



REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br



SCIENTIFIC ARTICLE

Ketamine as an adjunct to bupivacaine in infra-orbital nerve block analgesia after cleft lip repair



Hala Saad Abdel-Ghaffar*, Nawal Gad Elrab Abdel-Aziz, Mohamed Fathy Mostafa, Ahmed Kamal Osman, Nehad Mohamed Thabet

Assiut University, Faculty of Medicine, Pediatric Hospital, Assiut, Egypt

Received 22 April 2017; accepted 3 January 2018
Available online 10 February 2018

KEYWORDS

Postoperative pain;
Cleft lip;
Local analgesia;
Infra-orbital nerve;
Bupivacaine;
Ketamine

Abstract

Objectives: We conducted this study to investigate the safety and analgesic efficacy of the addition of Ketamine to Bupivacaine in bilateral extra-oral infra-orbital nerve block in children undergoing cleft lip surgeries.

Methods: Sixty patients were randomly allocated into two groups ($n=30$), Group B received infra-orbital nerve block with 2 mL of 0.25% Bupivacaine and Group BK received 0.5 mg.kg⁻¹ Ketamine for each side added to 1 mL of 0.5% Bupivacaine solution diluted up to 2 mL solution to 0.25% Bupivacaine concentration. Assessment parameters included; hemodynamics, recovery time, time to first oral intake, postoperative Faces Legs Activity Cry Consolability (FLACC) scores, Four-point Agitation scores, analgesic consumption and adverse effects.

Results: Patients in Group BK showed lower postoperative FLACC scores during all recorded time points ($p < 0.0001$). Two patients in Group BK versus 12 in Group B requested for postoperative rescue analgesia ($p < 0.001$). There were no differences between groups in time, minutes (min), to first request for rescue analgesia. Patients in Group BK reported lower analgesic consumption (366.67 ± 45.67 vs. 240.0 ± 0.0 mg, $p < 0.04$). The time to first oral intake was significantly reduced in Group BK (87.67 ± 15.41 vs. 27.33 ± 8.68 min, $p < 0.001$). Lower postoperative Agitation scores were recorded in Group BK patients that reached a statistical significance at 45 min (0.86 ± 0.11 vs. 0.46 ± 0.16 , $p < 0.04$) and in the first hour (h) postoperatively (1.40 ± 0.17 vs. 0.67 ± 0.14 , $p < 0.003$). Higher parent satisfaction scores were recorded in Group BK ($p < 0.04$) without significant adverse effects.

Conclusions: The addition of Ketamine to Bupivacaine has accentuated the analgesic efficacy of infra-orbital nerve block in children undergoing cleft lip repair surgeries.

© 2018 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author.

E-mail: hallasaad@yahoo.com (H.S. Abdel-Ghaffar).

PALAVRAS-CHAVE

Dor pós-operatória;
Lábio leporino;
Analgésia local;
Nervo infraorbitário;
Bupivacaína;
Cetamina

Cetamina como adjuvante de bupivacaína em bloqueio do nervo infraorbitário para analgesia após correção de lábio leporino

Resumo

Objetivos: Realizamos este estudo para avaliar a segurança e eficácia da analgesia com a adição de cetamina à bupivacaína em bloqueio do nervo infraorbitário, bilateral e extraoral, em crianças submetidas à cirurgia de lábio leporino.

Métodos: Foram randomicamente alocados 60 pacientes em dois grupos ($n=30$): o Grupo B recebeu bloqueio do nervo infraorbitário com bupivacaína a 0,25% (2 mL) e o Grupo BC recebeu bloqueio com cetamina ($0,5 \text{ mg.kg}^{-1}$) em cada lado, mais a adição de 1 mL de solução de bupivacaína a 0,5% diluída até 2 mL da concentração a 0,25%. Os parâmetros de avaliação incluíram: hemodinâmica, tempo de recuperação, tempo até a primeira ingestão oral, escores da escala FLACC (que avalia a expressão facial [Face], os movimentos das pernas [Legs], a atividade [Activity], o choro [Cry] e a consolabilidade [Consolability]), escores de agitação em escala de quatro pontos, consumo de analgésicos e efeitos adversos no pós-operatório.

