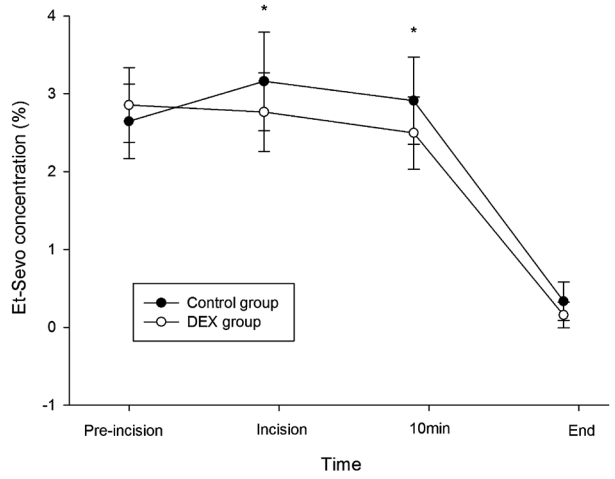

Fig. 2. End-Tidal Sevoflurane (Et-Sevo) Concentration during Surgery

Pre-incision, value before surgical incision; Incision, value after surgical incision; 10 min, value 10 min after iincision; End, value at the end of surgery. *$p<0.05$.

During the postoperative period, the FLACC pain score was lower in the DEX group than in the control group at 30 min of PACU (Fig. 3A). The DEX group demonstrated a significantly lower frequency of EA and a higher sedation score at arrival and after 30 min in PACU. The discharge time was comparable in both groups (Table 2). No differences in adverse events were noted between the two groups during recovery.

After discharge, the time to the first analgesic request was significantly longer in the DEX group compared with the Control group (Table 2, Fig. 4). However, the frequency of analgesic requirement was not significantly different ($p=0.058$). There were no adverse events related to surgical wound and general condition in all children for the study period.

DISCUSSION

This is the first study to compare the effect of caudal DEX with HVLC ropivacaine on postoperative analgesia in children. In this study, we used 1 μg/kg of DEX with ropivacaine for caudal block based on a study by Saadawy *et al.*[12] The primary endpoint of this study was time to first rescue analgesics request by subjects in the DEX and the control groups. In this current study, 1 μg/kg DEX, compared to HVLC alone, was effective in prolonging the analgesic duration by 1.4-fold (11.8 h *vs.* 8.5 h).

α_2-Adrenoceptor-induced antinociception is mediated by an inhibition of synaptic transmission within the dorsal horn of the spinal cord.[18] DEX has a greater binding affinity for α_2-adrenoceptors in the spinal cord than in brain.[19] Thus, the relative antinociceptive potency of extradural DEX may depend on the binding affinity to α_2-adrenoceptors in the spinal cord.[19] As the sacral region has the largest concentration of α_2-adrenoceptors than the lumbar or thoracic regions in humans,[20,21] caudally administered DEX combined with local anesthetics could provide effective analgesia. In this current study, although the analgesic duration was shorter than that in other studies that used a higher concentration (0.25%) of bupivacaine[4,10–13] or ropivacaine,[17] the analgesic duration

