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Comparing the effects of three different doses of caudal ketamine plus bupivacaine on pain control after paediatric surgery

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Abstract

Introduction: Adding ketamine to bupivacaine in caudal anaesthesia is likely to increase its analgesic effect. However, it is not clear which dose of ketamine will have the greatest impact and the lowest level of complications. Thus, the purpose of this study was to compare the effects of three different doses of caudal ketamine plus bupivacaine on pain control after pediatric surgery. **Methodology**: The present double-blinded clinical trial was conducted on 69 pediatric patients, of age ranging from 6 months to 10 years. Patients were assessed via the American Society of Anaesthesiologists (ASA) physical status classification system (ASA I-II), and had been also hospitalized for herniorrhaphy and orchidopexy. The patients were randomly divided into three groups. The first group received 0.75 mg/kg of 0.25% bupivacaine plus 0.25 mg/kg of ketamine, the second group received 0.75 mg/kg of 0.25% bupivacaine and 0.5 mg/kg of ketamine, and the third group received 0.75 mg/kg of 0.25% bupivacaine with 0.75 mg/kg of ketamine (as caudal anaesthesia). The duration of motor block and analgesia, as well as sedation levels, were measured for each study group. Each patient's level of pain was also measured (at 1, 2, 3, 4, 6 and 24 hours after the surgery) via the All India Institute of Medical Sciences (AIIMS) pain discomfort scale. The data were then compared using SPSS Statistics (Version 22), with descriptive statistics, analysis of variance (ANOVA), and Chi-square test. **Results**: The findings revealed that gender distribution did not differ significantly in the three study groups (p=0.896). The mean age of the first, second, and third group were reported to be 2.82±1.86, 3.1±2.4, and 2.48±1.06, respectively; thus, there was no significant difference in terms of age between the three groups (p=0.569). Upon examining the AIIMS pain discomfort scale scores during the first 24 hours following surgery, it was observed that the pain intensity was higher in the first group than in the second and third groups. Moreover, evaluation of the pain intensity in the first and the second groups revealed comparable results, while those of the second and the third groups did not show a significant difference in this respect. **Conclusion**: The results demonstrated that the most effective and safest dose of ketamine, in this study, for pain control after pediatric surgery in the inguinal region was the 0.5 mg/kg dose.

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1. Background

One of the factors which contribute to patient suffering after surgery is the post-operative pain, which can also affect the cardiovascular and respiratory metabolic functions of patients, and which can sometimes determine the outcome of the surgery [1]. It should be noted that infants and children are prone to experience more pain than adults since they are not able to express pain the way adults can [2]. Post-operative pain may also be associated with sleep disorders and sleep-wake cycles, and increased pain perception. In this respect, it may consequently disturb nutrition as well as the neuroendocrine system and slow down the patient's recovery [3].

There are several ways to control post-operative pain in infants and children. One of the most common ways of controlling pain in pediatric patients undergoing surgery in the lower abdomen is to use the cadaveric catheter. In this domain, the benefits of caudal anaesthesia can be faster movements, prevention of pulmonary infections, and reduction of the need for narcotic drugs, which can all lead to analgesia without sedation and rapid recovery after surgery. The most important problem of caudal anaesthesia for surgery is its short-acting duration, even if long-acting anaesthetic medications can be also administered [4]. A common method for the induction of anaesthesia during surgery and the control of post-operative pain is the *caudal epidural block* (CEB) with bupivacaine. However, infusion of a single dose of bupivacaine can result in anaesthesia for only 2-4 hours, while most pediatric patients need to have a longer-lasting anaesthesia for the control of their post-operative pain [4,5].

A new approach to anaesthesia, particularly regional anaesthesia, is the use of drugs in such a way that they can have minimal impact on chemical functions and responses of the body [6]. The administration of some sedatives prior to surgery can similarly reduce post-operative pain through neuronal desensitization [7,8]. One of these drugs that can do so for a long time is the one attached to the N-methyl D-Aspartate (NMDA) receptor [9,10]. Indeed, the use of a NMDA antagonist, such as ketamine, can have its own analgesic and neural desensitization effects [11,12] , which have been observed in adults when administered intravenously.

However, there is no agreement about pain management, in the case of infants and children, whether it be for control of tonsillectomy pain or in epidural use [13]. A study by Clerc *et al*., in this area of research, showed that the addition of ketamine and ketorolac in patients undergoing inguinal hernia repair surgery could increase the analgesic effect of bupivacaine [14]. A comparative study conducted by Weber *et al*. also reported lower levels of pain following inguinal surgery on pediatric patients, in those who had received 5.0 mg/kg of ketamine added to bupivacaine, than those who received bupivacaine alone [15].