Resultados: Os pacientes do Grupo BC apresentaram escores FLACC mais baixos em todos os momentos mensurados no pós-operatório ($p < 0,0001$). Dois pacientes do Grupo BC *versus* 12 do Grupo B solicitaram analgesia de resgate no pós-operatório ($p < 0,001$). Não houve diferenças entre os grupos em relação ao tempo até a primeira solicitação de analgesia de resgate. Os pacientes do Grupo BC relataram consumo menor de analgésicos ($366,67 \pm 45,67$ vs. $240,0 \pm 0,0 \text{ mg}$, $p < 0,04$). O tempo em minutos (min) até a primeira ingestão oral foi significativamente reduzido no Grupo BC ($87,67 \pm 15,41$ vs. $27,33 \pm 8,68 \text{ min}$, $p < 0,001$). Escores mais baixos de agitação no pós-operatório foram registrados para os pacientes do Grupo BC, com significância estatística no tempo de 45 min ($0,86 \pm 0,11$ vs. $0,46 \pm 0,16$; $p < 0,04$) e na primeira hora de pós-operatório ($1,40 \pm 0,17$ vs. $0,67 \pm 0,14$; $p < 0,003$). Índices mais altos de satisfação dos pais foram registrados no Grupo BC ($p < 0,04$), sem efeitos adversos significativos.

Conclusões: A adição de cetamina à bupivacaína acentuou a eficácia analgésica do bloqueio do nervo infraorbitário em crianças submetidas à cirurgia de correção de lábio leporino.

© 2018 Sociedade Brasileira de Anestesiologia. Publicado por Elsevier Editora Ltda. Este é um artigo Open Access sob uma licença CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Cleft lip and palate (CLP) is one of the most common surgical abnormalities requiring surgical treatment in early years of life.¹ Corrective surgical procedures subject those children to intense pain, postoperatively. Postoperative pain management in CLP includes; local anesthetic (LA) infiltration by the surgeon, nerve blocks, opioid and non-opioid analgesics.²

The popularity of regional anesthesia in conjunction with general anesthesia in children is increasing as it provides satisfactory operating conditions and excellent perioperative analgesia.³ The infra-orbital nerve is a branch of the maxillary division of the trigeminal nerve that supplies not only the upper lip, but much of the skin of the face between the upper lip and the lower eyelid, except for the bridge of the nose.⁴ Unilateral or bilateral infra-orbital nerve block has been performed with a very high success rate.^{5,6} Various adjuvant to local anesthetics have been studied to improve the duration of the block.^{7,8}

Ketamine has an analgesic action at many sites both centrally and peripherally. Besides its role as N-methyl-D-aspartate receptor antagonist, Ketamine induces an analgesic effect by nitric oxide synthase inhibition.⁹ Ketamine is widely used as an adjunct to analgesics during the perioperative period.^{10,11}

The aim of this study was to evaluate the safety and analgesic efficacy of Ketamine addition to Bupivacaine in bilateral infra-orbital nerve block for postoperative analgesia in children undergoing cleft lip repair.

Patients and methods**Patients**

This prospective, randomized, double blind, comparative study was conducted in Assuit University hospital after IRB approval from our Medical Ethics Committee. Trial registration was prospectively undertaken in clinical trial.gov (ID: NCT02514980). A written informed consent was obtained from the parental or guardian authorized representative before participation in the study. All collected data were confidential and were used for the purpose of scientific research only. Every research participant guardian had the complete right and freedom to withdraw at any time from the study with no negative consequences on the medical service provided to his/her child. Sixty patients of either sex aged less than 6 years, (ASA I or II) and scheduled for elective cleft lip repair under general anesthesia were included in this study. Exclusion criteria included; local infection at the block injection site, history suggestive of drug allergy,

any systemic disease that compromises the cardiovascular, respiratory or neurological function, other congenital anomaly, history of upper or lower airway disease, coagulation disorders, thrombocytopenia, and children with history of sleep apnea and in whom postoperative ventilation may be required were excluded from the study.

