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Research Article

Analgesic Efficacy of Dexamethasone and Dexmedetomidine as an Adjuvant to Bupivacaine Infiltration in Unilateral Cleft Lip Surgery: A Randomized, Double-Blinded Study

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ABSTRACT

Background: In the majority of cases, the treatment method for Cleft lip is surgery. Providing adequate pain control during and after surgery for children, is too important. Also, different methods are used for pain relief like analgesic prescription and nerve block and different adjuvants can be added to anesthetics to reduce pain.
Aims: This trial was aimed to compare the analgesic effect of Bupivacaine with or without dexmedetomidine or dexamethasone for cleft lip surgery.
Methods: This study is a prospective, double-blinded, randomized trial which conducted on 75 pediatrics, aged between 3 to 10 months, who needed unilateral cleft lip surgery. Patients were divided into 3 groups (n=25 in each group). Children in group A, were given a combination of bupivacaine and 0.5 µg/kg of dexmedetomidine, those in group B, 0.1 mg/kg of dexamethasone as an adjuvant to bupivacaine, and in group C, plain 1 cc of bupivacaine 0.5% was injected in the operation site. Outcomes were assessed via FLACC and WATCHA scores.
Results: The mean age among children was 4.3 ±1.29 months and mean weight was 6.3± 1.09 kg. Pain score and frequency of analgesic request intra and post-operation in group A was lower than others ($p<0.0001$). Also, FLACC and WATCHA scores were significantly lower in group A ($p<0.0001$) and parental and surgeon satisfaction was higher in group A ($p<0.05$).
Conclusion: Our study showed that, dexmedetomidine as an adjuvant to bupivacaine 0.5% is more effective to improve the analgesia, in children who underwent unilateral cleft lip surgery.

Introduction

A cleft lip is an X-linked genetic disorder. If some genes responsible for the formation and integration of the lips are damaged in some way, when the tissues are developing and connecting in the embryo, a gap is created between the upper lips [1]. This disorder is seen in unilateral or bilateral. Orofacial clefts including cleft lip and cleft palate are the most common congenital defect in the maxillofacial region [2]. It happens 1 in every 500 to 1000 birth in the various ethnic and geographic groups [3-4]. The treatment method for this disorder is almost always surgery, and an expert

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surgeon repairs the cleft lip at the age of three to six months. One of the most important duties of the paediatric anaesthesiologist is to provide adequate pain control during and after surgery [5-6]. Different methods are used for pain relief like analgesic prescription and nerve block. The maximum amount of postoperative pain in cleft lip surgery is during the first 24 to 48 hours, morphine is one of the common drugs used to relieve pain after surgery, but it requires 24-hour respiratory monitoring in the recovery or intensive care unit, and also it is associated with the risk of causing complications such as airway obstruction and respiratory arrest [7]. The use of right nerve block methods for lip surgery, including infra-orbital nerve block and injection at the operation site, while creating appropriate analgesia, does not affect systemic or respiratory conditions [8-9].

One of the most practical local anaesthetic drugs is bupivacaine. Previously dexamethasone and dexmedetomidine adjuvant therapy had been surveyed in tonsillectomy, abdominal surgery, and herniorrhaphy in children [10-13], but our study is the first one that examines bupivacaine infiltration effect in pain management of cleft lip surgery. A long-acting local anaesthetic is used in the combination of adjuvants in cleft lip surgery.

Methods

This study was a prospective, double-blinded, randomized trial which conducted on 75 paediatrics, who needed unilateral cleft lip surgery in Imam Hossein hospital, Isfahan, Iran from April 2021 to April 2022, in accordance with the Declaration of Helsinki of 1975 (2013). The trial was registered in the Iranian Registry of Clinical Trials (URL: https://en.irct.ir/;) with the code of IRCT2016102226390N5. Children aged 3 to10 months, with American Society of Anesthesiologist (ASA) physical status 1 and 2, who had no previous lip surgery, known allergy to any of the studied drugs, or surgery with primary nose repair were enrolled into the study after getting parental informed consent. Lasting surgery duration more than two hours, occurring hemodynamic changes which required supportive treatment, the need to repeat local injection of epinephrine at the operation site, and the allergy of patients to the studied drugs, were the exclusion criteria's of this study. Randomization was done by using computer-generated random number table (www.random.org) and participants randomly assigned to one of the three groups of study: A, B, and C, which 25 patients included in each group. Surgeon and outcome assessor were blinded to these three groups.

