Comparison of the Effect of Caudal Ropivacaine, Ropivacaine-Clonidine and Ropivacaine-Magnesium on Postoperative Analgesia and Stress Response in Children

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Abstract

**Background:** Caudal analgesia is widely used for various surgical procedures in children. In order to decrease intra and postoperative analgesic requirements after caudal blockade, various additives can be added with local anesthetics.

**Objective:** The aim of this study was to compare the efficacy of pre-emptive caudal blockade using ropivacaine 0.25% alone or combined with clonidine, or magnesium sulfate on stress response and postoperative pain relief in children.

**Methods:** We performed a prospective, randomized study on 60 children, aged 4-10 years, undergoing hypospadias surgery. Patients were randomly assigned into three groups to receive either caudal ropivacaine alone (group R), caudal ropivacaine + clonidine (group RC) or caudal ropivacaine + magnesium sulfate (group RM) prior to a standardized sevoflurane anesthetic. Postoperative pain and analgesic requirements, postoperative sedation, catecholamines plasma levels, as well as hemodynamic parameters were compared among the three groups.

**Results:** Group RC had significantly lower objective pain scale (OPS) scores than group R & group RM in the first six postoperative hours. Fewer patients in group RC required postoperative analgesics than in groups R & RM. The time to 1st analgesic dose & number of analgesic doses in each group were significantly less in group RC than in groups R & RM. The sedation score was significantly higher only during the first 2 postoperative hours in group RC than groups R & RM. There was a significant decrease in the mean values of plasma epinephrine (E) and norepinephrine (NE) at the end of surgery and 1 hour after recovery compared to pre-block values in all groups.

**Conclusion:** The addition of clonidine to ropivacaine 0.25% significantly increases the duration of caudal analgesia and decreases postoperative analgesic requirements in children. The addition of magnesium to ropivacaine is comparable to the effect of ropivacaine alone. Caudal analgesia resulted in a significant reduction in catecholamine levels.

**Key Words:** Caudal ropivacaine – Ropivacaine-clonidine – Magnesium on postoperative analgesia – Stress response in children.

Introduction

CAUDAL analgesia, a relatively simple technique with a predictable level of blockade, provides excellent postoperative analgesia and reduced general anesthetic requirement. Ease of performance and reliability makes caudal analgesia the most common of all blocks performed in children [1]. It is widely used for various surgical procedures, such as lower abdominal, urological and lower limb surgery [2,3].

Long acting local anesthetics, such as bupivacaine, have had a well-defined role in regional anesthesia and analgesia for many years [4]. Ropivacaine is a long acting local anesthetic agent that offers a wider margin of safety than bupivacaine, with a lower potential for central nervous system and cardiovascular side effects [5-8].

In order to decrease intra and postoperative analgesic requirements after caudal blockade, various additives such as morphine, fentanyl, ketamine, adrenaline, clonidine and magnesium can be added with local anesthetics [9,10].

Clonidine, an a2-adrenergic agonist, produces analgesia without significant respiratory depression after systemic, epidural, or intrathecal administration. The addition of clonidine also prolongs the duration of action of ropivacaine 0.2% as a mixture of 0.2% ropivacaine 1ml/kg and clonidine 2 µg/kg has been shown to produce a longer duration of caudal analgesia in children after lower half of the body surgery than if ropivacaine was used alone [11].

Recently, the importance of magnesium in anesthetic practice has been highlighted. Magnesium
blocks N-Methyl-D-Aspartate (NMDA) channels in a voltage-dependent matter and such NMDA antagonism prevents the induction of central sensitization from peripheral nociceptive stimulation. Administration of IV magnesium sulfate during surgery reduces intra and postoperative opioid requirements. Koinig and colleagues reported that magnesium administration led to a significant reduction in fentanyl consumption in the peri- and postoperative periods [12]. However, IV magnesium, even high doses, is associated with limited passage across the blood-brain barrier [13]. An experimental study has shown that intrathecal magnesium potentiates opioid antinociception in acute incisional model of rats [14]. The suppression of nociceptive response by intrathecal magnesium has also been demonstrated in a rat model of neuropathic pain and its safety profile has been evaluated, including histopathological analysis [15].

