Comparing caudal and intravenous ketamine for supplementation of analgesia after Salter innominate osteotomy

Hamid Reza Amiri · Ramin Espandar ·
Mehdi Sanatkar

Received: 12 March 2012 / Accepted: 2 November 2012 / Published online: 16 November 2012
© EPOS 2012

Abstract

Purpose Previous studies claim that caudal administration of ketamine causes effective analgesia. The aim of this study was to assess the clinical effectiveness of ketamine after caudal or intravascular administration in pediatric patients that underwent orthopedic surgery to distinguish between local and systemic analgesia.

Methods After the induction of general anesthesia, 36 patients, aged 18 months to 10 years, assigned to undergo orthopedic surgery, received a caudal injection of bupivacaine and were randomly blinded into two groups: one group received 1 mg/kg S(+)-ketamine as the caudal group and the other group received 1 mg/kg S(+)-ketamine as the intravascular group. Postsurgical measurements included the effectiveness of postsurgical analgesia, which was assessed by using the observational pain scale (OPS), duration of analgesia, sedation score, and hemodynamic and respiratory monitoring.

Results The mean time to first analgesia was clearly longer in the caudal ketamine group (13.35 h) than in the intravenous ketamine (9.93 h) group ($P < 0.01$). During the 24-h observation time, fewer children asked for additional analgesic drugs in the caudal group (8 of 18, 44.4 %)

than in the intravenous group (12 of 18, 66.6 %; $P = 0.01$). The times to first micturation and spontaneous leg movements and the incidence of nausea and vomiting were similar in the two groups. The OPS and sedation scores after operation showed no obvious differences between the groups at any time.

Conclusion Although caudal ketamine provides good postsurgical analgesia due to its potential neurotoxicity and only small clinical differences with intravenous ketamine, the administration of intravenous ketamine might be a reasonable option to potentially extend the postsurgical analgesic effect of the caudal administration of local anesthetics in children undergoing Salter osteotomy.

Keywords Salter innominate osteotomy · Caudal analgesia · Ketamine · Pediatrics

Introduction

Caudal analgesia is widely used in pediatric operations where the surgical site is subumbilical [1]. The most significant disadvantage of local anesthesia is its short duration due to single administration. To overcome this limitation, certain drugs are suggested in combination with the local anesthetic agent [2–4]. Caudal ketamine has been shown to prolong the duration of postsurgical analgesia in children [5]. The analgesic effect and effectiveness of caudal epidural ketamine is probably due to its interaction with the glutamate *N*-methyl-D-aspartate (NMDA) receptors or opioid receptors [6] on the spinal cord. However, we cannot rule out the supraspinal effect of ketamine from systemic resorption. Subanesthetic intravenous doses of ketamine were used as an adjunct to systemic opioid analgesia without side effects [7, 8]. The aim of this study

H. R. Amiri
Department of Anesthesiology, Imam University Hospital,
Tehran University of Medical Sciences, Tehran, Iran

R. Espandar (✉)
Department of Orthopedic Surgery, Imam University Hospital,
Tehran University of Medical Sciences, Keshavarz Blvd.,
1419733141 Tehran, Iran
e-mail: espandar@gmail.com

M. Sanatkar
Autoimmune Bullous Disease Research Center, Razi Hospital,
Tehran University of Medical Sciences, Tehran, Iran

was to compare the postoperative analgesic efficacy of low-dose *S*(+)-ketamine administered either caudally or intravenously to supplement caudally administered plain bupivacaine in children undergoing Salter innominate osteotomy.

Methods

This was a randomized and double-blinded study. Our study was approved by the ethical committee in our center. This study was powered on the basis of a pilot study of 10 patients. A sample size of 18 patients in each group was calculated with $\alpha = 0.05$, $\beta = 0.2$, $\sigma_1 = 3.2$, $\sigma_2 = 3.2$, $\mu_1 = 13$, and $\mu_2 = 10$. Our patients were aged from 18 months to 10 years, with American Society of Anesthesiologists (ASA) physical status I–II from July 2009 to July 2011 in our center. Any child who had no contraindications to caudal block was enrolled in the study. Patients younger than 18 months and older than 12 years, patients with known allergy to the drugs planned to be used, and the patients who have contraindication to regional blockade (coagulopathy, infection, sepsis, and anticoagulant intake) or patients who received any additional analgesic medications during anesthesia were excluded from the study. We used caudal block (with bupivacaine) for postoperation pain control in all of these 36 patients scheduled for Salter innominate osteotomy. By using the “blocking method”, the patients were randomized into two groups. The caudal ketamine group patients received a combination of 0.1 mg/kg bupivacaine from 0.5 % solution and 0.5 mg/kg *S*(+)-ketamine (preservative-free; Daiichi Sankyo Propharma, Kanagawa, Japan) caudally. The intravenous ketamine group received the same dose of bupivacaine (0.1 mg/kg from bupivacaine 0.5 % solution) for caudal block and 0.05 mg/kg *S*(+)-ketamine (preservative-free; Daiichi Sankyo Propharma, Kanagawa, Japan) administered intravenously. The bupivacaine was diluted for the administration of a sufficient dose of the drug to the patients. The drugs that were used were prepared by an anesthetist not involved in any other session of the study. The anesthetist prepared either “bupivacaine and ketamine” or “bupivacaine alone” for caudal and “ketamine” or “saline” (as placebo) for intravenous administration to the patients. Premedication included 0.5 mg/kg midazolam rectally in all patients. General anesthesia was induced with sevoflurane and an intravenous catheter was then inserted. Adequate muscle relaxation was established with 0.1 mg/kg cisatracurium and endotracheal intubation was performed. Under sterile conditions, caudal anesthesia was performed with a 22-gauge Quincke needle. Anesthesia was maintained with 1–1.2 % isoflurane in 50 % O₂ and

