Addition of dexmedetomidine, tramadol and neostigmine to lidocaine 1.5% increasing the duration of postoperative analgesia in the lower abdominal pain surgery among children: a double-blinded randomized clinical study

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Abstract

Pain is a common complication after surgery. Insufficient control of postoperative pain has adverse effects on the physiological, metabolic and psychological state of the child. The use of local analgesics and anesthetics alone cannot produce complete anesthesia and intraoperative comfort. The addition of adjuvant drugs is commonly used to improve the quality of the block. Therefore, adding new supplements may increase the duration of analgesia. The aim of this study was to compare the addition of dexmedetomidine, tramadol and neostigmine to lidocaine 1.5% in increasing the duration of postoperative analgesia in the lower abdominal pain surgery in children aged 2-8 years. This double-blind randomized clinical trial was conducted on children candidate for lower abdominal surgery. The 96 patients were randomly divided into 3 groups including dexmedetomidine, neostigmine, and tramadol. For all children, 3 mg of midazolam was administered orally before entering the operating room. The patients underwent general anesthesia with 2 µg/kg fentanyl, 0.03 mg/kg midazolam, 0.5 mg/kg atracurium and 5-6 mg/kg thiopental. After determining the hiatus membrane, 2 mL syringes containing air and distilled water (each of which 1 mL) slowly entered the space. After eliminating caudal resistance, 1.5% lidocaine was injected at dose of 0.5 mL/kg. A total of 96 patients were enrolled in this study. The results revealed that pain scores in the dexmedetomidine group in recovery, 2, 6 and 12 hours after surgery were less than the other two groups. Furthermore, the tramadol group showed a lower score in comparison with the neostigmine group and the duration of analgesia in the dexmedetomidine group was more than the other two groups. In addition, the mean of analgesic at 24 hours after operation in the dexmedetomidine group was lower as compared to the other two groups, indicating the effect of dexmedetomidine as an adjuvant in increasing the duration of analgesia and reducing postoperative pain in patients along with lidocaine 1.5%. All three drugs (neostigmine, tramadol and dexmedetomidine drugs), along with other local anesthetic, increased the duration of analgesia and decreased postoperative pain in children. The effect of dexmedetomidine was greater than the other two drugs. The study was approved by the Ethics Committee of Arak University of Medical Sciences, Iran (approved No. IR.ARAKMU.REC.1396.112) on October 28, 2017, and registered at Iranian Registry of Clinical Trials (registration No. IRCT20141209020258N83) on August 29, 2018.

Key words: dexmedetomidine; neostigmine; tramadol; lidocaine; postoperative analgesia; pain; children

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INTRODUCTION

Pain is a common postoperative complication, and its control and reduction after surgery are important goals of anesthetists.¹ Insufficient control of postoperative pain has undesirable effects on the physiological, metabolic and psychological state of the child.² Postoperative pain control results in satisfaction of patients and reduction of hospitalization time and treatment costs. Although control of pain during surgery is an essential goal, new methods of analgesia have attracted much attention to postoperative pain control. Perhaps the greatest advancement in pediatric anesthesia is the development of postoperative analgesia.^{3,4} The use of analgesic and analgesic drugs alone does not have the ability to produce complete and proper anesthesia during surgery.⁵ Therefore, the addition of adjuvant drugs is common in improving the quality of the block.⁶ Regional anesthesia is an essential part of the development of children's anesthesia. Accepting the techniques of this analgesia is increasing by parents.

Today, caudal anesthesia is the most useful and most commonly used regional block in children.⁷ The caudal anesthesia is becoming increasingly popular in the world, due to the lack of drug injection and the side effects of oral and injectable drugs. The effectiveness of this method in reducing postoperative pain compared with oral and injectable painkillers includes: reduction of recovery time, early discharging of the patient and lower length of stay in a hospital, early movement of the patient and reduction of constipation and early normalization of intestinal function. In addition, the incidence of restlessness can be reduced by effective analgesia after surgery.⁸ The caudal block is one of the most commonly used analgesic techniques in pediatric patients, which is roughly easy to accomplish. This procedure can be performed before and after surgery, with general anesthesia or immediately after surgery, or in some procedures of the lower abdominal and lower limbs as an alternative for anesthesia.¹ Easy access to sacrum and sacral hiatus facilitates the ability to perform caudal anesthetic technique. The equilateral triangular drawn between the apex of the sacral hiatus and the posterior and upper lip of the sacrum determines the location of the hiatus, and a triangle with two sacral corneas appears at the site of the hiatus, where the needle is inserted to inject the drug.