**Aim of the study:**

This study was designed to compare the efficacy of pre-emptive caudal blockade using ropivacaine 0.25% alone or combined with clonidine, or magnesium sulfate-on stress response and postoperative pain relief in the pediatric age group.

**Subjects and Methods**

After obtaining ethical committee approval and written parental consent, 60 ASA I and II male children aged from 4 to 10 years presenting for hypospadius surgery under general anesthesia, were enrolled in this study. Exclusion criteria included major hepatic, renal, or cardiovascular dysfunction, previously known allergy to magnesium sulfate or other study drugs, coagulation disorders, prior treatment with opioids and anticoagulants, local skin infection and neurological or spinal diseases.

All surgeries were performed at the Cairo University Specialized Pediatric Hospital. Patients were randomly assigned using sealed envelopes to three groups; group (R): Ropivacaine alone (n=20), group (RC): Ropivacaine + clonidine group (n=20), group (RM): Ropivacaine + magnesium sulfate group (n=20).

No child received any premedication or preoperative opioids. All patients, were fasting 6 hours preoperatively. On arrival to operating room a 20-22G intravenous cannula was inserted on the dorsum of the hand after alcohol sterilization. The following monitors were applied before induction: ECG, non invasive blood pressure and pulse oximetry. Inhalational induction with sevoflurane 6% and N2O 50% in O2 was done and the airway was secured by tracheal intubation. Anesthesia was maintained by 2.5% sevoflurane. No neuromuscular blocking drugs were administered and all children were allowed to breath spontaneously with fresh gas flow of the three times the minute volume. Ayers T piece, manual assisted ventilation was performed to keep ET CO2 of 33-40mmHg.

When adequate level of anesthesis was obtained, the children were turned to lateral position, after preparation of skin, a 22G sterile needle was inserted into the caudal space through the sacrococcygeal ligament, after aspiration test was negative for blood and CSF, caudal injection of the studied drug was given randomly. Group R received ropivacaine 0.25% 0.5ml/kg, Group RC received a mixture of ropivacaine 0.25% 0.5ml/kg with 2µg/kg clonidine, Group RM received ropivacaine 0.25% 0.5ml/kg and preservative free magnesium sulfate 50mg. The volume of caudal solution given by diluting with normal saline (0.9%) to each child was 0.5ml/kg to a maximum of 20ml.

The time elapsed between caudal injection and skin incision was 15 minutes. After skin incision, the sevoflurane was reduced to the level at which the patient did not respond to surgical stimuli with movement or increase in heart rate (HR) from baseline for more than 10 minutes. All patients were adequately hydrated using lactated Ringer’s solution at a rate of 4-6ml/kg/hr.

Intraoperative hemodynamic measurements including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and HR were measured every 5 minutes and recorded before induction (baseline), before caudal injection, after skin incision and then every 15min till the end of surgery.

Blood samples of 2ml for catecholamines plasma level: Epinephrine (E) and norepinephrine (NE) were obtained before caudal injection, at the end of surgery and in the PACU 1 hour after recovery. All samples were centrifuged for 10 minutes to separate the plasma and stored at -70 °C. Catecholamines level was measured by reversed-phase high performance liquid chromatography with electrochemical detection. The normal range of catecholamine level in children is: Epinephrine (E)=20-500pg/ml and Norepinephrine (NE)=70-1500pg/ml [16].

After emergence from anesthesia, the children were transferred to the PACU to be observed for one hour then discharged to the ward. Pain level was assessed using objective pain scale (OPS).
Score
0
1
2

Arterial pressure:
± 10% increase from preoperative value
>20% of preoperative value
>30% of preoperative value

Tears:
Absent
Present, but child can be consoled
Present and child cannot be consoled

Movement:
Absent
Moderate agitation (does not sit still)
Intense agitation (risk of trauma)

Behavior:
Sleeping or calm
Grimacing, trembling voice, can be calmed down
Frightened, sticks to parents, cannot be calmed down

Verbal or bodily expression:
Sleeping or calm
Moderate, non-localized pain, general discomfort
or positioned with flexed legs and arms
crossing the tummy
Localized pain expressed verbally or pointed out by finger

Each criterion scored from (0-2) to give total score of 0-10. Pain was assessed and recorded every hour for the first 6 hours after surgery. Analgesics (15mg/kg paracetamol orally) were given if OPS ≥ 4.