Randomization and blindness

Patients were randomly assigned into two groups of 30 patients each; Group B (Bupivacaine group) and Group BK (Bupivacaine–Ketamine group). All patients received bilateral extra-oral, infra-orbital nerve block with 1 mL of solution on each side. Group B received block with 0.25% Bupivacaine, Group BK received 0.25% Bupivacaine with Ketamine 0.5 mg.kg⁻¹.

Randomization was performed in the morning before surgery using a computer-generated randomized number table. The envelopes were opened 1 h before induction of anesthesia and the study drugs were prepared by a trained nurse not involved in the study. All clinical staff (including surgeons, anesthetists, nurses, investigators, observers) and the parents were blinded to treatment-group assignment.

Study protocol

After standard fasting times and without premedication, anesthesia was induced with Sevoflurane 8% in 100% oxygen via Jackson Rees Breathing Circuit. Monitoring included electrocardiogram, pulse oximetry, non-invasive arterial blood pressure (NIBP), end tidal CO₂ (ETCO₂) and temperature. An intravenous cannula was placed after induction of anesthesia and patients received intravenous fentanyl 1 µg.kg⁻¹ and propofol 1–2 mg.kg⁻¹. A cuffed endotracheal tube of appropriate size was then inserted and anesthesia was maintained with 2–3% Sevoflurane in 50% oxygen/air mixture.

Bilateral extra-oral infra-orbital nerve block was given to all the patients by a well-trained anesthetist after establishment of general anesthesia and before the start of the surgery. The approach for infra-orbital block advocated by BÖsenberg and Kimble was used in all patients.¹² The patient was placed in supine position with the head in neutral position. The infra-orbital foramen was identified by palpation in a sagittal plane passing through midpoint of palpebral fissure and the angle of the mouth, lying at a point approximately 7.5 mm from the alar base. A 25 G needle was introduced perpendicular to the skin and advanced until bony resistance was felt. The needle was then withdrawn slightly and after a negative aspiration test for blood, the study drug was injected. In Group B, 2 mL of 0.25% Bupivacaine solution was prepared by adding 1 mL of saline to 1 mL of 0.5% Bupivacaine. In Group BK, 0.5 mg.kg⁻¹ Ketamine from a 50 mg.mL⁻¹ formulation for each side was drawn up using an insulin syringe and added to 1 mL of 0.5% Bupivacaine solution. The resulting mixture was reconstituted with saline to a volume of 2 mL, maintaining a Bupivacaine concentration of 0.25%. As per randomization, 1 mL of solution was injected at each site by an anesthetist blinded to the nature of the injected drug. Pressure was applied for 2 min and the injection point was massaged. Injections were performed while palpating the infra-orbital rim at the location of the

infra-orbital foramen to avoid penetration of the foramen and to protect the orbit. The procedure was repeated on the other side. The block was regarded as being successful if there were no significant hemodynamic changes (>20% from baseline) at skin incision and during the operation and if there was no excessive cry on recovery.

The mean arterial blood pressure and heart rate were maintained within ±20% of baseline values by adjusting the Sevoflurane concentration. Patients also received intravenous dexamethasone (0.1 mg.kg⁻¹). Spontaneous breathing was maintained during surgery and normal saline intravenous infusion was administered at 10 mL.kg⁻¹.h⁻¹. At the end of surgery, patients were extubated awake and were taken to the Post-Anesthetic Care Unit (PACU) then to the ward when they became hemodynamically stable, pain free and there was no postoperative vomiting.

