An evaluation of intrathecal bupivacaine combined with intrathecal or intravenous clonidine in children undergoing orthopedic surgery: a randomized double-blinded study

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Introduction

During the last decade, the selective alpha 2-adrenoceptor agonist, clonidine, with intrinsic analgesic effect and perioperative sedation and anxiolysis, has been extensively studied in pediatric anesthesia, particularly when administered caudally or intrathecally with a local anesthetic agent (1–3). Orally or intravenously administered clonidine has been known to decrease the consumption of propofol sedation (4,5). However, to...
In our knowledge, there were few reports about the effect of intrathecal clonidine on requirement of propofol sedation during spinal anesthesia in children.

Furthermore, there is ongoing controversy regarding the most effective route for clonidine administration. There is some evidence that clonidine’s analgesic effects were more pronounced after neuroaxial administration than systemic administration, suggesting a spinal site of action and favoring neuroaxial administration. Intrathecal clonidine demonstrated prolonged analgesia and decreased morphine consumption postoperatively more than by the oral route (6). Both epidural and intravenous routes might achieve postoperative analgesia, but the overall dose of clonidine was lower by the epidural route (7). On the contrary, some studies suggested that these routes of administration might be via other mechanisms excluding spinal effect or share some mechanisms of action. In orthopedic or perineal surgery, epidural and intramuscular administration of clonidine produced similar postoperative analgesia and side effects (8). Both oral and intrathecal clonidine prolong the duration of action of intrathecal local anesthetics (9). The analgesic effect of clonidine as an adjunct to caudal block with bupivacaine was similar whether administered intravenously or caudally (10). Therefore, further studies are required to investigate which route of administration of clonidine is more beneficial.

With this background, we performed a randomized, double-blind, controlled study. The primary outcome measures were to compare the effect of intrathecal and intravenous clonidine on postoperative analgesia/sedation. Intraoperative propofol requirements and perioperative adverse events were also assessed as secondary outcome measures.

**Material and methods**

The study protocol was approved by the Institutional Ethical Committee of 455 Hospital of PLA and the Second Military Medical College affiliated Changzheng Hospital, Shanghai, China on 15 July 2009. After written informed parental consent was obtained from each child, sixty ASA physical status I-II children, aged 6–8 years, undergoing elective hip or knee arthroplasties were enrolled in this study. Exclusion criterion included any known contraindication for spinal anesthesia, such as increased intracranial pressure, neurological disorders, hemorrhagic diathesis, or infection at the puncture site. Allergy to bupivacaine or clonidine or cardiorespiratory diseases was excluded.

A double-blind, randomized, controlled study design with three groups was used. A computer-generated table of random numbers was used in the randomization. The children were randomized into the following three groups: group B patients received intrathecal 0.5% hyperbaric bupivacaine (AstraZeneca China Ltd, Wuxi, China) 0.2–0.4 mg·kg⁻¹ and intravenous 2 ml saline, group BClit patients received intrathecal 0.5% hyperbaric bupivacaine 0.2–0.4 mg·kg⁻¹ along with 1 μg·kg⁻¹ clonidine (Catapressan; Boehringer-Ingelheim, Frankfurt, Germany) and intravenous 2 ml saline, and group BCiv patients received intrathecal 0.5% hyperbaric bupivacaine 0.2–0.4 mg·kg⁻¹ along with intravenous 1 μg·kg⁻¹ clonidine in 2 ml of saline. Demographic data including age, gender, weight, and height were recorded.

After standard fasting times, all children had EMLA (AstraZeneca) applied to the dorsum of both hands 1 h before surgery, and 30 min before surgery, they received midazolam 0.5 mg·kg⁻¹ orally. On arrival to the operation theater, an intravenous access was established and fluids (0.45% saline in 5% dextrose) 6 ml·kg⁻¹·h⁻¹ were infused and supplemental oxygen 3 l·min⁻¹ was administered by a facemask. Noninvasive arterial blood pressure, heart rate, and oxygen saturation were monitored at baseline and every 2 min for the first 10 min after spinal injection, and thereafter, every 5 min during the surgery. A bolus of 1.5–2 mg·kg⁻¹ of propofol was administered for lumbar puncture. An investigator who prepared the drug was blinded to the group assignment. The intrathecal block was performed with the children positioned in the left lateral position at the L4–5 interspaces with 25G pencil-point needle (B.Braun China Ltd, Shanghai, China) with an introducer needle after subcutaneous lidocaine infiltration. After free flow of CSF was observed, bupivacaine was injected intrathecally alone and along with clonidine. Simultaneously, 2 ml of 0.9% saline with or without clonidine was administered intravenously. The level of sedation was monitored with bispectral index (BIS). According to previous reports (11,12), the target BIS ranges (60–70) for intraoperative sedation were maintained with infusion of propofol 20–50 μg·kg⁻¹·min⁻¹. Propofol was stopped at the end of surgery, and the total propofol dose including the bolus and the intraoperative infusion to maintain adequate sedation was recorded.