Table (1): The objective pain scale.

<table>
<thead>
<tr>
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<tbody>
<tr>
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<td>Absent</td>
<td>Absent</td>
<td>Sleeping or calm</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&gt;20% of preoperative value</td>
<td>Present</td>
<td>Moderate agitation (does not sit still)</td>
<td>Grimacing, trembling voice, can be calmed down</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&gt;30% of preoperative value</td>
<td>Present and child cannot be consoled</td>
<td>Intense agitation (risk of trauma)</td>
<td>Frightened, sticks to parents, cannot be calmed down</td>
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</tr>
</tbody>
</table>

Sahar Elshal, et al. 13

(Time 1) [17]. Each criterion scored from (0-2) to give total score of 0-10. Pain was assessed and recorded every hour for the first 6 hours after surgery. Analgesics (15mg/kg paracetamol orally) were given if OPS ≥ 4.

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</table>

Statistical analysis:

Data were statistically described in terms of mean ± SD, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Kruskal Wallis analysis of variance (ANOVA) test with posthoc multiple 2-group comparisons. Within group comparisons were done using Friedman’s test with Wilcoxon rank test as posthoc 2 comparison test. For comparing categorical data, Chi square ($\chi^2$) test was performed. Yates correction equation 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 programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

Results

We enrolled 60 patients in this study with 20 patients in each group. There were no statistically significant differences between the three groups in patient’s characteristics and duration of surgery (Table 2).

<table>
<thead>
<tr>
<th>Group R (n=20)</th>
<th>Group RC (n=20)</th>
<th>Group RM (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>6.3±2.4</td>
<td>5.7±2.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>21.6±5.8</td>
<td>19.6±6.5</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>18/2</td>
<td>17/3</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>101.3±30.8</td>
<td>97.6±27.3</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number of patients.
R = Ropivacaine.
RC = Ropivacaine + clonidine.
RM = Ropivacaine + magnesium.

Intraoperative period:

Fig. (1) shows the changes in SBP after caudal analgesia. At the beginning of operation there was no significant difference in SBP. After 15 min following caudal block, there was a significant difference between group RC and the other two groups. Group RC was the lowest of the three groups during the first hour. During the second hour, there was no significant difference between the three groups.
Fig. (1): Intraoperative changes in systolic blood pressure (SBP) (mean ± SD).

* * p<0.05 group RC Vs. groups R and RM.

Fig. (2) shows the changes in DBP after caudal analgesia. There was no significant statistical difference in DBP at the beginning of the operation. There was significant statistical difference between group RC and the other two groups from 30min following caudal block till end of 1st hour. Group RC showed the lowest mean DBP. During the second hour, there was no significant difference between the three groups.

Fig. (3): Intraoperative changes in heart rate (HR) (mean ± SD).

* * p<0.05 group RC Vs. groups R and RM.

*Postoperative period:

Fig. (4) shows changes in SBP in the postoperative 6 hour period among the studied groups. It showed a significant difference between groups in SBP postoperatively in the first 4 hours. Group RC had lower readings in relation to the other two groups.
Fig. (5) shows changes in DBP in the postoperative 6 hours period among the studied groups. It showed that there was a significant statistical difference between the groups in DBP during the first 4 hours postoperatively. Group RC had lower readings in relation to the other two groups.

There was a significant difference between groups in postoperative OPS scores. Group RC showed significantly less scores than groups R and RM up to 6 hours postoperatively (Table 3). Three children in group RC required postoperative analgesia in the first 6 hours postoperatively (paracetamol) compared to 10 children in group RM and 12 children in group R (p<0.05) (Table 4). The time interval to the administration of the first analgesic dose was significantly longer in group RC than the other two groups. The total number of paracetamol doses required during the first 12 hours postoperatively in each group was significantly higher in groups R and RM compared to group RC (Table 4).