Despite the simplicity and high success rate of this method, it has some limitations due to the short duration, which can be resolved by adding adjuvant drugs to local anesthetics.⁹ These drugs include tramadol, neostigmine, and dexmedetomidine. Tramadol inhibits the neuronal uptake of serotonin and also strengthens the effects of local anesthetic drugs when combined with peripheral nerve blocks.¹⁰ Dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist and is defined to be over 8 times more specific for α 2 receptors as compared to clonidine. This reduces the unwanted side effects of alpha-1 receptor. Neostigmine is also used in spinal anesthesia, which may increase the analgesic intensity and length *via* spinal cord and releasing nicotine.^{11,12}

Therefore, the aim of this study was to compare the effects of neostigmine, dexmedetomidine and tramadol as adjuvant drugs along with lidocaine (1.5%) for increasing the duration of postoperative analgesia among children aged 2–8 years with lower abdominal surgery.

SUBJECTS AND METHODS Subjects

This double-blinded randomized clinical trial was performed on children aged 2–8 years. All children were candidates for lower abdominal surgery who referred to Valiasr Hospital and Amiralmomenin Hospital, Arak, Iran. The patients with inclusion criteria were randomly divided into 3 equal groups (dexmedetomidine, neostigmine, tramadol). The study was approved by the Ethics Committee of Arak University of Medical Sciences (approved No. IR.ARAKMU.REC.1396.112) on October 28, 2017, and registered at Iranian Registry of Clinical Trials (registration No. IRCT20141209020258N83) on August 29, 2018. The writing and editing of the article were performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) Statement.

Inclusion criteria

1) All children aged 2–8 years undergoing lower abdominal surgery; 2) Having informed written consent from the legal guardians; 3) Patients with American Society of Anesthesiologists Class I or II; 4) All patients without heart disease, pulmonary, liver disease; 5) Patients without seizure history; 6) Patients with a operation duration of 45–90 minutes; 7) Lack of allergy to local anesthetics, dexmedetomidine, tramadol and neostigmine.

Exclusion criteria

1) Patients whose duration of operation was more than 90 minutes; 2) Patients with caudal block failure.

Initially, all parents of children were informed by written consent. For all children, 3 mg of sublingual midazolam (Aboreyhan Co., Iran) was given for relaxation before going to the operating room. For them, IV (intravenous) was fixed through a peripheral venous catheter with a size 20. Then children received 2–3 mL colloidal crystal as CVE (compensatory volume expand). The normal rhythms of the heart, blood pressure and oxygen saturation were recorded in the questionnaire. The patients underwent general anesthesia with 2 µg/kg fentanyl (Caspian Co., Iran), 0.03 mg/kg midazolam (Exir drug Co., Iran), 0.5 mg/kg atracurium (Caspian Co.) and 5–6 mg/kg thiopental (Exir drug Co.), and then placed under the ventilator.

During surgery, 0.5–1 mL of minimum alveolar concentration (MAC) isoflurane (Baxter Co., USA) was given to all children. After anesthesia and surgery, patients were left laterally on the edge of the bed (for a right handed physician [LP position1]) without removing inhaled gases. After determining posterior superior iliac spine, an equilateral triangle was formed, the base of which was made up of two spines, and the vertex of the triangle was located in the area of hiatus.