A second consultant anesthetist who was blinded to the assigned group performed following all assessments. After surgery, the children were transferred to the postanesthesia care unit, and sensory and motor blocks were assessed every 15 min when the children were awake. The spread of sensory block was tested with a pinprick method, and the degree of motor blockade was assessed with modified Bromage scale.
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(0 = free movement of legs and feet, 1 = just able to flex knees with free movement of feet, 2 = unable to flex knees, but with free movement of feet, 3 = unable to move legs or feet) (13). Time for regression of the sensory block to L2 and the time to full recovery of motor block were recorded.

According to previous reports (14), postoperative analgesia was assessed using the Children and Infants Postoperative Pain Scale (CHIPPS) every 30 min during the first 4 h and at every 2 h thereafter until the end of the study period (12 h). If the CHIPPS score was 4 or higher, tramadol 1–2 mg·kg⁻¹ IV was used for rescue analgesia. The time to the first supplemental tramadol was recorded and defined the time from the intrathecal injection to analgesic administration. At the same time point, postoperative sedation was assessed using the Ramsay sedation score (15).

All adverse effects including hypotension (>20% decrease in systolic blood pressure from baseline), bradycardia (HR < 60 beats·min⁻¹), respiratory depression, nausea/vomiting, urinary retention, and shivering were recorded and treated in perioperation periods. Hypotension and bradycardia were treated with ephedrine 3 mg IV and atropine 0.01 mg·kg⁻¹ IV, respectively.

Statistical analysis

The variables on testing by Kolmogorov–Smirnov test were found to be normally distributed. The sample size of our study was based on the assumption of a minimum difference of 25% in the duration of sensory block and an increase of 30% in the time interval from the intrathecal injection to the first request for supplemental analgesia. Power analysis suggested that 17 patients per group were required to achieve a power of 90% at the two-sided 0.05 level of significance to detect a difference among the three groups. The consort diagram for the study is summarized in Figure 1. Of the 60 children enrolled in the study, 59 children were randomized for the study to account for possible exclusion. One child was not included for randomization because of cancelation of surgery, and further two children randomized to the study were excluded for inadequate blockade. Statistical analysis was performed using SPSS15.0 software, and data are presented as mean ± sd and number (%) of cases as appropriate. Parametric data were analyzed using one-way ANOVA between the groups. Enumeration data were analyzed with the chi-square test. The analgesic efficacy in the three groups, as judged by the time to first analgesic rescue, was analyzed using a Kaplan–Meier survival curve method followed by the log-rank test. In all cases, a P < 0.05 was considered statistically significant.

Results

There were no significant differences in the patient demographics data and surgical duration and bupivacaine dose (Table 1). There was no difference in the number of children requiring rescue analgesia among the three groups. However, the median time to first dose of rescue analgesic was significantly longer in group BCit (462 ± 124 min) and group BCiv (425 ± 110 min) compared to group B (365 ± 108 min) (P < 0.05; Table 2). Using a log-rank test, we compared the fraction of children who did not use rescue analgesia over time in each group (P < 0.05; Figure 2). The total and maintenance requirements of propofol infusion in group BCit and group BCiv were significantly reduced in comparison with group B (P < 0.05; Table 2).

All children were assessed using CHIPPS and Ramsay scale methods up to 12 h postoperatively. In group BCit, the mean CHIPPS scores of children were significantly lower than in group B at all times through 210 min (P < 0.05), while the pain scores were lower in group BCiv in the early phase (60 min) after surgery (P < 0.05; Figure 3). In the early phase (4 h), the mean postoperative sedation scores were higher in groups BCit and BCiv when compared to group B (P < 0.05; Figure 4).

The time to regression of the sensory block and recovery of motor block was significantly longer in the group BCit than in the groups B and BCiv (P < 0.05; Figure 5). There were no significant differences among the three groups regarding the incidence of perioperative adverse events (Table 3).