It is important to consider post-operative pain control in infants and children. Most of the previous studies conducted in this domain had simply dealt with the effect of ketamine on the increased duration of analgesia. Thus far, no research had been carried out to find the optimal dose of ketamine with the highest duration of analgesia and the lowest level of pain. Given the above, the present study was conducted to compare the effects of three different dosages of caudal ketamine with bupivacaine on pain control after pediatric surgery.

2. Methods

This double-blinded clinical trial was performed on children hospitalized for selective *herniorrhaphy* and*orchidopexy* after approval by the Vice-Chancellor's Office for Research and Technology at Zahedan University of Medical Sciences (Iran). Permission was obtained from the Ethics Committee of the university, as well as informed consent from the patients' legal guardians. The sample size was chosen to be 69 paediatric patients, based on previous studies as well as the formula for calculation of the sample size. The patients were divided into three groups (of 23 individuals each) after enrolment in the study [15,16]. The inclusion criteria included: having an age between 6 months and 10 years, meeting the American Society of Anaesthesiologists (ASA) physical status classification system class I and II (ASA I-II), being candidates for selective

herniorrhaphy and orchidopexy, and having no active central nervous system disorders nor infection in the place of caudal catheters, coagulation disorders (e.g. hemophilia, intravascular coagulation, idiopathic thrombocytopenia, or dysfunction of coagulation tests), nor abnormalities of the sacrum. The exclusion criteria included: dissatisfaction of the patients' companions with the continuation of the study, absence of anaesthesia following the administration of the drug, and/or the need for general anaesthesia.

The patients were randomly divided into three groups after meeting the inclusion criteria. For all the patients, a peripheral venous catheter (PVC) No. 22 was fixed at the back of the arm, and then the infusion of 10 cc/kg of normal saline serum was administered. Non-invasive monitoring of the heart rhythm, oxygen saturation of arterial blood, and blood pressure were done using a monitoring device (made by SAADAT Co., Iran). Subsequently, anaesthesia was administered using 5 mg/kg of thiopental sodium, halothane, and nitrous oxide (N_2O); these were given without the use of opiate analgesics. To maintain the anaesthesia, 1% halothane gas was used. After induction of the anaesthesia, the patients were placed in the lateral position and a caudal catheter with a 23-gauge needle was then placed in the patient using sterile conditions. After confirmation of the placement of the catheter in the epidural space, the first group of patients received 0.75 mg/kg of 0.25% bupivacaine plus 0.25 mg/kg of ketamine, the second group received 0.75 mg/kg of 0.25% bupivacaine plus 0.5 mg/kg ketamine, and the third group received 0.75 mg/kg of 0.25% bupivacaine plus 0.75 mg/kg of ketamine (as caudal anaesthesia).

It should be noted that the ketamine used had been made by ROTEXMEDICA Pharmaceutical Company (Germany) and the bupivacaine had been manufactured by the Swedish ASTRAZENECA Pharmaceutical Company. The drugs used were prepared by the researchers and were injected by an anaesthesiologist who was unaware about the patients in the groups. Moreover, the patients' repair surgery was performed by the same surgical team.

To assess the pain relief impact on patients undergoing surgery, the monitoring process continued while the surgery was being performed, and the increase in the patients' heart rate and their systolic pressure more than 15% of the base level was considered as having pain. The All India Institute of Medical Sciences (AIIMS) pain discomfort scale was also used at the end of the surgery, following the patients' wakening, to assess their analgesia. The given scale contained 5 criteria, including..... (RR), ... (HR), and positioning status- crying and pain in the surgical site. Each of these criteria was given a score between 0 and 2, and each patient could obtain a total score between 0 and 10, in which a score lower than 4 could indicate lack of pain. This scale had already been used in numerous articles and its efficiency, validity, and reliability had been also confirmed [4,17]. The pain score of each patient was also measured at 1, 2, 4, 6, and 24 hours after surgery at each stage; if the score $\geq$4, the patients were given 1 mg/kg of pethidine.

The duration of the caudal anaesthesia, until the first dose of pethidine, was recorded as the duration of analgesia. The duration of the motion block, which was the start of the caudal anaesthesia, was also recorded for the patients until they could move their feet. Moreover, the sedation rate was calculated based on the score of 0 (if the eyes had been opened spontaneously), 1 (if the eyes had been opened with sound), and 2 (if the eyes had been opened with painful stimulation), at 1 and 4 hours following surgery for each patient. The post-operative complications (including cognitive impairment, agitation, urinary retention, and opioid rate used by each patient) were also recorded within the first 24 hours after surgery. It should be noted that all data needed by trained nurses (who did not know about the patients in the study groups) were also collected. Subsequently, the data were analysed using the SPSS Statistics (Version 22), using descriptive statistics and analysis of variance (ANOVA) to compare the quantitative variables, and Chi-square test to compare the qualitative ones.