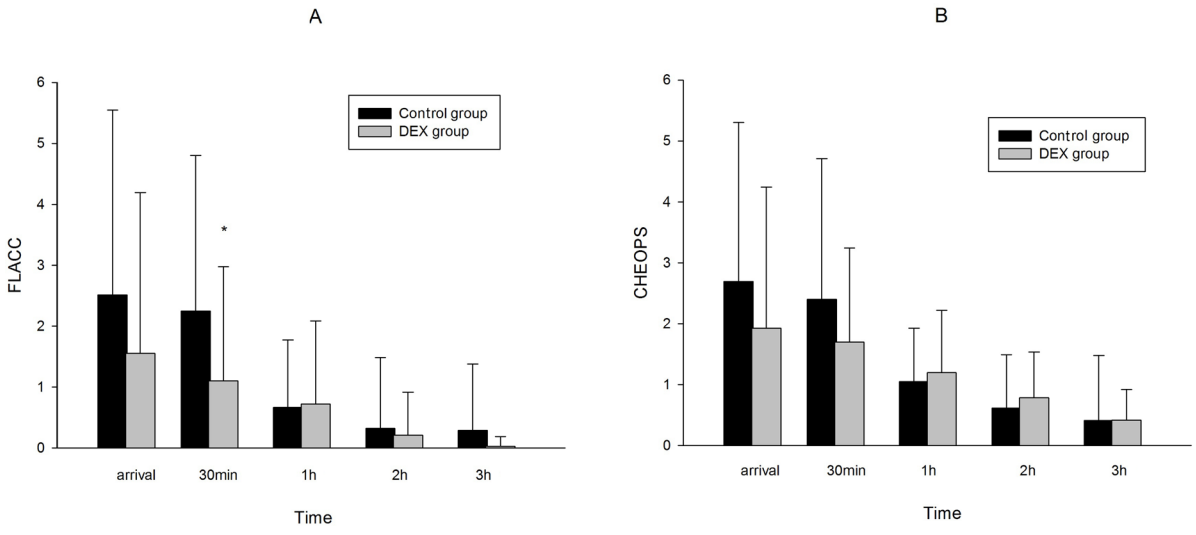

Fig. 3. Pain Scores during the 3 h Postoperative Period

FLACC (Face, Legs, Activity, Cry, Consolability scale); CHEOPS (Children's Hospital of Eastern Ontario Pain Scale); arrival, value at the arrival in post anesthetic care unit; 30 min, value at postoperative 30 min; 1 h, value at postoperative 1 h; 2 h, value at postoperative 2 h; 3 h, value at postoperative 3 h. *$p<0.05$.

Table 2. Postoperative Characteristics

	Control group (n=40)	DEX group (n=40)	p-Value
In PACU			
Emergence agitation			
Arrival	18 (45%)	3 (7.5%)†	<0.001
30 min	7 (17.5%)	4 (10%)	0.116
Sedation score			
Arrival	0.9 (0.9)	1.5 (0.8)	0.296
30 min	0.2 (0.5)	1.1 (0.9)*	0.004
Rescue fentanyl	1	2	1.000
Vomiting	1	1	1.000
Motor weakness	0	1	1.000
Discharge time (min)	226.9 (53.3)	228.6 (55.0)	0.767
After discharge			
Time to first acetaminophen (min)	521.2 (235–960)	707.1 (380–1320)*	0.015
Number of patients	22 (55%)	14 (35%)	0.058

Data are shown as mean±S.D., median (range) or number (%). PACU (post-anesthetic care unit). *p<0.05, †p<0.001

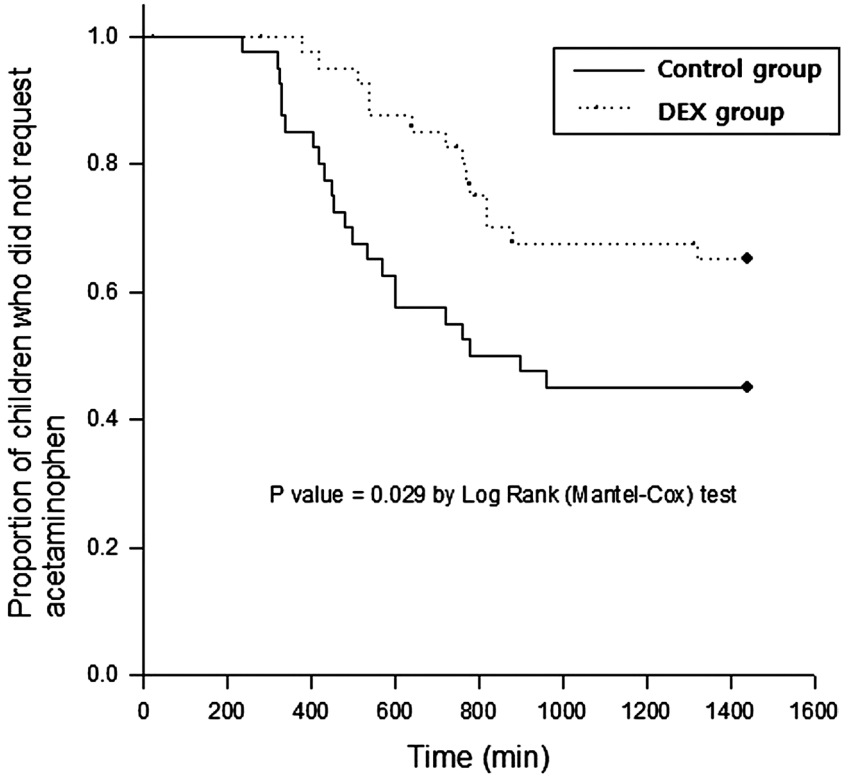

Fig. 4. Kaplan–Meier Curve for the Time to the First Analgesic Request

The proportion of the patients who did not request oral acetaminophen was significantly higher in the DEX than in Control group (p=0.029).