Discussion

The results of the present study indicated that no matter administered intrathecally or intravenously, clonidine 1 µg·kg⁻¹ could exert better efficacy of postoperative sedation and analgesia and prolong time to first rescue analgesia after surgery and reduce the requirements of propofol for intraoperative sedation. However, only intrathecal clonidine with bupivacaine prolonged the duration of both sensory and motor blocks in children undergoing orthopedic surgery. Hermanns et al. (16) showed that the presumed mechanism for sedative effect after spinal anesthesia was that the decreased proprioceptive input to the reticular activating system diminished afferent conduction to reticulo-thalamo-cortical projection pathways.
and hence decreased the arousal level of the brain. However, the sedative effect of spinal anesthesia alone could not provide satisfactory level of sedation in the pediatric population. Propofol was an ideal sedative medication in pediatric patients for readily sedation and rapid recovery during spinal anesthesia. A recent study indicated that intrathecal clonidine significantly reduced not total requirements but the maintenance infusion requirements of propofol in infant undergoing lower abdominal surgery (17). However, our results showed that intrathecally administered clonidine significantly reduced not only the total requirements but also the maintenance infusion requirements of propofol in children undergoing orthopedic surgery. Clonidine might exert its sedative action via the stimulation of alpha 2 receptors in locus coeruleus, which was responsible for sleep and arousal (18). Furthermore, it has been hypothesized in adults that clonidine’s propofol-sparing affect was a pharmacokinetic rather than pharmacodynamic effect as hepatic clearance would be affected by alpha 2-agonists (19).

Table 1 Demographic data

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th>Surgery (hip/knee)</th>
<th>Surgical duration (min)</th>
<th>Bupivacaine dose (mg·kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B</td>
<td>7.4 ± 1.2</td>
<td>25 ± 8</td>
<td>10/9</td>
<td>88 ± 25</td>
<td>0.26 ± 0.08</td>
</tr>
<tr>
<td>Group BCit</td>
<td>7.2 ± 1.3</td>
<td>24 ± 10</td>
<td>9/10</td>
<td>92 ± 18</td>
<td>0.27 ± 0.08</td>
</tr>
<tr>
<td>Group BCiv</td>
<td>7.3 ± 1.1</td>
<td>25 ± 9</td>
<td>8/11</td>
<td>99 ± 26</td>
<td>0.27 ± 0.09</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD and number of cases (%). Group B, intrathecal bupivacaine; Group BCit, intrathecal bupivacaine plus clonidine; Group BCiv, intrathecal bupivacaine plus intravenous clonidine.
Previous studies demonstrated that the combined epidural or intrathecal administration of clonidine with the local anesthetics lidocaine (9), tetracaine (20) and bupivacaine (21) prolonged duration of the motor and sensory blocks and provided better postoperative analgesia than the administration of either substance alone. However, there are contrasting results regarding the clinical effects of clonidine observed after different routes of administration. Alkin et al. (3) reported that clonidine given caudally provided better postoperative analgesic effect than administered intravenously after caudal levobupivacaine in children undergoing inguinal hernia repair or orchidopexy surgery, suggesting that clonidine exerted its analgesic effect through a direct spinal site of action. On the contrary, Hansen et al. (10) indicated that the analgesic effect of clonidine as an adjunct to caudal block with bupivacaine was similar whether administered intravenously or caudally in children undergoing hypospadias repair. In the present study, we compared the effects of intrathecal and intravenous clonidine on postoperative analgesia after intrathecal bupivacaine for orthopedic surgery in children. Our study indicated that the number of patients and time to first rescue analgesia were similar with clonidine administered intrathecally or intravenously. Therefore, our data suggest that clonidine has not only a direct spinal action but also a central action at the locus coeruleus.

