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Analgesic Effects of Caudal and Intramuscular S(+)-Ketamine in Children

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Background: **Previous studies suggest that caudal administration of ketamine cause effective analgesia. The purpose of the current study was to compare the clinical effectiveness and plasma concentrations of S(+)-ketamine after caudal or intramuscular administration in children to distinguish between local and systemic analgesia.**

Methods: **After induction of general anesthesia, 42 patients, aged 1 to 7 yr, scheduled to undergo inguinal hernia repair randomly received a caudal (caudal group) or intramuscular (intramuscular group) injection of 1 mg/kg *S*(+)-ketamine. Intraoperatively, heart rate (HR), mean arterial pressure (MAP) and arterial oxygen saturation were measured. Postoperative measurements included duration of analgesia, a four-point sedation score, and hemodynamic and respiratory monitoring for 6 h in the recovery room. Analgesic requirements in the recovery room were assessed by an independent blinded observer using an observational pain/discomfort scale (OPS). Plasma samples for determination of ketamine concentrations were obtained before and 10, 20, 30, 45, 60, 90, 120, and 180 min after injection of *S*(+)-ketamine.**

Results: **A significantly longer duration of analgesia ($P < 0.001$) was observed after caudal administration (528 min [220–1,440 min]; median [range]) when compared with intramuscular administration (108 min [62–1,440 min]) of *S*(+)-ketamine. Plasma levels of ketamine were significantly lower from 10 to 45 min after caudal administration than after intramuscular injection.**

Conclusion: **Caudal *S*(+)-ketamine provides good intra- and postoperative analgesia in children. Despite similar plasma concentrations during most of the postoperative observation period, caudal *S*(+)-ketamine provided more effective analgesia than did intramuscular *S*(+)-ketamine, indicating a local analgesic effect. (Key words: NMDA antagonist; pain; spinal.)**

CAUDAL analgesia is a popular regional anesthetic procedure used in pediatric surgery.[1] Motor blockade after local anesthetic injection and several reports of systemic toxic reactions after accidental intravenous injection of bupivacaine[2,3] or respiratory depression after opioid administration have been the stimulus for the development of new local anesthetics and the epidural administration of other analgesic drugs.

The dissociative anesthetic agent ketamine is a noncompetitive blocker of glutamate *N*-methyl-D-aspartate (NMDA) receptors; it exhibits analgesic properties in rodents and exerts a direct antinociceptive effect at the spinal level.[4] In humans, racemic ketamine provides intra- and postoperative analgesia alone in pediatric caudal block,[5] and as an additive to epidural administration[6] in adults, but is not recommended for epidural and spinal anesthesia because of the potential neurotoxicity of preservative agents added to commercially available ketamine preparations.[7]

S(+)-Ketamine is produced as a preservative-free solution. The *S*(+)-enantiomer of ketamine was shown to be clinically superior to the racemic mixture of ketamine with regard to anesthetic potency, the extent of analgesia and amnesia, the incidence of side effects, and the psychotic reactions and agitation.[8–10]

The analgesic effectiveness of caudal or epidural ketamine is likely to result from the interaction with NMDA[11] or opioid receptors[12] on the spinal level. However, supraspinal effects from systemic resorption cannot be ruled out.

To differentiate between local and systemic drug effects, we compared the intra- and postoperative analgesic effectiveness of caudally and intramuscularly administered *S*(+)-ketamine and assessed systemic absorption by measuring ketamine blood levels.

Materials and Methods

After approval from the institutional ethics committee of the University of Vienna and obtaining written informed parental consent, we enrolled 42 pediatric patients aged 1–7 yr (American Society of Anesthesiologists [ASA] physical status I–II) in a prospective, randomized, double-blind study. Children were scheduled to undergo inguinal hernia repair and randomized, using a systematic random-sample technique, for either caudal block with 1 mg/kg *S*(+)-ketamine, 0.1% (caudal group), or intragluteal injection of 1 mg/kg *S*(+)-ketamine, 0.5% (intramuscular group). Surgery was performed by applying the same surgical technique and patient treatment in all study participants.

Premedication consisted of 0.5 mg/kg rectal midazolam (maximum dose 15 mg) according to the standard guidelines of the pediatric anesthesia department. General anesthesia was induced with use of sevoflurane and an intravenous catheter was then inserted. After intravenous injection of 3 mg/kg propofol, a laryngeal mask was

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positioned and Ringer's lactate solution was infused at a rate of 10 ml · kg^{-1} · h^{-1}. Thereafter, during aseptic conditions and with the child in a lateral position, either caudal block with use of a 22-gauge Quincke needle or intragluteal injection with use of a 24-gauge intramuscular needle was performed by an independent anesthesiologist, who was not further involved in the study. After slow injection of the drug, the child was turned into the supine position. To ensure that the anesthesiologist responsible for the child during the operation and the observers in the recovery room and at the ward were blind to drug administration, tape was put on the gluteal and caudal skin in each child.