3. Results

Of the 69 children in this study, 45 individuals (65.2%) were male and 24 of them (34.8%) were female. Examining the gender distribution, using the results of the Chi-square test, also showed no significant difference between the three groups (p=0.896). The mean age of the pediatric

patients participating in the study was 3.42±2.06 years. The mean age of the first, second, and third groups of patients were also reported to be 2.82±1.86, 3.1±2.4, and 2.48±1.16, respectively; thus, there was no significant difference observed with respect to age among the three study groups (p=0.569).

The mean duration of immobility after anaesthesia in the first, second, and third groups of patients were 42.17±18.07, 43.04±16.63, and 43.52±15.54 minutes, respectively. Thus, there was no significant difference observed between the first group and the second group (p=0.983), or between the first and the third group (p=0.960). There was also no significant difference between the second and third group, in terms of the duration of immobility (p=0.995).

The mean duration of the post-operative analgesia was equivalent to 211±52 minutes in the first group, 267±2.58 minutes in the second group, and 271±4.84 minutes in the third group. Comparing the three study groups in terms of the mean duration of analgesia, using the results of the ANOVA, also demonstrated that the duration of analgesia in the second group (p=0.002) and the third group (p=0.001) were significantly different from the first group; however, no significant difference was reported between the second and third groups in this respect (p=0.996).

The comparison of the three study groups in terms of their scores from the AIIMS showed that pain intensity in the first group was higher than those in the second and the third groups at all stages. Moreover, comparing the mean scores using the results of the repeated measures ANOVA indicated a significant difference between the first and second groups in terms of pain intensity at most stages; a similar result was reported between the first and third groups in this regard. Nevertheless, no significant difference was shown between the second and the third groups except for the second time of measurement (**Table 1**).

The mean amount of opioid used during the first 24 hours was equivalent to 1.82±0.93 mg/kg in the first group, 1.13±0.34 mg/kg in the second group, and 1.04±0.20 mg/kg in the third group. These indicated a significantly low use by the second and third groups (p=0.001) than the first group, but there was no significant difference between the second and the third groups in terms of opioid use (p=0.871). Examining the sedation score at the first hour after surgery showed that in the first group, 7 patients had scored 0, 8 patients had scored 1, and 8 patients had scored 2. In the second group, 4 patients had scored zero, 11 patients had scored 1, and 8 patients had scored 2. Lastly, in the third group, 1 patient had scored zero, 6 patients had scored 1, and 16 patients had scored 2. Thus, there was a significant difference between the first and second groups in terms of the sedation score (p=0.003). Besides, there was a statistically significant difference between the first and third groups, and between the second and third groups (p=0.04).

The examination at 4 hours after surgery, in group 1, showed that 16 patients had scored zero and 7 patients had scored 1. In the second group, 17 patients had scored zero and 6 patients had scored 1. In the third group, 18 and 5 patients had scored 0 and 5, respectively. Thus, no significant difference was observed among the three groups in terms of the sedation score; (p=0.798), (p=0.878), and (p=0.658), respectively. According to the results, no complications resulting from ketamine injection were observed in the first group, but 2 patients in the second group (8.9%) suffered from cognitive impairment and restlessness, and 4 patients in the third group (17.8%) suffered from cognitive impairment and restlessness.

4. Discussion

The results of the present study showed that the addition of ketamine to caudal anaesthesia with bupivacaine could be effective in controlling post-operative pain in pediatric patients and consequently reduce the need for opioids to control pain after surgery. Although the given effect was dose-dependent, the best dosage of ketamine was equivalent to 0.5 mg/kg, and the use of higher doses was reported to cause problems and complications. Previously, Ozbek *et al.* divided children admitted for the treatment of hypospadias into three groups, and administered alfentanil to the first group, ketamine to the second group, and a combination of the two drugs to the third group [18]. They then evaluated the duration of analgesia and pain intensity after the surgery. In their study, they reported that the use of 0.5 mg/kg of ketamine, with or without alfentanil, could

Table 1. Comparison of the mean scores of AIIMS in the three study groups

Groups	Comparison of the mean score of pain, 1 hour after the surgery	P	Comparison of the mean score of pain, 2 hours after the surgery	P	Comparison of the mean score of pain, 3 hours after the surgery	P	Comparison of the mean score of pain, 4 hours after the surgery	P	Comparison of the mean score of pain, 6 hours after the surgery	P	Comparison of the mean score of pain, 24 hours after the surgery	P
First	1.47±0.6	0.01	1.82±0.8	0.02	3.04±0.96	0.00	3.37±1.06	0.221	3.21±0.88	0.361	2.65±0.87	0.002
Second	0.65±0.11		1.04±0.66		1.86±0.25		3.08±1.02		3.47±0.95		1.86±0.68	
First	1.47±0.6	0.000	1.82±0.8	0.000	3.04±0.96	0.001	3.37±1.06	0.001	3.21±0.88	0.001	2.65±0.87	0.00
Third	0.52±0.02		0.86±0.2		1.69±0.31		2.47±1.26		2.17±1		1.82±0.63	
Second	0.65±0.11	0.655	1.04±0.66	0.00	1.86±0.25	0.623	3.08±1.02	0.131	3.47±0.95	0.897	1.86±0.68	0.586
Third	0.52±0.02		0.86±0.2		1.69±0.31		2.47±1.26		2.17±1		1.82±0.63	