From the Hiatus area, two 2 mL syringes, containing air and distilled water (each 1 mL), were slowly entered in to the space. After eliminating caudal resistance, in all three groups, 1.5% lidocaine (Aboreyhan Co.) was injected at a dose of 0.5 mL/kg. In first group, 1 μ g/kg (1 mL) dexmedetomidine (Precede, Hospira Co., USA) was added to the lidocaine (Aboreyhan Co.), 1 mg/kg of tramadol (1 mL; Aboreyhan Co.) in the second group and, 1.5 μ g/kg (0.6 mL) of neostigmine (Alborz Co., Iran) as adjuvant in the third group were added to lidocaine.

Evaluation

In each group, the volume of injected drug was reached to about 10 mL and the volume of injections was the same in all three groups. After the anesthetizing by caudal block, the patients were placed in a supine position and after being assured of the number of respiration, and children were extubated and then transferred to the recovery. After entering the recovery, we measured pain score by using Visual Analog Score ruler in recovery, 2, 6, and 12 hours after operation and we recorded mean duration of postoperative analgesia and the average drug use in 24 hours after operation in recovery. Finally, the data obtained from the questionnaire were completed by the medical intern.

Sample size

The patients were divided into 3 groups of 32 patients and the following formula was used for calculation of sample size.

$$N = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (\delta_1 + \delta_2)^2}{(\mu_1 - \mu_2)^2} = 32$$

$$Z_{1-\alpha/2} = 1.96, Z_{1-b} = 2.33, \sigma_1 = 10, \sigma_2 = 10, \mu_1 = 280, \mu_2 = 265.$$

Statistical analysis

In this study, the obtained data were analyzed using SPSS

23.0 software (IBM, Armonk, NY, USA). The data were analyzed by statistical tests such as analysis of variance and Mann–Whitney *U* test.

Ethical considerations

A letter was received from the university authorities for introduction to research centers. The purpose of the study was explained to all research units and written consent was obtained from them. Then, informed consent was obtained from the child's parents. Information for all patients was kept confidential. After obtaining the ethic code, IRCT code was also obtained for this study.

RESULTS

A total of 96 patients were enrolled in this study. They were divided into three groups (n = 32/group), different variables were evaluated after operation including mean age, frequency, pain score, duration of analgesia, side effects, mean blood pressure, heart rate and arterial oxygen saturation.

In **Table 1**, there was no significant difference between the three groups of dexmedetomidine, neostigmine, tramadol (P = 0.6). The mean age of the patients was similar in the three groups. There was no significant difference between the males and females in terms of sexual distribution (P = 0.4). The sexual frequency was 66% in males and 33% in females (**Table 1**).

According to **Table 2**, there was a significant difference between three groups in terms of pain scores in recovery (P

= 0.01), 2 hours (P = 0.03), 6 hours (P = 0.02) and 12 hours after operation (P = 0.04). Moreover, pain score was less common in the dexmedetomidine group than other groups, and in the tramadol group it was less than neostigmine, and therefore dexmedetomidine was more effective than the other two adjuvants, and tramadol was better than dexmedetomidine (**Table 2**).

The comparison of the duration of analgesia was shown in **Table 3** and, given the fact that *P*-value is 0.03, it is statistically significant; therefore, the findings indicates that the duration of analgesia in the group of dexmedetomidine is higher than the other two groups. Furthermore, the duration of analgesia in the tramadol group was found to be more than the neostigmine group (**Table 3**).

The incidence of adverse complication such as nausea, vomiting and postoperative shivering was compared where there was no significant difference between the three groups (P > 0.05; **Table 4**) and shivering and vomiting were not seen in the three groups (**Table 4**).

The mean blood pressure, heart rate and arterial oxygen saturation were evaluated, and *P*-value for blood pressure was determined as 0.4, and 0.6 for the heart rate and arterial oxygen saturation, which were not significantly different, indicating that there was no difference between the three groups and the same hemodynamic parameters were observed in all of these groups (**Table 5**).