Anesthesia was maintained with 1.2% sevoflurane and 70% nitric oxide in oxygen. Noninvasive mean arterial pressure, heart rate, and percutaneous oxygen saturation (Spo_2) were recorded after general anesthesia was induced, immediately after caudal or intramuscular injection of *S*(+)-ketamine, and every 5 min thereafter during the operation. Skin incision was performed 15 min after injection of the study drug. All children breathed spontaneously with manual assistance throughout the anesthetic and surgical procedures. Volatile anesthetic agents were discontinued at the beginning of skin closure. An intraoperative increase of heart rate or mean arterial pressure of more than 20% was defined as insufficient analgesia and would be treated by intravenous administration of nalbuphine (0.2 mg/kg) as rescue medication. None of the children received nalbuphine during the study.

After patients were awake, they were brought to the recovery room breathing room air. After arrival, mean arterial pressure, heart rate, and Spo_2 were documented every 15 min until 6 h after caudal or intramuscular injection of *S*(+)-ketamine. Respiratory depression was defined as a decrease of Spo_2 to less than 93%. In this case, supplemental oxygen was provided *via* mask.

Table 1. Patient Characteristics

Group	Caudal	I.M.
N	22	20
Age (yr)	3.5 ± 1.3	4.1 ± 1.9
Weight (kg)	15.8 ± 4.2	16.9 ± 4.3
Height (cm)	101 ± 9.7	104 ± 13.7
Duration of surgery (min)	23.6 ± 6.2	26.7 ± 7.4

Values are mean ± SD

Caudal = caudal administration group; I.M. = intramuscular administration group.

Postoperative analgesic effectiveness was documented using an observational pain/discomfort scale (OPS)[11] and by the duration of analgesia, which was defined as the interval from caudal or intramuscular drug injection until administration of first postoperative pain medication. The OPS assesses behavioral objective parameters (crying, facial expression, position of torso, position of legs, motor restlessness). Each parameter is scored from 1 to 3 (corresponding to none; moderate; or severe) to obtain a cumulative score of 5–15 to estimate the quality of analgesia (*e.g.*, 5 = excellent, 15 = ineffective). If the OPS score, which was evaluated by a study nurse, was more than 11 in two subsequent measurements, or if the patient had obvious signs of pain, 20 mg/kg acetaminophen was administered as a suppository. Children with these scores were excluded from further evaluation. A 4-point patient sedation score was assigned as follows: 1 = asleep, not able to be aroused by verbal contact; 2 = asleep, able to be aroused by verbal contact; 3 = drowsy, not sleepy; and 4 = alert, awake. The times from caudal or intramuscular drug injection to first spontaneous voiding after anesthesia were also documented. After a 6-h observation period in the recovery room, the patients were discharged to the ward. To achieve a 24-h observation period, nurses at the ward were asked to assess

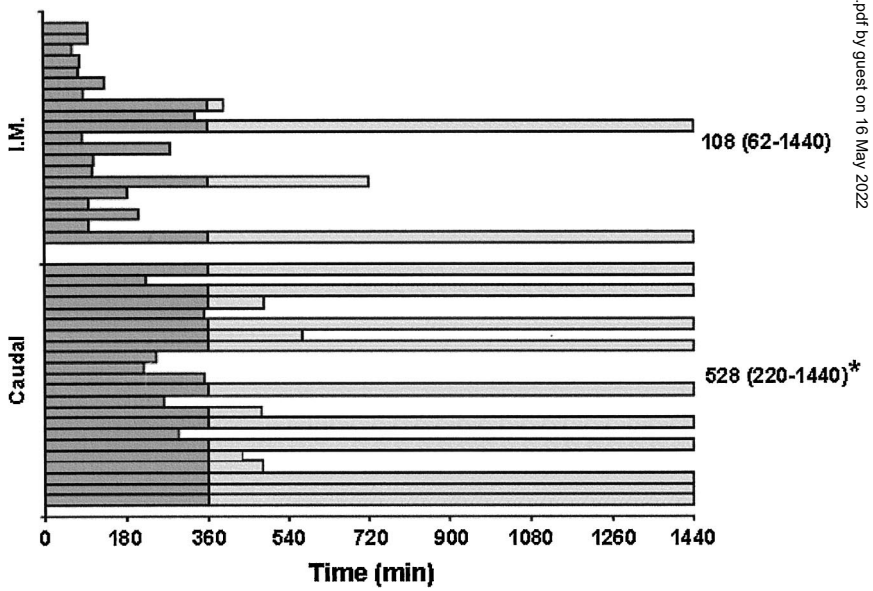

Fig. 1. The duration of analgesia for each patient during the 6-h observation period in the recovery room (dark gray columns), and the 18-h observation period at the ward (light gray columns). Numeric values are presented as median (range). Caudal = caudal administration of *S*(+)-ketamine; I.M. = intramuscular administration of *S*(+)-ketamine. *Values for the caudal group were significantly different from the other group.