For premedication, all of the children received midazolam 0.01 mg/kg intravenously 30 minute before surgery started and subsequently, they entered in to operating room.

In the operating room, standard anaesthesia monitoring (pulse oximetry, electrocardiogram, and non-invasive blood pressure) was performed, then induction of anaesthesia was performed via intravenous fentanyl 1-2 µg/kg, propofol 3 mg/kg, and atracurium 0.5 mg/kg and maintained with 33% O2, 67% N2 and 1% isoflurane. After ventilation via face mask and %100 oxygen, the patient was intubated with a suitable endotracheal tube and fixed on the lower jaw. When the hemodynamic conditions became stable, basic vital signs (blood pressure, heart rate, o2 saturation, temperature and breathing rate) were recorded. Then, surgery with standard protocol for all children was started. For patients in group A: a combination of 1:200.000 of epinephrine, 1 cc of bupivacaine 0.5%, and 0.5 µg/kg of dexmedetomidine, for group B: a combination of 1:200,000 epinephrine, 1 cc of bupivacaine 0.5% and 0.1 mg/kg of dexamethasone and for children in group C, a combination of 1:200,000 epinephrine, 1 cc of bupivacaine 0.5% was injected.

The main researcher prepared the drugs with the appropriate dose in a specific syringe, and then surgeon injected the drug into the cleft lip operation site with a G27 needle in the same volume (2cc) without knowing the content of the drugs.

Fifteen minutes after injection, vital signs were checked and recorded. If the blood pressure and heart rate increased by more than 20% of the baseline, 0.5 µg/kg fentanyl was injected. Vital signs were recorded at the surgery termination, before extubation and 15 minutes after entering to recovery room. Finally, extubation of the trachea was done with the position of head down left lateral.

Data collection

Children's demographic data, surgery and anaesthesia time were collected. The primary outcome of this study was pain intensity after surgery. To examine the behaviour of pain in children, the Face, Legs, Activity, Cry, and Consolability questionnaire (FLACC), which designed by Voepel et al. (1997), [14] was used. It consists of 5 section and each section carries a score of 0-2. A higher score indicates a greater behavioural response to pain [15]. Score 0 indicates no pain and score 10 indicates the worst possible pain.

Moreover, The Watcha's four-point scale was used to assess the child's emergence of delirium in recovery room. This scale includes 4 observational-behavioural reactions [16]. FlACC and Watcha scores were recorded every 15 minute by a nurse, before transferring the children to their ward.

In cases of FLACC higher than 4, a dose of 10 mg/kg acetaminophen was given and its injection time was recorded. Also, when the Watcha score was higher than 2, a dose of 1 mg/kg propofol was injected and its time was recorded, too. During the first 24 hours, the frequency and amount of analgesic request. Also parents and doctor's satisfaction were recorded.

Data analysis

SPSS version 24 software was used for all statistical analysis. Percentage and frequency were used for qualitative variables and mean and standard deviation was used for quantitative variables. Qualitative variables were compared using chi-square or Fisher's exact test and quantitative variables were compared using an independent t-test or analysis of covariance. By using one-way ANOVA test relationship between the three groups was surveyed. A significant level was considered less than (p-value ≤ 0.05).

Results

Based on statistical analysis results, table 1 illustrates demographic characteristics of children, which based on that, the mean age among children was 4.3 ±1.29 months and the mean weight was 6.3± 1.09 kg (Table 1).

One-way ANOVA test demonstrated that, mean arterial pressure before injection (MAP 0) and heart rate before injection (HR0) was lower in group C and remain lowest 15 minutes after injection (MAP1 & HR1). HR at the end of the surgery (HR2) and duration of surgery was lower in group C. Although, there was no significant relationship between groups in terms of age, weight, MAP 0, 1, HR 1, 2, and duration of surgery (TIMEJ) (p-value>0.05). There was shown that, MAP at the surgery termination (MAP2) and during entering to recovery room (MAP3) between the three intervention groups, had a significant difference with each other. In such a way that, MAP2 and MAP3 were lower in group A (p=0.001 & P<0.0001, respectively).