was significantly longer in DEX group than in control group. This result is not consistent with the results of the studies that used clonidine (2 μg/kg) with a low concentration (0.125%) of bupivacaine (1 mL/kg), in which analgesic efficacy was not significantly improved.[22–24] The authors of those studies speculated that clonidine 2 μg/kg may not be effective with a low-concentration of bupivacaine, although the exact mechanism is unclear. However, DEX is a more selective α2-adrenoceptor agonist and is eight times potent than clonidine. Thus, 1 μg/kg DEX can provide a prolonged analgesic duration when added to HVLC local anesthetics, as demonstrated in this current study. Additionally, caudal DEX with a low-concentration of local anesthetics induces less adverse effects (motor weakness, delayed micturition of urinary retention) that may affect early discharge from hospital, compared with a higher concentration of local anesthetics.[3,4,10,12,13,23]

DEX has anxiolytic, sedative, and hypnotic properties caused by stimulation of the α2-adrenoceptor in the locus coeruleus in brain where it decreases a neuronal activation[9,24] and can reduce the requirement of concomitantly administered hypnotics, analgesics, or anesthetics.[25] Intravenous DEX significantly decreases the sevoflurane requirement[5,26] for anesthesia and EA during recovery.[5,27] Caudally administered DEX was also associated with a decreased sevoflurane requirement and increased the duration of postoperative sedation in children.[12,28] The sedative and analgesic properties of

DEX might account for the anesthetic-sparing effect.[12] Our study showed a decreased sevoflurane requirement in the DEX group compared with the control group. During surgery, Et-Sevo was 22–25% lower in the DEX group than in the control group. The reduction was not as great as in a study by Saadawy *et al.*[12] in which DEX was given caudally with a higher concentration (0.25%) of bupivacaine, and anesthesia was maintained with sevoflurane in 70% nitrous oxide. Nitrous oxide is thought to mediate analgesia *via* α_{2B}- and α_{2A}-adrenoceptor subtypes within the spinal cord, similar to dexmedetomidine.[29] It was speculated that DEX is likely to provide enhanced analgesia with nitrous oxide. In our study, nitrous oxide was not used. Thus, the greater degree of reduced sevoflurane requirement in a study by Saadawy *et al.* could be explained by the effect of nitrous oxide in combination with a higher concentration of caudal bupivacaine.

DEX has advantage of reducing the frequency of EA after sevoflurane anesthesia with its analgesic and sedative effects.[30] In our study, the frequency of EA was significantly lower in the DEX group compared with the control group (7.5% *vs.* 55%), which is similar to the results of a study by Saadawy *et al.*[12] The cause of EA is multifactorial, and sevoflurane has been considered to be a major factor. Although the reason for frequent EA following sevoflurane is not clear, sevoflurane may exert an irritating effect on the central nervous system.[31,32] Thus, the decreased frequency of EA may be related to the decrease in sevoflurane concentration and the sedative effect of caudal DEX.[5,33] Sedation score was relatively high in the DEX group at arrival and at 30 min of PACU, but comparable afterwards and the discharge time was similar in both groups. Caudally administered DEX prolongs the postoperative sedation, but it helps in reducing the parents' anxiety as the children remain calm and sedated.[12,34]

DEX, α2-agonist, decreases the MAP and HR dose-dependently. However, these adverse effects appear to be less prominent in children compared with adults.[12] In this current study, HR decreased significantly in DEX group compared with the Control group at 10 min after surgical incision. Considering the surgical preparation time after caudal block, the time to decrease in HR and MAP after caudal DEX was similar to the previous studies (25–35 min after caudal block).[10,12] HR was recovered to the near baseline value by the end of surgery (Fig. 1).

In conclusion, 1 μg/kg of DEX co-administered with 1.5 mL/kg of 0.15% ropivacaine *via* the caudal route prolonged the analgesic duration in children who underwent ambulatory orchiopexy. Caudal DEX also significantly reduced the sevoflurane requirement for anesthesia and the frequency of EA.

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Conflict of Interest The authors declare no conflict of interest.

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