moderate post-operative pain without causing respiratory complications, thereby confirming that 0.5 mg/kg of ketamine was the best and safest dose. However, there was a strong difference between their study and ours in terms of the duration of analgesia; specifically, theirs had a longer duration than what was reported in our present study. The observed differences cannot be interpreted as superiority of results since they had used narcotics for caudal anaesthesia; the objective of using ketamine was to reduce the use of opioids so as to prevent the occurrence of respiratory complications [18].

Contrary to the results of our present study, Khan *et al*. compared the effects of the use of a *bupivacaine-tramadol combination* and ketamine-bupivacaine combination, and reported that the first compound had a much better effect than the second compound, in terms of controlling post-operative pain after inguinoscrotal surgery and having fewer side effects. These results were reported in conditions using a far greater dose of ketamine (1 mg/kg), compared with the dose administered in our present study [19]. According to this investigation, it was reported that use of a α2-agonist, such as *dexmedetomidine,* at a dose of 1 μg/kg in order to increase the effect of caudal anaesthesia with bupivacaine and have fewer side effects [20]. These results were confirmed by another study in which pediatric patients had been divided into two groups, one receiving 1 cc/kg of 0.25% bupivacaine with 1 cc of NS, and the other group receiving 1 cc of NS added with 1 mg/kg of dexmedetomidine. That study showed that the use of dexmedetomidine can significantly reduce the duration of analgesia and anaesthesia without any side effects [3].

Although the type of drug used in these two studies was different from that used in the present study, it was confirmed that the use of drugs with an analgesic effect with different mechanisms than bupivacaine can be safe in terms of side effects and can lower the duration of analgesia in children, create a more satisfactory experience for patients. Another study was also carried out on pediatric patients admitted for inguinal herniorrhaphy. After general anaesthesia and 5 minutes prior to the onset of surgery, bupivacaine infiltration was performed in one group, and ketamine and ketorolac were co-administered with bupivacaine to the other group in the study. It was reported that the addition of these drugs could increase the effect of bupivacaine [14]. Comparing the results of these two studies, it was concluded that these drugs could have better effects in caudal administration.

Furthermore, Fernandes *et al*. compared the addition of epinephrine by bupivacaine, morphine epinephrine, and clonidine epinephrine, as well as morphine clonidine and epinephrine with 0.166% bupivacaine, and the medicine alone. It was reported that only adding morphine-epinephrine composition to caudal anaesthesia was likely to reduce the rate of opioid use after surgery, but it could increase nausea and vomiting after surgery, while the addition of clonidine had no beneficial effects [21]. In another study, infants undergoing umbilical hernia surgery were divided into four groups; the first group received 0.75 ml/kg of 0.25% bupivacaine, the second group received 0.75 ml/kg of 0.25% bupivacaine plus 1 μg/kg of clonidine, the third group received 0.75 ml/kg of 0.25% bupivacaine with 0.5 mg/kg of ketamine, and the fourth group received 0.75 ml/kg of 0.25% bupivacaine and 1 μg/kg of fentanyl (as caudal anaesthesia). Comparing the groups, the researchers found that the best analgesic effects had been observed in the second group, which were not consistent with the results of the study conducted by Fernandes *et al*. Moreover, comparing the results of those investigations with the findings of our present study, it can be concluded that the dose of ketamine used in that study was equivalent to the one used in the present study, although the drugs and procedures employed in both studies were completely different. Moreover, the purpose of the present study was to obtain the effective dose of ketamine rather than comparing the effects of drugs with other ones [22].

5. Conclusions

Adding ketamine to caudal anaesthesia proved effective in controlling post-operative pain and reducing the use of opioids for pain control. Moreover, the most effective and the safest dose of ketamine for controlling pain after surgery on inguinal region in children was reported to be 0.5 mg/kg dose (plus 0.75 mg/kg of 0.25% bupivacaine).

6. Open Access

7. Competing interests

No conflict of interest was declared by the authors in this study.

8. Authors' contributions

Aliakbar Keykha: Compilation of the paper and Editing and revising this paper carefully; Reza davoodi: participation in implementation of research and data collection; Masoum Khoshfetrat: participation in implementation of research and supervision over data collection and revising this paper.

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