Assessments

Health care personnel providing direct patient care, patients and their parents were blinded to the patient's group assignment. Assessment parameters included; patients' demographic and clinical data included age, weight, sex, anesthesia time, operation time, and operative procedure, recovery time and time to 1st oral intake. Intraoperative vital signs included; the heart rate, mean arterial blood pressure and peripheral arterial oxygen saturation. These parameters were recorded before the block, every 10 min after the block and at the end of the operation.

Postoperative pain was assessed using the Faces Legs Activity Cry Consolability (FLACC) Scale.¹³ Postoperative pain intensity was evaluated on arrival to the recovery room (0) and 1, 2, 3, 4, 6, 8, 12, and 24 h, postoperatively. FLACC scale is applicable for assessment of pain in children aged 2 months to 7 years and was interpreted as; 0: relaxed, comfortable; 1–3: mild discomfort; 4–6: moderate pain; 7–10: severe pain or discomfort or both. When the child's FLACC scale score was ≥4, intravenous paracetamol 15 mg.kg⁻¹ was given for rescue analgesia. The time from the administration of the block to first request for rescue analgesia, number of analgesic requests and the total analgesic consumption in the 1st 24 h postoperatively were recorded.

Postoperative agitation was evaluated at 0, 15, 30, 45 and 60 min up to 6 h after recovery from anesthesia using a Four-Point Agitation Scale (FPAS) (1 = the child is calm, quiet, 2 = crying but can be consoled, 3 = crying, cannot be consoled, and 4 = agitated, restless and thrashing around).¹⁴ Postoperative agitation was defined as a score of ≥3.

Any perioperative adverse event such as injury to the nerve or accompanying artery, puncturing the orbit floor, vomiting, respiratory depression, sedation, hematoma, erythema, or edema was treated and recorded.

At the end of the study, the parents were asked to evaluate their satisfaction regarding pain control of their children using a 4 point Likert scale (1 = excellent; 2 = good; 3 = fair; 4 = poor).¹⁵

Statistical analysis

The primary endpoint of this study was the postoperative FLACC Scale scores. Based on previous studies,^{7,8} a target