Table 1: Mean age and sex distribution of the lower abdominal pain surgery children with dexmedetomidine, t	ramadol
and neostigmine anesthesia	

Item	Dexmedetomidine group $(n = 32)$	Neostigmine group $(n = 32)$	Tramadol group ($n = 32$)	P-value (Mann–Whitney U test)
Average age (year)	4.66±1.1	4.25±0.96	4.37±0.98	0.6
Frequency distribution of sex (%)				0.4
Male	67	65	67	
Female	33	35	33	

Note: Data are analyzed by analysis of variance and Mann–Whitney U test.

Table 2: Comparison of pain scores in lower abdominal pain surgery patients with dexmedetomidine, tramadol and neostigmine anesthesia

Time	Dexmedetomidine group $(n = 32)$	Neostigmine group $(n = 32)$	Tramadol group ($n = 32$)	P-value (Mann–Whitney U test)
Recovery	0	1.7±0.43	0	0.01
2 hours after operation	1.1±0.28	2.1±0.33	1.7±0.22	0.03
6 hours after operation	1.2±0.41	2.6±0.85	2.1±0.44	0.02
12 hours after operation	0	0.38±0.11	0.29±0.16	0.04

Note: Data are expressed as the mean ± SD, and analyzed by analysis of variance and Mann–Whitney U test.

Table 3: Comparison of pain time of the lower abdominal pain surgery children with dexmedetomidine, tramadol and neostigmine anesthesia

	Dexmedetomidine group $(n = 32)$	Neostigmine group ($n = 32$)	Tramadol group ($n = 32$)	<i>P</i> -value (Mann–Whitney <i>U</i> test)
Pain time (hour)	14.8±1.7	12.2±2.6	13.1±3.2	0.03

Note: Data are expressed as the mean ± SD, and analyzed by analysis of variance and Mann–Whitney U test.

Table 4: Comparison of postoperative side effects of the lower abdominal pain surgery children with dexmedetomidine,				
tramadol and neostigmine anesthesia				

Group	Dexmedetomidine group $(n = 32)$	Neostigmine group ($n = 32$)	Tramadol group ($n = 32$)	P-value
Nausea-vomiting	0	0	0	> 0.05
Shivering	0	0	0	> 0.05

Note: Data are analyzed by analysis of variance and Mann–Whitney U test.

Table 5: Comparison of mean blood pressure and heart rate and arterial oxygen saturation of the lower abdominal pain surgery children with dexmedetomidine, tramadol and neostigmine anesthesia

Item	Dexmedetomidine group $(n = 32)$	Neostigmine group $(n = 32)$	Tramadol group ($n = 32$)	P-value (Mann–Whitney U test)
Blood pressure (mmHg)	65.2±1.1	67.6±3.4	66.6±2.7	0.4
Heart rate (beat/minute)	105.6±3.1	106.7±3.7	104.2±2.9	0.6
Arterial oxygen saturation (%)	96.6	97.4	96.2	0.6

Note: Data are expressed as the mean ± SD in blood pressure and heart rate, and analyzed by analysis of variance and Mann–Whitney U test.

DISCUSSION

Pain is a complex medical problem that can affect children's physical and mental status and lack of adequate control of postoperative pain may have adverse effects on the child's condition.¹ Postoperative pain control in children has always been a major challenge for surgeons and anesthesiologists who have always undesired surgical procedures for children and their parents. Therefore, postoperative pain control is one of the most important indicators of health, well-being, relaxation and health in children.¹³

In the meantime, caudal analgesia is one of the most useful and common methods of regional blocks in children, which can have a significant effect on postoperative pain control. This technique is a safe and simple method that provides postoperative analgesia for lower abdominal surgery in children. Achieving proper ingredients and adjuvants along with local anesthetics for use in analgesia is one of the most important goals of anesthetists and pediatricians.¹⁴ Therefore, in this study, the effect of adding dexmedetomidine and neostigmine and tramadol to lidocaine 1.5% in caudal analgesia was used to reduce postoperative pain in children.