Table (3): Postoperative pain score.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group R (n=20)</th>
<th>Group RC (n=20)</th>
<th>Group RM (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hour</td>
<td>3.6±1.1</td>
<td>2.3±0.9*</td>
<td>3.7±1.3</td>
</tr>
<tr>
<td>2nd hour</td>
<td>3.9±1.4</td>
<td>2.9±0.8*</td>
<td>3.8±1.5</td>
</tr>
<tr>
<td>3rd hour</td>
<td>4.3±1.6</td>
<td>3.1±1.1*</td>
<td>4.1±1.3</td>
</tr>
<tr>
<td>4th hour</td>
<td>5.2±1.7</td>
<td>3.3±1.3*</td>
<td>4.9±1.6</td>
</tr>
<tr>
<td>5th hour</td>
<td>5.7±1.5</td>
<td>3.8±1.0*</td>
<td>5.4±1.2</td>
</tr>
<tr>
<td>6th hour</td>
<td>6.2±1.4</td>
<td>4.2±1.2*</td>
<td>5.9±1.6</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
R = Ropivacaine.
RC = Ropivacaine + clonidine.
RM = Ropivacaine + magnesium.
* p<0.05 group RC Vs. groups R and RM.

Table (4): Postoperative analgesia.

<table>
<thead>
<tr>
<th>Time to 1st analgesic dose (hrs)</th>
<th>Group R (n=20)</th>
<th>Group RC (n=20)</th>
<th>Group RM (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st analgesic dose</td>
<td>3.2±0.9</td>
<td>6.6±1.3*</td>
<td>3.7±0.7</td>
</tr>
<tr>
<td>Number of children</td>
<td>12 (60%)</td>
<td>3 (15%)*</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>requiring postoperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>analgesia in the first 6h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postoperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of analgesic doses</td>
<td>19</td>
<td>8*</td>
<td>16</td>
</tr>
<tr>
<td>in each group in the first 12h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postoperative</td>
<td></td>
<td></td>
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</tr>
</tbody>
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Values are mean ± SD or number (%).
R = Ropivacaine.
RC = Ropivacaine + clonidine.
RM = Ropivacaine + magnesium.
* p<0.05 group RC Vs. groups R and RM.

After induction and before caudal block the epinephrine (E) and nor-epinephrine (NE) levels were within the normal range and were comparable among the three groups. There was a significant decrease in the mean values of plasma (E) and
(NE) at the end of surgery and 1 hour after recovery compared to pre-block values in all groups, as shown in Figs. (7,8).

![Graph showing postoperative changes in serum epinephrine](image)

* $p<0.05$ in comparison to before caudal injection.

![Graph showing postoperative changes in serum norepinephrine](image)

* $p<0.05$ in comparison to before caudal injection.

Sedation score was significantly higher only during the first 2 postoperative hours in group RC than groups R and RM (Table 5). The 3 groups were comparable as regards to residual motor blockade at recovery and at 3 hours after recovery. The overall incidence of postoperative side effects was comparable in all groups.

Table (5): Postoperative sedation score.

<table>
<thead>
<tr>
<th></th>
<th>Group R (n=20)</th>
<th>Group RC (n=20)</th>
<th>Group RM (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hour</td>
<td>1.6±0.7</td>
<td>2.5±0.8 *</td>
<td>1.5±0.7</td>
</tr>
<tr>
<td>2nd hour</td>
<td>1.2±0.5</td>
<td>1.9±0.6 *</td>
<td>1.3±0.6</td>
</tr>
<tr>
<td>3rd hour</td>
<td>0.9±0.3</td>
<td>1.2±0.5</td>
<td>1.0±0.4</td>
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<td>0.7±0.4</td>
<td>0.9±0.4</td>
<td>0.8±0.4</td>
</tr>
<tr>
<td>5th hour</td>
<td>0.5±0.3</td>
<td>0.6±0.3</td>
<td>0.5±0.4</td>
</tr>
<tr>
<td>6th hour</td>
<td>0.4±0.2</td>
<td>0.5±0.3</td>
<td>0.4±0.3</td>
</tr>
</tbody>
</table>

Values are mean ± SD. R = Ropivacaine. RC = Ropivacaine + clonidine. RM = Ropivacaine + magnesium. * $p<0.05$ group RC Vs. groups R and RM.

Discussion

Administration of regional anesthesia before surgery is a safe and widely accepted technique, providing adequate pain relief, thus reducing the general anesthesia requirements and allowing calm and satisfactory recovery [20]. Various studies report that caudally administered ropivacaine provides satisfactory analgesia in children [21,22].