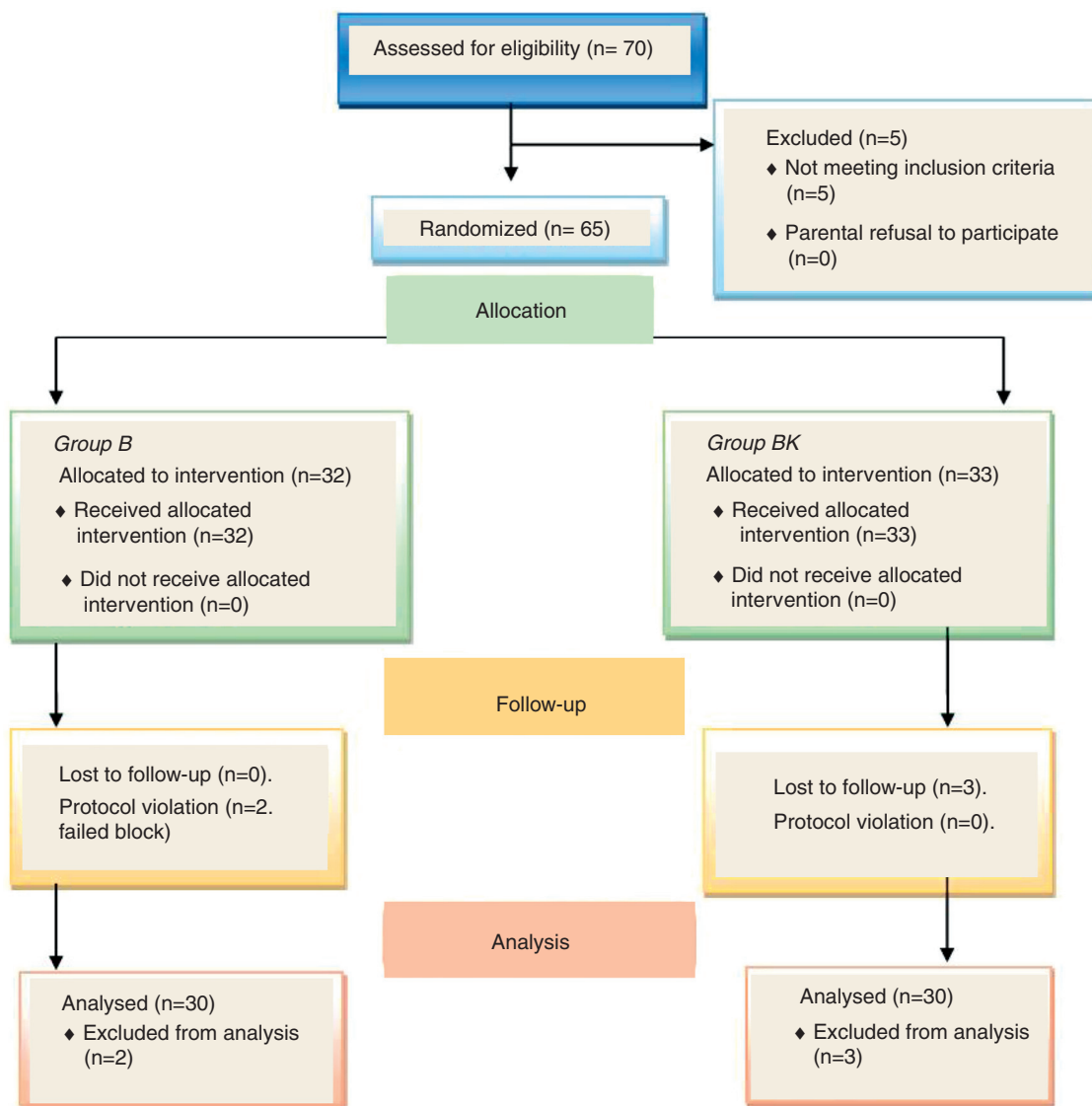


Figure 1 Participant flow diagram.

sample size was calculated. A power analysis estimated that a sample size of 30 patients in each group would have an 80% power at the 0.05 level of significance to detect a statistically significant difference between groups in the primary outcome parameter.

Distribution of baseline variables was assessed by the Shapiro–Wilk test. Continuous data were reported as mean \pm SD and were analyzed using independent sample *t*-test or analysis of variance for multiple comparisons with least significant difference test for post hoc analysis. Categorical data were reported as percentages and were analyzed using the Chi-square test or Fisher exact test as appropriate. Nonparametric data such as pain scores were analyzed using the Mann–Whitney *U*-test. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics version 20 (SPSS Inc., Chicago, IL, USA).

Results

Seventy patients were screened for eligibility to participate in this study and 65 patients were subsequently parentally consented and enrolled. Two patients were excluded from statistical analysis because of failed block. Three patients in Group BK were dropped from postoperative follow up and excluded from statistical analysis. A final of 60 patients were subjected to statistical analysis and were equally distributed in the two groups ($n=30$ per group) (Fig. 1). There were no significant differences between groups in the demographic and clinical characteristics regarding age, sex, weight, either in anesthesia time, surgical time, operative procedure or time of recovery (Table 1).

There were no significant differences between groups in the intra-operative hemodynamics at any recorded time points (data not represented).

Table 1 Patients demographic and clinical characteristic.