50 % N₂O mixture. Cardio-acceleration changes following surgical stimulation [increasing heart rate (HR) and blood pressure (BP) more than 15 % in response to noxious surgical stimulation] were interpreted as insufficient analgesia and appropriate doses of opioids were administered [9, 10]. Noninvasive mean arterial pressure, HR, and oxygen saturation were registered during the operation and in the recovery room. An intraoperative decrease in BP or HR of more than 30 % from preoperative values was defined as hypotension or bradycardia, respectively, and treated with rapid infusion of fluids or with atropine 0.01 mg/kg when needed. Following the awakening, the patients were taken to the recovery room. The effectiveness of postsurgical analgesia was assessed using a modified observational pain scale (OPS) (Table 1) [11], and values equal ≥ 4 were defined as an indication of analgesic requirement. All patients received a standard rescue dose of acetaminophen and ibuprofen if the OPS was ≥ 4 . The time of first analgesic administration (duration of analgesia) and total analgesic dose during the first 24 h were recorded. The evaluation of sedation levels (sedation score) were assessed using the Wilson sedation scale (Table 2) [12]. Demographic data were compared using the Student's *t*-test. Distribution frequencies were analyzed by using the χ^2 test. The OPS and patient sedation scores were evaluated using the Mann–Whitney test. *P*-values <0.05 were assumed to be statistically significant.

Results

The demographic data of the two groups are compared in Table 3. None of the patients received additional intraoperative analgesic drugs. The mean duration of analgesic effect of the technique used, as indicated by the time to the administration of first analgesia, was longer in the caudal group (13.35 h) than in the intravenous group (9.93 h, $P < 0.01$). During the 24-h observation time, fewer children asked for additional analgesic drugs in the caudal group (8 of 18, 44.4 %) than in the intravenous one (12 of 18, 66.6 %; $P = 0.01$). The times to first micturation and spontaneous leg movements and the incidence of nausea and vomiting were similar in the two groups. Adverse psychological effects were not seen in either group. The hemodynamic parameters did not indicate any significant differences over time or between the groups. Respiratory depression was not seen in both groups (Table 4). The results of the OPS assessment of postsurgical anesthesia is shown in Fig. 1. There were no obvious and statistically significant differences between the groups at any time. Also, there was no difference between the groups in the sedation scores.

Table 1 The modified observational pain/discomfort scale (OPS)

Score	0	1	2
Crying	No crying	Crying/ moaning	Screaming
Facial expression	Smiling/ positive	Neutral	Grimace
Verbal expression	Positive statement	Negative statement	Suffering from pain, another complaint
Torso	Neutral	Variable, taut, upright	Stretched
Legs	Neutral	Kicking	Stretched, continuous movement

Table 2 Wilson sedation scale

Score	Degree of sedation
1	Fully awake and oriented
2	Drowsy
3	Eyes closed but rousable to command
4	Eyes closed but rousable to mild physical stimulation (earlobe tug)
5	Eyes closed but unrousable to mild physical stimulation

Table 3 Patient characteristics in each group

Group	Caudal group	IV group	<i>P</i> -value
Number	18	18	–
Age (years)	3.25	3.2	0.92
Gender (male/female)	1.25	1	0.66
Weight (kg)	12.2 ± 6.1	12 ± 4.8	0.74
Height (cm)	88 ± 10.8	86 ± 13.6	0.80
ASA class	1.4	1.42	0.44
Duration of surgery (min)	48.2 ± 12.2	45.4 ± 14.4	0.22

Discussion

Caudal analgesia along with general anesthesia is a very popular regional technique for prolonged postoperative analgesia in different pediatric surgical procedures. Koinig et al. [13] showed that only 52 % of patients who underwent caudal block with ropivacaine maintained a sufficient level of analgesia for the first 24 h after operation. An attempt to overcome these problems was performed by combining local anesthetic agents with other drugs such as ketamine, opioids, and clonidine [14–16]. Ketamine added to bupivacaine in caudal analgesia as an adjuvant agent was shown to increase analgesia duration. Semple et al. [17] found that different doses of ketamine (0.25, 0.5, and 1 mg/kg) added to caudally applied bupivacaine (0.25 %) presented with analgesia durations of 7.9, 11, and 16.5 h, respectively.