In the current study, ropivacaine was found to produce the least significant hemodynamic changes in all groups. In the other two groups there was more decrease in intraoperative HR, but it was most significant in group RC. Several studies and reports described severe bradycardia or atrioventricular conduction disturbance during clonidine therapy either if used intravenously or in regional anesthesia [21]. In this study, clonidine used caudally was shown to decrease HR intraoperatively, but no serious bradycardia has occurred. This is in agreement with the study of Kirno et al. [24] which concluded that, the comparable inhibition of resting sympathetic nerve activity was paralleled by a decrease in HR and BP after both epidural and intramuscular clonidine. Clonidine induced bradycardia may be dose dependent, so it has to be avoided in patients with atrioventricular conduction. As regards the postoperative period, we noted that addition of clonidine and magnesium sulphate caused reduction of blood pressure more than in ropivacaine group alone. This coincided with De Negri et al. [25] who studied the hemodynamic effect of clonidine and ketamine.

For reduction of stress response as measured by plasma catecholamine level, a significant reduction (E and NE) was found in this study after caudal block throughout the procedure and postoperatively, but there was no significant difference between the three groups. The inhibitory effect of combined general and caudal epidural anesthesia on the stress response has been reported in pediatric population [26]. Also, this study agrees with studies done by Gaitini et al. [27,28] demonstrating that the addition of caudal block to general anesthesia significantly reduces the neurohormonal response in children undergoing inguinal herniorrhaphy.

The present study also estimated that adding clonidine (2 [$\mu$g/kg]) to ropivacaine (0.25%) 1ml/kg provided postoperative analgesia for 6.6±1.3h compared to 3.2±0.9 and 3.7±0.7 in ropivacaine and ropivacaine magnesium groups respectively ($p<0.05$). Pain measurement in children is difficult and unreliable; each method has its limitation, particularly in non verbal children [29]. The OPS
is a valid, sensitive and reliable tool in evaluating postoperative pain in children. In this study clonidine was found to have a greater effect on analgesia compared to the other two groups and this is comparable with other studies [11,25].

The time dependent sedative effect of caudal clonidine was studied before in adults. Postoperative sedation for 9 hours was reported when 2 g/kg caudal clonidine was used [30]. In agreement with these findings, in the present study, sedation score was significantly higher in children received caudal clonidine (group RC). No observed side effect had occurred in this study in all groups (hemodynamic, respiratory alterations, toxic reactions, lumbar pain, or odd behavior), except for nausea and vomiting in all groups, one case in ropivacaine group and two cases in the other two groups.

Magnesium is known to be an NMDA receptor antagonist. It is assumed that NMDA receptors play an important role in the development of central sensitivity after noxious peripheral stimulation [31]. Administration of IV magnesium sulphate during surgery reduces intra and postoperative opioid requirements [32]. Koinig and colleagues reported that magnesium administration led to a significant reduction in fentanyl consumption in the peri and postoperative period [12]. However, IV magnesium, even in high doses, is associated with limited passage across the blood-brain barrier [33].

In this study, the results revealed that there is no significant effect of magnesium added to ropivacaine, more than ropivacaine alone, on postoperative analgesia and analgesic requirement. This is comparable with the results reported by Birbicer et al. [33] who compared ropivacaine 0.25% plus 50mg magnesium to ropivacaine 0.25% alone for caudal anesthesia in children. They concluded that the addition of magnesium as an adjuvant agent to local anesthetics for caudal analgesia has no effect on postoperative pain and analgesic need. Buvanendran et al. [34] used magnesium intrathecally and demonstrated that 50mg intrathecal use of magnesium prolonged analgesia in adults. Our failure to produce similar results with caudally administered magnesium may be due to the following reasons: (1) It may be possible that epidurally applied magnesium is less effective in passing the blood brain-barrier compared to its intrathecal use and is unable to form effective CSF concentration. (2) The dose used in this study was based on the reference of intrathecal application and may not be sufficient for postoperative analgesic achieved through epidural use.

Conclusion:

The addition of clonidine to ropivacaine 0.25%, when administered caudally in children, prolongs the duration of postoperative analgesia. The need for subsequent postoperative analgesic is also reduced. The addition of magnesium to ropivacaine is comparable to the effect of ropivacaine alone. Caudal analgesia resulted in a significant reduction in catecholamine levels. Further studies with higher magnesium doses used epidurally are needed in children.

References