Item	Group B (n = 30)	Group BK (n = 30)	p-Value
Age (months)	11.40 ± 1.85	12.53 ± 1.82	0.665
Sex (male/female)	20/10	16/14	0.215
Weight (kg)	9.05 ± 4.54 (6–22)	7.99 ± 2.55 (5.5–21)	0.270
ASA Class I/II	30/0	30/0	–
Anesthesia time (min)	53.60 ± 10.41	52.46 ± 10.58	0.674
Operative time (min)	31.00 ± 9.68 (20–60)	29.67 ± 11.51 (20–51)	0.629
Operative procedure			0.171
1ry Bil CLR	6 (20.0%)	4 (13.3%)	
1ry Unil CLR	16 (53.3%)	16 (53.3%)	
2ry. Bil CLR	0 (0%)	4 (13.3%)	
2ry Unil CLR	6 (20.0%)	6 (20.0%)	
Incomplete CLR	2 (6.7%)	0 (0%)	
Time of recovery (min)	11.00 ± 2.46	13.00 ± 3.24	0.594
Time of 1st oral intake (min)	87.67 ± 15.41 (30–120)	27.33 ± 8.68 (10–45)	0.001 ^a

Data are expressed as mean ± SD, range, number and percentages. Group B, Bupivacaine Group; Group BK, Bupivacaine–Ketamine Group; ASA, American Society of Anesthesiologists; CLR, cleft lip repair; Unil, unilateral; Bil, bilateral.

^a $p < 0.01$.

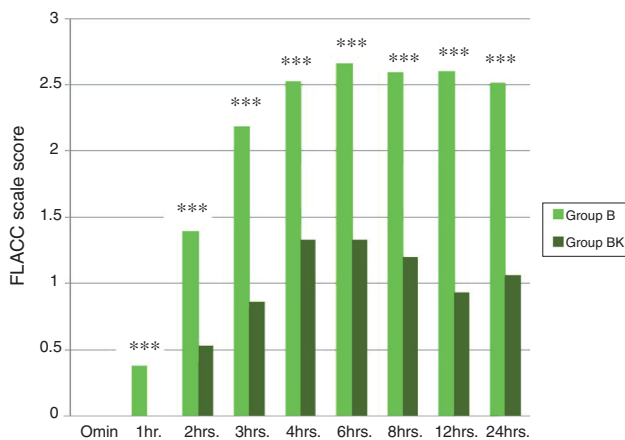


Figure 2 Postoperative FLACC scale scores in the two studied groups. Patients in Group BK showed significantly lower mean postoperative FLACC scale scores during all recorded time points in the study compared with patients in Group B. (FLACC) scale, Faces Legs Activity Cry Consolability Scale; Group B, Bupivacaine group; Group BK, Bupivacaine–Ketamine Group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Since the admission to the PACU till end of the study, patients in Group BK showed significantly lower mean postoperative FLACC scale scores during all recorded time points in the study compared with patients in Group B ($p < 0.001$) (Fig. 2). Two patients in Group BK versus 12 in Group B requested for postoperative rescue analgesia ($p < 0.001$). There were no differences between groups in the time to first request for rescue analgesia (5.33 ± 1.57 vs. 6.00 ± 0.0 h, $p = 0.569$). Patients in Group B had a significantly higher IV paracetamol consumption compared with patients in Group BK (366.67 ± 45.67 vs. 240.0 ± 0.0 mg, $p < 0.04$) (Table 2). The time to first oral intake was significantly reduced in Group BK compared

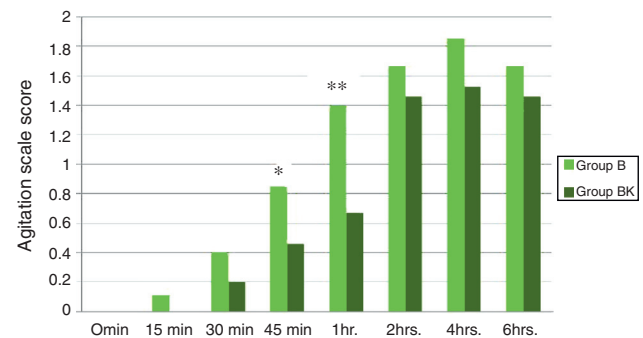


Figure 3 Postoperative Agitation scale scores in the two studied groups. Lower mean postoperative Agitation scores were recorded in Group BK patients that reached a statistical significance at 45 min ($p < 0.04$) and in the 1st h ($p < 0.003$), compared with Group B patients. Group B, Bupivacaine group; Group BK, Bupivacaine–Ketamine Group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

with Group B (27.33 ± 8.68 vs. 87.67 ± 15.41 min, $p < 0.001$) (Table 1).