Score pain in the dexmedetomidine group in recovery, 2, 6, and 12 hours after surgery was found to be less than the other two groups. Furthermore, scores of pain in the tramadol group was less than neostigmine group. Moreover, the duration of analgesia in the dexmedetomidine group was reported to be more than the other two groups, and the mean of the used analgesics was lower in the dexmedetomidine group 24 hours after operation as compared to the other two groups, indicating the effect of dexmedetomidine as an adjuvant in increasing the duration of analgesia and reducing postoperative pain along with lidocaine 1.5%. The results from this study were consistent with previous studies. Islam et al.¹⁰ have shown that the levels of analgesia in the tramadol and bupivacaine groups were significantly longer than bupivacaine alone. On the other hand, pain score in the combined group was lower than the bupivacaine group alone. The results of the Islam et al.'s study¹⁰ were consistent with this study because tramadol

resulted in an increase in the duration of analgesia and a reduction in pain scores after the operation of patients. Another study by Priyan et al.15 in India was conducted on 60 children to compare 3 ropivacaine groups alone and combined group including rupivacaine, tramadol, and dexmedetomidine in caudal blocks. The results of this study showed that adding dexmedetomidine to ropivacaine resulted in an increase in the duration of analgesia and a reduction in postoperative pain, and its effect on tramadol was better. The results of the study Priyan et al.¹⁵ were fully consistent with the current study because two drugs including dexmedetomidine and tramadol, increased the duration of postoperative analgesia, on the other hand, dexmedetomidine had a greater and better effect on increasing the duration of postoperative analgesia. In another study by Prajapati et al.¹⁶ in 2016, it has been shown that the addition of neostigmine to bupivacaine as a long-acting local anesthetic resulted in an increase in the duration of analgesia without any special side effects. Girgis¹⁷ in Egypt in 2014 examined the effect of adding dexmedetomidine to bupivacaine by caudal block method in 80 children aged 2-8 years undergoing lower abdominal surgery. They reported that this combination was capable of increasing the duration of analgesia and reducing postoperative nausea and vomiting. The results of two studies by Girgis¹⁷ and Prajapati et al.¹⁶ were coincided with our study, because the used of dexmedetomidine and tramadol resulted in an increase in the duration of analgesia in patients.

Another study by Xiang et al.¹⁸ in 2012 evaluated caudal supplementation of caudal bupivacaine with dexmedetomidine in children undergoing inguinal hernia repair. The results of mentioned study demonstrated that addition of dexmedetomidine to caudal bupivacaine was capable of increasing in the duration of postoperative analgesia in these children as compared to ketamine. The result of this study was also consistent with our study. In our study, the effect of dexmedetomidine as an adjuvant was evident in addition to local anesthetics, and only difference was the type of medication used in this study, so that dexmedetomidine was compared with tramadol and neostigmine, while aforementioned study evaluated supplementation of caudal bupivacaine with dexmedetomidine in

comparison with ketamine.

Approximately, all studies indicated that the use of neostigmine, tramadol, and dexmedetomidine drugs have been associated with an increased duration of analgesia.

All three neostigmine, tramadol, and dexmedetomidine drugs along with other local anesthetic are capable of increasing the duration of analgesia and reducing the postoperative pain in children, which the effect of dexmedetomidine was found to be greater than the other two drugs.

Author contributions

This work was carried out in collaboration among all authors. THG and AK designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. BY and GNB managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

Conflicts of interest

There is no conflict of interest.

Financial support

None.

Institutional review board statement

The study was approved by the Ethics Committee of Arak University of Medical Sciences, Iran (approved No. IR.ARAKMU. REC.1396.112) on October 28, 2017, and registered at Iranian Registry of Clinical Trials (registration No. IRCT20141209020258N83) on August 29, 2018.

Declaration of patient consent

The authors certify that they have obtained patients' legal guardians consent forms. In the form, their legal guardians have given their consent for the patients' images and other clinical information to be reported in the journal. Their legal guardians understand that the patients' names and initials not be published and due efforts will be made to conceal their identity.

Reporting statement

The writing and editing of the article was performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) Statement.

Biostatistics statement

The statistical methods of this study were reviewed by the biostatistician of Arak University of Medical Sciences, Iran.

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Data sharing statement

Datasets analyzed during the current study are available from the corresponding author on reasonable request.

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