FLACC score was 1.68 ± 1.46 and Watcha score was 1.20 ± 0.5 in group A. It was shown that, FLACC and Watcha score was significantly lower in group A (P<0.0001) and more details have presented in (Table 2).

The frequency of need for analgesia in the first 24 hours (Analgesic 24) was 0.08 ± 0.27 in group A, which was significantly lower in comparison to others (P<0.0001). Based on Chi-Square test analysis, a significant difference between groups in terms of using analgesics in recovery room (ACET), using intraoperative narcotics (FENT), and parents and surgeon satisfaction, was observed (p<0.005).

In group B 16 (64%) and group C 15 (60%) of children had no need, while in group A, 24 (96%) patients needed for FENT. Which it can show effectiveness of dexmedetomidine compared to other groups (p=0.007). ACET variable between groups had significant differences, so in group A 92% of patients needed no more postoperative analgesia (P<0.0001). More details have shown in (Table 3).

Table 1- Demographics and clinical variables at times 0, 1, 2, 3*.

Variable	Mean ± SD
Age (years)	4.3 ± 1.29
Weight (kg)	6.3 ±1.09
Mean arterial pressure (MAP/mmHg)	
MAP0	66.2± 11.06
MAP1	59.1 ±8.92
MAP2	57.4 ±8.09
MAP3	58.2±10.5
Heart Rate (HR/ per minute)	
HR0	161.1 ±13.5
HR1	158.06± 11.8
HR2	148.3 ±13.6
HR3	145.8± 15.1
FLACC	4.05± 2.5
Watcha	1.8± 0.83
TIMEJ (min)	90.9± 3.35
TIMER (min)	52.6 ±7.22
Analgesic 24	±0.11

*Time 0: before injection, Time 1:15 minutes after injection, Time 2: at end of the surgery, Time 3: during recovery time.
FLACC: postoperative pain scale ranging from (0-10), Watcha : postoperative restlessness scale ranging from (1-4) , Analgesic 24: the number of times analgesics were used in the first 24 hours after surgery, TIMEJ: Duration of surgery in minutes, TIMER: The length of time remaining in recovery in minutes.

Table 2- Demographics and clinical variables by groups of intervention.

Variable	Intervention group (Mean±SD)			P value
	A (n=25)	B (n=25)	C (n=25)	
Age	4.08± 1.35	4.12 ±1.07	4.12 ±1.07	0.167
Weight	6.38 ± 0.96	6.46 ± 0.96	9.32 ±1.36	0.905
MAP0	67.68 ±7.32	67.84 ±14.29	63.20± 10.24	0.245
MAP1	59.48± 8.06	61.92 ±11.22	56.08± 6.06	0.065
MAP2	54.52± 5	62.16± 10.98	55.52± 4.49	0.001

MAP3	52.72± 6.42	64.20 ± 12.6	65.24 ±6.65	<0.0001
HR0	166.12± 11.13	161.84± 9.38	155.56 ±17.17	0.019
HR1	159 ±12.02	160.48± 9.15	154.72± 13.51	0.203
HR2	146.60 ±12.57	153.64± 12.06	144.88 ±15.16	0.054
HR3	136.32± 13.81	151.24± 15.18	149.96 ±12.07	<0.0001
FLACC	1.68± 1.46	5 ± 2	5.48± 2.31	<0.0001
WATCHA	1.20± 0.5	2.12 ±.83	2.08± 0.81	<0.0001
Analgesic 24	0.08 ± 0.27	1.12± 0.97	1.40 ±1.08	<0.0001
TIMEJ	90.40 ±3.51	90.80± 2.76	91.60 ±3.74	0.443
TIMER	46.80 ±4.97	56± 5.59	55.20± 7.14	<0.0001

Group A: bupivacaine and dexmedetomidine, Group B: bupivacaine and dexamethasone, Group C: bupivacaine alone.

Table 3- Association between ACENT, FENT, parent's and surgeon's satisfactions by groups of intervention.