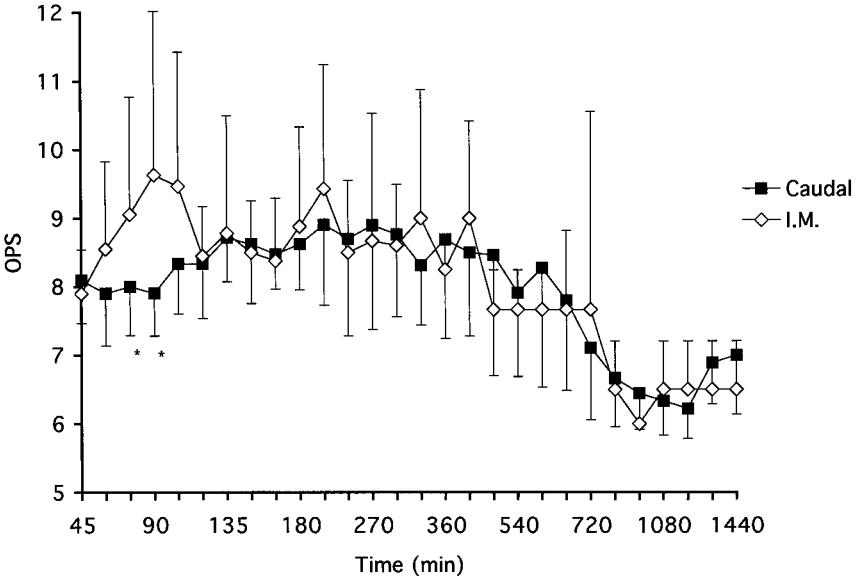

Fig. 2. Observational pain scores (OPS) for both groups. Caudal = caudal administration of *S*(+)-ketamine; I.M. = intramuscular administration of *S*(+)-ketamine. *Mean OPS was significantly lower ($P < 0.05$) after caudal injection of *S*(+)-ketamine.

the child every 2 h during the 18 h after discharge from the recovery room. The duration of postoperative analgesia was defined as the time between *S*(+)-ketamine injection and the first rectal acetaminophen administration. If no rectal acetaminophen was necessary within the 24-h observation period, the duration of analgesia was assumed to be 1,440 min. All observers involved in the procedure (one in the operating room responsible for intraoperative assessment of analgesic effects, one in the recovery room, and one at the ward responsible for postoperative assessment of analgesic effects and additional analgesic drug administration if needed) were blind to the therapeutic intervention during the study period. Each observer completed assessments during the 6-h observation period of a single patient in the recovery room and during the 18-h observation period at the ward.

To measure total plasma concentrations of ketamine, peripheral blood samples (2 ml) were collected *via* the established intravenous access in the first 17 patients (8 in the caudal group, 9 in the intramuscular group). Blood samples were taken before and 10, 20, 30, 45, 60, 90, 120, and 180 min after injection of *S*(+)-ketamine. The samples were collected in heparinized tubes, and plasma was separated by centrifugation at room temperature within 30 min of collection. The plasma samples were stored at −30°C until drug assay. The quantitative assay of plasma ketamine was performed by high-performance liquid chromatography.[14] The concentration of ketamine was given in nanograms per milliliter.

Statistical Analysis

All data are presented as the mean ± SD, except duration of analgesia, which is presented as median and range because of censored data. Demographic data were compared using the unpaired Student *t* test. Hemodynamic data were compared with the baseline values