Table 4 The intraoperative and postoperative characteristics of both groups

Group	Caudal group	IV group	<i>P</i> -value
Average mean arterial blood pressure (mmHg)	68 ± 12	69 ± 18	0.44
Mean heart rate	95 ± 28	97 ± 24	0.62
Mean duration of analgesic effect (h)	13.35 ± 1.2	9.93 ± 1.6	<0.01
Asked for additional analgesic drugs	8 (44.4 %)	12 (66.6 %)	0.01
Time to first micturation (h)	3.4 (2.8–5.5)	3.2 (2.5–5)	0.84
Time to spontaneous leg movement (h)	2.1 (0.5–4)	2 (0.6–4.5)	0.60
Nausea and vomiting	1	2	0.44
Adverse psychological effects	0	0	–
Respiratory depression	0	0	–

Fig. 1 The mean observational pain scale (OPS) score in each group of patients after surgery over time. The differences were not statistically significant

Previous studies showed that the postoperative analgesia duration of caudal ropivacaine (1 mg/kg 0.2 %) plus ketamine (0.25 mg/kg) was 12 h [3]. De Negri et al. found an analgesia duration of 291 min with 2 mg/kg 0.2 % ropivacaine, which was increased to 701 min with 0.2 % ropivacaine combined with 0.5 mg/kg *S*-ketamine [18]. The results of the present study indicate that *S*(+)-ketamine, when administered caudally, would prolong the duration of postsurgical analgesia and decrease the necessity for subsequent postsurgical analgesia more than intravenous *S*(+)-ketamine in children undergoing orthopedic operation. Ketamine may interact with antinociceptive spinal receptors. This effect might possibly be related to the drug concentration in the epidural tissue and not to that of the plasma. Ketamine, a derivative of phencyclidine, is an antagonist at NMDA receptors, which are found throughout the central nervous system, including the spinal cord, with a stereoselectivity regarding *S*(+)-ketamine [19]. Ketamine

also binds at μ opioid receptors and is apparently shown to be stereoselective for the *S*(+)-enantiomer [20]. In our study, the hemodynamic variables were similar between the two groups. None of the patients in either group demonstrated hypotension or bradycardia. Ödeş et al. [21] also showed no hemodynamic changes after caudal 2 mg/kg 0.2 % ropivacaine plus 0.5 mg/kg ketamine. In our study, we did not encounter any respiratory depression. De Negri et al. reported no respiratory changes or depression after caudal 0.02 % ropivacaine and 0.2 % ropivacaine and *S*-ketamine mixture [18]. Previous studies have shown that caudal ketamine reduced the incidence of motor block when added to the procedure after reducing the dosage of local anesthetic agent, but in our study, motor block scores revealed no significant differences in both groups. Similar to our results, none of the previous studies reported more sedation in patients who underwent caudal block with local anesthetic and ketamine compared to caudal block with only local anesthetic [21, 22].

The neurotoxic effects of ketamine after intrathecal administration were observed in animal studies [23] and after continuous intrathecal administration for the management of neuropathic cancer pain [24]. Consequently, its administration in the epidural space has been seriously questioned recently [25].

The major limitation of our study was the lack of comparison with a control group without ketamine.

In conclusions, although fewer patients in the caudal ketamine group asked for additional analgesic drugs ($P = 0.01$) and more patients were pain free for a longer time postoperatively ($P < 0.01$), it did not result in any significant differences in OPS scores, sedation scores, hemodynamic change, respiratory depression, time to first micturation, and motor block scores in comparison to intravenous ketamine. In other words, according to the results, the use of caudal ketamine only resulted in a small clinical difference with intravenous ketamine. Due to the potential neurotoxic effects of the epidural administration of ketamine, the administration of intravenous ketamine might be a suitable alternative aiming to achieve a long-lasting analgesic effect after the caudal administration of bupivacaine.

Conflict of interest None.