Several possible mechanisms for the analgesic effect of clonidine have been presented from previous studies. The entire effect of clonidine could be attributed to systemic uptake irrespective of the site of administration. Clonidine is highly lipophilic, easily crossed the blood brain barrier, and therefore might interact

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### Table 2: Need for rescue analgesia and propofol requirements

<table>
<thead>
<tr>
<th></th>
<th>Group B (n = 19)</th>
<th>Group BCit (n = 19)</th>
<th>Group BCiv (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients requiring rescue analgesia</td>
<td>16 (84)</td>
<td>11 (58)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>Time to first rescue analgesia (min)</td>
<td>365 ± 108</td>
<td>462 ± 124*</td>
<td>425 ± 110*</td>
</tr>
<tr>
<td>Propofol requirements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (mg·kg⁻¹·h⁻¹)</td>
<td>4.4 ± 0.5</td>
<td>3.1 ± 0.4*</td>
<td>2.9 ± 0.5*</td>
</tr>
<tr>
<td>Propofol maintenance infusion (µg·kg⁻¹·min⁻¹)</td>
<td>36.5 ± 8.4</td>
<td>21.6 ± 5.8*</td>
<td>19.4 ± 6.7*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± so and number of cases (%). Group B, intrathecal bupivacaine; Group BCit, intrathecal bupivacaine plus clonidine; Group BCiv, intrathecal bupivacaine plus intravenous clonidine. *P < 0.05 compared to group B.

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**Figure 2** Log-rank curves for duration of pain relief. Kaplan–Meier survival curve showed the fraction of children from the three groups (1.0 = 100%) who did not require rescue analgesia over time. (†P < 0.05).

**Figure 3** Children and Infants Postoperative Pain Scale score in groups. Postoperative pain scores were recorded every 30 min during the first 4 h and at every 2 h thereafter until the end of the study period (12 h). Group B: intrathecal bupivacaine; Group BCit: intrathecal bupivacaine plus clonidine; Group BCiv: intrathecal bupivacaine plus intravenous clonidine. Data presented are mean ± so, n = 19. *P < 0.05 compared with Group BCit, †P < 0.05 compared with Group BCiv.
with α-adrenergic receptors both at spinal and supraspinal sites within the CNS and various other locations (22). Clonidine might interact with α-adrenergic receptors in the dorsal horn that are believed to be associated with spinal modulation and/or potentiation of the inhibitory effects of local anesthetics on C fiber activity (23). Clonidine might affect peripheral sensory nerves by inhibition of neurotransmission in both Aδ and C nerve fibers (24). The findings of the present study support the first two mechanisms of action. Further studies are required to elucidate the exact mechanisms of analgesia from clonidine when administered together with local anesthetic agent.

Although similar effect of intrathecal or intravenous clonidine on postoperative sedation and analgesia was observed in our study, we found that only intrathecal clonidine significantly prolonged the time to regression of the sensory block and recovery of motor block. A prolonged time for regression of motor and sensory block might be an advantage of intrathecal clonidine over intravenous clonidine resulting in prolonged surgical anesthesia. The mechanism that clonidine administered intrathecally prolonged the motor and sensory block effects of local anesthetics is not completely known. Some studies suggested that epidural clonidine exerts an antinociceptive action through its direct suppression of nociceptive neurons in the spinal cord (25,26).

In the present study, hypotension and bradycardia were more frequent in both clonidine groups compared to the control group, but there were no statistical difference in the incidence of hypotension and bradycardia among the three groups. Moreover, few other adverse events were observed in the present study.

We utilized the BIS system to adjust the infusion dose of propofol during operation. Some studies reported the BIS has been validated with children undergoing general anesthesia and had good correlation between BIS monitor results and Ramsay Sedation Scale results among children (27,28). However, a wide variation in the depth of sedation with the BIS monitor and the University of Michigan Sedation Scale was found (29). Therefore, a potential limitation of our study design was that BIS might remain controversial to assess the level of sedation.

<table>
<thead>
<tr>
<th>Perioperative adverse events</th>
<th>Group B (n = 19)</th>
<th>Group BCit (n = 19)</th>
<th>Group BCiv (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>3 (16)</td>
<td>5 (26)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2 (11)</td>
<td>3 (16)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>1 (5)</td>
<td>2 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1 (5)</td>
<td>2 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Shivering</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are number of cases (%). Group B, intrathecal bupivacaine; Group BCit, intrathecal bupivacaine plus clonidine; Group BCiv, intrathecal bupivacaine plus intravenous clonidine. There were no significant differences between the groups.
In conclusion, our study demonstrated that the combined intrathecal or intravenous clonidine with bupivacaine similarly provided better postoperative analgesia and sedation than the administration of bupivacaine alone and reduced the intraoperative requirements of propofol in children undergoing orthopedic surgery. Moreover, only intrathecal clonidine could prolong the duration of sensory and motor blocks during bupivacaine spinal anesthesia.

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None.

References