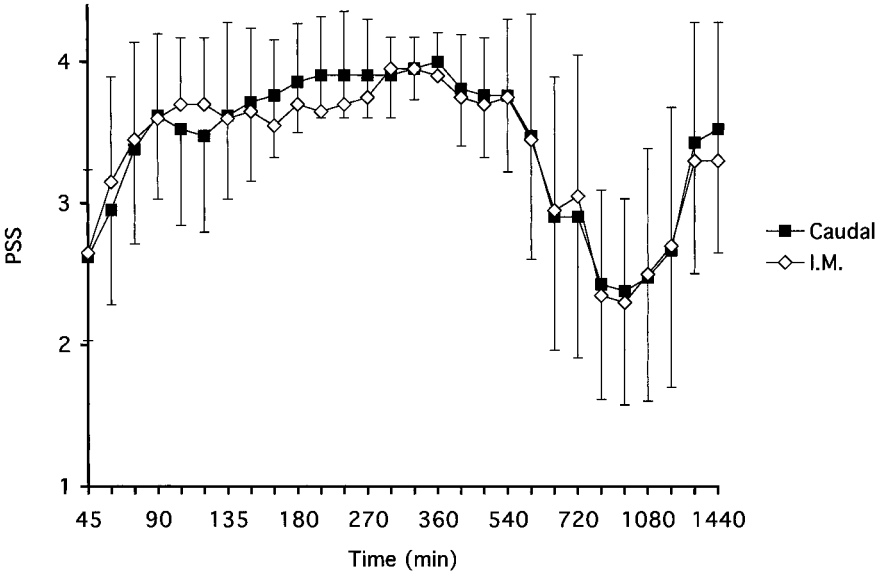

Fig. 3. Patient sedation scores (PSS) for both groups. Caudal = caudal administration of *S*(+)-ketamine; I.M. = intramuscular administration of *S*(+)-ketamine.

within each study group, and with corresponding time points among the groups, by using the Student *t* test and one-way analysis of variance. The OPS, patient sedation score, and duration of analgesia were evaluated by use of the Mann–Whitney test. Distribution frequencies were analyzed by use of the the chi-square test. Probability values < 0.05 were considered to be statistically significant.

Results

The study groups were comparable with respect to age, height, weight, and duration of surgery (table 1). All children underwent the same type of surgery (*i.e.*, inguinal hernia repair according to standardized surgical conditions). All 42 patients included in the study were then evaluated. None of the children required additional intraoperative analgesic drugs. Duration of analgesia was significantly longer in the caudal group than in the intramuscular group (fig. 1; $P < 0.001$). During the 24-h observation period, fewer children required additional analgesic drugs in the caudal group (12 of 22) than in the intramuscular group (18 of 20; $P < 0.001$). OPS scores were similar 45 and 60 min after injection of *S*(+)-ketamine, but at 75 and 90 min ($P < 0.05$), OPS values were significantly lower in the caudal group (fig. 2). Patient sedation score after arrival in the recovery room was comparable between both groups (fig. 3). Time to first spontaneous voiding was 285 ± 56 min in the caudal group and 271 ± 48 min in the intramuscular group. Adverse psychologic effects were not observed in either group. The hemodynamic parameters (data not shown) showed no significant differences over time or between the groups. Respiratory depression was not observed, and intra- and postoperative Spo_2 values were not different among groups.

The plasma concentration-*versus*-time curves for ketamine after intramuscular and caudal injection are illustrated in figure 4. Ketamine levels were significantly lower 10, 20, 30, ($P < 0.01$) and 45 min ($P < 0.05$) after caudal injection than after intramuscular administration.

Table 2. Pharmacokinetics of Ketamine and Duration of Analgesia after Caudal and IM Administration in Children

Group	Caudal	IM
N	8	9
Duration of analgesia*	485 (263–1440)	99 (62–1440)‡
C_{max} (ng/ml)†	120 ± 52.5	366.9 ± 130.5‡
t_{max} (min)†	21.2 ± 2	11.2 ± 5.4‡

Values represent a subset of the study population.

* Values are median (range).

† Values are mean ± SD.

‡ Significant difference between groups ($P < 0.05$).

C_{max} = maximum plasma concentration; IM = intramuscular; t_{max} = time of C_{max} after drug administration.

In addition, maximum plasma concentrations (C_{max}) were lower ($P < 0.01$), and time to reach maximum plasma concentration (t_{max}; $P < 0.01$) was longer after caudal administration of the drug (table 2).

Discussion

The current results indicate sufficient intra- and postoperative analgesic effectiveness of caudal *S*(+)-ketamine. Caudally administered *S*(+)-ketamine was more effective in terms of duration of analgesia and OPS; however, ketamine blood levels were significantly lower after caudal administration when compared with intramuscular injection. Hemodynamics and postoperative sedation scores were similar in both groups, suggesting equivalent quality of intraoperative analgesia for both routes.

Caudal analgesia in combination with general anesthesia is a very popular regional anesthetic technique for various pediatric surgical procedures. Possible systemic toxicity[2,3] after intravascular injection of local anesthetics or possible respiratory depression[15] after caudal opioid administration has been the motivation for caudal or epidural administration of ketamine.