References

- Melman E, Penuelas JA, Marrufo J (1975) Regional anesthesia in children. *Anesth Analg* 54(3):387–390
- Naguib M, Sharif AM, Seraj M, el Gammal M, Dawlatly AA (1991) Ketamine for caudal analgesia in children: comparison with caudal bupivacaine. *Br J Anaesth* 67(5):559–564
- Lee HM, Sanders GM (2000) Caudal ropivacaine and ketamine for postoperative analgesia in children. *Anaesthesia* 55(8):806–810
- Köknal Talu G, Ozyalçın NS, Balsak R, Karadeniz M (2008) The efficacy of preemptive ketamine and ropivacaine in pediatric patients: a placebo controlled, double-blind. *Agri* 20(2):31–36
- Klimscha W, Horváth G, Szikszay M, Dobos I, Benedek G (1998) Antinociceptive effect of the *S*(+)-enantiomer of ketamine on carrageenan hyperalgesia after intrathecal administration in rats. *Anesth Analg* 86(3):561–565
- Smith DJ, Bouchal RL, deSanctis CA, Monroe PJ, Amedro JB, Perrotti JM, Crisp T (1987) Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. *Neuropharmacology* 26(9):1253–1260
- Jahangir SM, Islam F, Aziz L (1993) Ketamine infusion for postoperative analgesia in asthmatics: a comparison with intermittent meperidine. *Anesth Analg* 76(1):45–49
- Dix P, Martindale S, Stoddart PA (2003) Double-blind randomized placebo-controlled trial of the effect of ketamine on postoperative morphine consumption in children following appendectomy. *Paediatr Anaesth* 13(5):422–426
- American Academy of Pediatrics; American Academy of Pediatric Dentistry, Coté CJ, Wilson S; Work Group on Sedation (2008) Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. *Paediatr Anaesth* 18(1):9–10
- van Dijk M, de Boer JB, Koot HM, Duivenvoorden HJ, Passchier J, Bouwmeester N, Tibboel D (2001) The association between physiological and behavioral pain measures in 0- to 3-year-old infants after major surgery. *J Pain Symptom Manage* 22(1):600–609
- McGrath PJ, Johnson G, Goodman JT, Schillinger J, Dunn J, Chapman JA (1985) CHEOPS: a behavioral scale for rating postoperative pain in children. In: Fields HL, Dubner R, Cervero F (eds) *Advances in pain research and therapy*, vol 9. Raven Press, New York, pp 395–402
- Wilson E, David A, MacKenzie N, Grant IS (1990) Sedation during spinal anaesthesia: comparison of propofol and midazolam. *Br J Anaesth* 64(1):48–52
- Koinig H, Krenn CG, Glaser C, Marhofer P, Wildling E, Brunner M, Wallner T, Grabner C, Klimscha W, Semsroth M (1999) The dose-response of caudal ropivacaine in children. *Anesthesiology* 90(5):1339–1344
- Turan A, Memiş D, Başaran UN, Karamanlioğlu B, Süt N (2003) Caudal ropivacaine and neostigmine in pediatric surgery. *Anesthesiology* 98(3):719–722
- Prosser DP, Davis A, Booker PD, Murray A (1997) Caudal tramadol for postoperative analgesia in pediatric hypospadias surgery. *Br J Anaesth* 79(3):293–296
- Cook B, Grubb DJ, Aldridge LA, Doyle E (1995) Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. *Br J Anaesth* 75(6):698–701
- Semple D, Findlow D, Aldridge LM, Doyle E (1996) The optimal dose of ketamine for caudal epidural blockade in children. *Anaesthesia* 51(12):1170–1172
- De Negri P, Ivani G, Visconti C, De Vivo P (2001) How to prolong postoperative analgesia after caudal anaesthesia with ropivacaine in children: *S*-ketamine versus clonidine. *Paediatr Anaesth* 11(6):679–683
- Zeilhofer HU, Swandulla D, Geisslinger G, Brune K (1992) Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. *Eur J Pharmacol* 213(1):155–158
- Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG (1999) Stereoselective interaction of ketamine with recombinant μ , κ , and δ opioid receptors expressed in Chinese hamster ovary cells. *Anesthesiology* 90(1):174–182

21. Ödeş R, Erhan ÖL, Demirci M, Göksu H (2010) Effects of ketamine added to ropivacaine in pediatric caudal block. *Agri* 22(2):53–60
22. Johnston P, Findlow D, Aldridge LM, Doyle E (1999) The effect of ketamine on 0.25% and 0.125% bupivacaine for caudal epidural blockade in children. *Paediatr Anaesth* 9(1):31–34
23. Vranken JH, Troost D, de Haan P, Pennings FA, van der Vegt MH, Dijkgraaf MG, Hollmann MW (2006) Severe toxic damage to the rabbit spinal cord after intrathecal administration of preservative-free S(+)-ketamine. *Anesthesiology* 105(4):813–818
24. Vranken JH, Troost D, Wegener JT, Kruis MR, van der Vegt MH (2005) Neuropathological findings after continuous intrathecal administration of S(+)-ketamine for the management of neuropathic cancer pain. *Pain* 117(1–2):231–235
25. Jöhr M, Berger TM (2012) Caudal blocks. *Paediatr Anaesth* 22(1):44–50