Variables		Intervention group n (%)			P value
		A (n=25)	B (n=25)	C (n=25)	
Gender	Male	10 (40%)	14 (56%)	9 (36%)	0.321
	female	15 (60%)	11 (44%)	16 (64%)	
FENT	No	24 (96%)	16 (64%)	15 (60%)	0.007
	Yes	1 (4%)	9 (36%)	10 (40%)	
ACET	No	23 (92%)	10 (40%)	8 (32%)	<0.0001
	Yes	2 (8%)	15 (60%)	17 (68%)	
Parents	No	0	13 (52%)	16 (64%)	<0.0001
Satisfaction	Yes	25 (100%)	12 (48%)	9 (36%)	
Surgeon	No	1 (4%)	14 (56%)	14 (56%)	<0.0001
satisfaction	Yes	24 (96%)	11 (44%)	11 (44%)	

FENT= intraoperative narcotic use, ACET= recovery analgesic use.

Discussion

Cleft lip as a common orofacial congenital anomaly is so important. Pain control is an important part of the management of anaesthesia in cleft lip surgery. Due to this reason, this study investigated adjuvant treatments along with bupivacaine (dexmedetomidine and dexamethasone).

Dexmedetomidine is a powerful α2 agonist that has central analgesia and anti-inflammatory effects [17]. In this study, we demonstrated that combination of 1 cc bupivacaine 0.5%, and 0.5 µg/kg of dexmedetomidine is more effective for pain management in cleft lip surgery.

In 2019, a clinical trial was down to compare the effect of dexmedetomidine and dexamethasone in composed with bupivacaine in infraorbital nerve block for cleft lip repair, which revealed that during the first postoperative 24 h, the FLACC score was significantly lower in dexmedetomidine group and parents were more satisfied [18]. Which it was similar to our results that FLACC and WATCHA score was significantly lower in group A (bupivacaine and dexmedetomidine). Also, in the patients who received this combination, all parents were satisfied with the pain situation in their child.

In another clinical trial in 2018, which conducted on 63 patients in three groups (bupivacaine, dexmedetomidine-bupivacaine, and dexmedetomidine- bupivacaine) who needed hypospadias surgery, was shown that pain degree was significantly lower in dexmedetomidine-bupivacaine group in 30 minute, 1, 2, and 6 hours after surgery [19]. This finding was in consistent with our result, which indicated group A, had less requirement to narcotics and analgesics administration during surgery and in the recovery room.

In a study conducted by Ribeiro et al., paediatric patients were given either bupivacaine alone or bupivacaine and intra neural dexamethasone (0.1 mg/kg) for supraclavicular nerve block. Their result demonstrated that, dexamethasone significantly increased the duration of postoperative analgesia [20], it was in contrast with our findings. Moreover, results of this study showed that, there were no significant differences in time of surgery between groups, while the time of recovery was significantly lower in a group which dexmedetomidine applied.

In the other study conducted in Brazil (2022), 97 children underwent laparoscopic herniorrhaphy divided randomly into three groups (a combination of bupivacaine and dexmedetomidine, a combination of bupivacaine and magnesium sulphate and bupivacaine-normal saline). Based on their findings, the FLACC score was higher in one-third of children in bupivacaine-normal saline group in comparison to other groups and also, parents' satisfaction was higher in other groups than bupivacaine- normal saline, which these reports are similar to our findings of study [21]. Another study surveyed a combination of bupivacaine and dexmedetomidine provided lesser rescue analgesic consumption and higher parents satisfaction post-laparoscopic appendectomy [22].

In our study, it was shown that group A had lower MAP and HR at the surgery termination and during recovery time than others, and recovery time was shorter and surgeons were more satisfied during surgery.

One limitation of our work was the lack of similar studies to compare our results, because according to our search on databases, we found no research on this topic in children who underwent cleft lip surgery.

Conclusion

In this randomized clinical trial study, for the first time, we examined the effect of the adjuvant therapy of dexmedetomidine and dexamethasone on pain management in patients who underwent cleft lip repair. We conducted that combination of dexmedetomidine and bupivacaine is a better choice for pain management in this group of children.

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