The epidural administration of racemic ketamine has been investigated in adults, with contradictory results. In previous studies, it was assumed that ketamine exerts

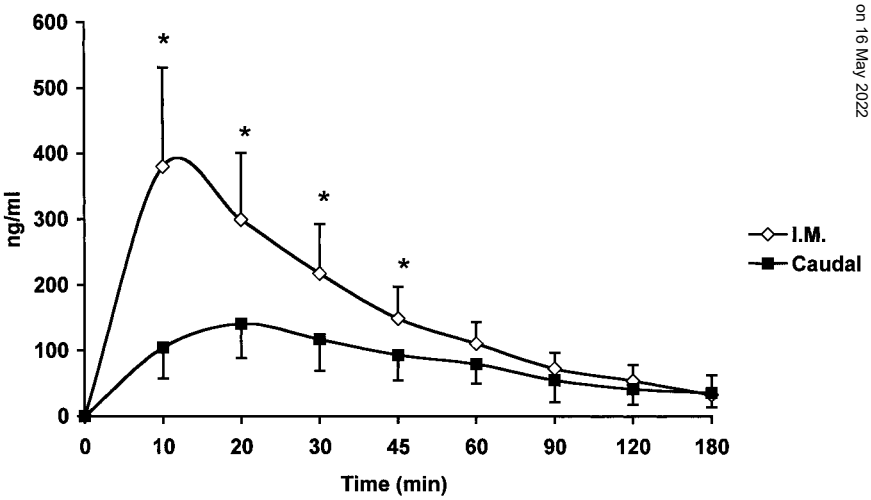

Fig. 4. Ketamine plasma concentrations in children in both groups. Values are presented as mean ± SD. Caudal = caudal administration of *S*(+)-ketamine; I.M. = intramuscular administration of *S*(+)-ketamine. *Plasma levels were significantly higher after intramuscular injection when compared to caudal administration.

analgesic effects after epidural, caudal, or intrathecal administration[16,17] because of its interaction with antinociceptive spinal receptors. Because the administration *via* the epidural route would bring the drug closer to the "target organ," the effective dose can be reduced, thus decreasing possible adverse effects. Although some studies have shown sufficient analgesic effectiveness of epidural ketamine,[16,18] other studies did not confirm these results.[19,20] Racemic ketamine has been used for pediatric caudal blocks,[5,21,22] and an analgesic potency comparable with that of bupivacaine has been found. Because of possible neurotoxicity of preservatives added to commercially available racemic ketamine preparations, the drug is not recommended for epidural or spinal administration.[23]

Compared with the racemic ketamine mixture, the *S*(+)-enantiomer, has a twofold higher analgesic potency,[24] whereas the other pharmacologic properties are similar,[8,9,25] and *S*(+)-ketamine is commercially available without preservatives added.

Lower maximum plasma concentrations (C_{max}) and longer time to reach maximum plasma concentrations (t_{max}) after caudal drug administration compared with intramuscular injection in this study may be explained by a lower hemoperfusion of the epidural fat compared with muscle, which is responsible for the slower penetration of ketamine from the caudal injection site into blood. Because the analgesic effect is also prolonged after caudal injection, this effect probably is related to the drug concentration in the epidural tissue and not to that of the plasma. This relation suggests a local analgesic effect of *S*(+)-ketamine in the epidural space.

Laboratory investigations have shown different target sites for the ketamine molecule, which can explain a spinal effect of the drug. Ketamine is an antagonist at NMDA receptors, with a stereoselectivity in favor of *S*(+)-ketamine.[11] NMDA receptor concentrations are high in the spinal cord and play an important role in the nociceptive processing.[26] Ketamine decreases the activation of dorsal horn neurons by inhibiting the ionotropic (ion-mediated channel) glutamate receptor opening and thus exhibits analgesic properties.[27] Furthermore, an agonist effect of ketamine at μ-opioid receptors[12] and the interaction with voltage-sensitive sodium channels[27] have been discussed as a possible target for the drug. The binding site of ketamine with μ- and χ-opioid receptors appears to be stereoselective for the *S*(+)-enantiomer.[28]

This is the first clinical study in pediatric patients that compares the analgesic effectiveness and measuring plasma concentrations after caudal and intramuscular administration of *S*(+)-ketamine. Based on our findings, postoperative analgesia is more effective after caudal *S*(+)-ketamine administration than after intramuscular injection. Because of the decreased potential for severe complications after caudal injection, *S*(+)-ketamine may be an alternative in pediatric caudal blockade.

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