Lower mean postoperative Agitation scores were recorded in Group BK patients that reached a statistical significance at 45 min (0.86 ± 0.11 vs. 0.46 ± 0.16 , $p < 0.04$) and in the 1st h (1.40 ± 0.17 vs. 0.67 ± 0.14 , $p < 0.003$), compared with Group B patients (Fig. 3).

There were no significant differences between groups in the overall incidence of postoperative adverse events ($p = 0.352$) and the detailed distribution of postoperative adverse events is listed in Table 2. Higher parent satisfaction scores ($p < 0.04$) were recorded in Group BK patients compared with patients in the Group B (Table 2).

Table 2 Postoperative analgesic consumption, adverse events and parents' satisfaction score in the two studied groups.

Item	Group B (n = 30)	Group BK (n = 30)	p-Value
<i>Patient's requests for rescue analgesia in the 1st 24 h postoperative</i>			<0.001 ^a
No request	18	28	
Once	6	2	
Twice	4	0	
>2 requests	2	0	
<i>Time of 1st request (hour)</i>	5.33 ± 1.57 (n = 12)	6.00 ± 0.0 (n = 2)	0.569
<i>Total consumption of iv paracetamol in the 1st 24 h postoperative.</i>	366.67 ± 45.67 (n = 12)	240.0 ± 0.0 (n = 2)	<0.04 ^b
<i>Postoperative adverse events</i>			0.352
Hematoma	2 (6.7%)	4 (13.3%)	
Vomiting	1 (3.3%)	2 (6.7%)	
Fever > 38°C	4 (13.3%)	4 (13.3%)	
Excess secretion	0%	2 (6.7%)	
<i>Parent satisfaction score</i>			<0.04 ^b
Excellent	8 (26.7%)	16 (53.3%)	
Good	10 (33.3%)	10 (33.3%)	
Fair	8 (26.7%)	2 (6.7%)	
Poor	4 (13.3%)	2 (6.7%)	

Data are expressed as mean ± SD, number and percentage. Group B, Bupivacaine group; Group BK, Bupivacaine-Ketamine Group.

^a $p < 0.01$.

^b $p < 0.05$.

Discussion

In this study, we have demonstrated that the addition of Ketamine to Bupivacaine in infra-orbital nerve block significantly accentuated postoperative analgesia in children undergoing surgeries for cleft lip repair. Patients in the Bupivacaine–Ketamine group showed lower postoperative pain scores, lower postoperative agitation scores, reduced time to first oral intake and higher parent satisfaction scores, compared with patients in the Bupivacaine group.

Infra-orbital nerve block provides excellent postoperative analgesia for cleft lip repair and many studies have confirmed its efficacy.^{7,8,16,17} However, the use of local anesthetic drugs alone does not provide an extended period of analgesia. The addition of different adjuvants to local anesthetics has been demonstrated to prolong the duration of the block such as pethidine⁷ and clonidine.⁸ In accordance with the above studies, the current study demonstrated that the addition of Ketamine to Bupivacaine in infra-orbital nerve block significantly accentuated postoperative analgesia in children undergoing surgeries for cleft lip repair. As patients in the Bupivacaine-Ketamine group showed significantly lower pain scores during all time points in the study and lower postoperative analgesic consumption.

In this study, Bupivacaine was chosen for the infra-orbital nerve block as lignocaine leads to a shorter pain-free period. We used 1 mL 0.25% on each side. We used this dose, as it is the safest and commonly used dose, however, the scientific literature does not clarify which volume should be used to make this block. There is evidence defending 0.5–1 mL of 0.5% Bupivacaine,¹⁸ 0.5 mL of 0.5% Bupivacaine in each side¹⁹ and 3 mL of 0.5% Bupivacaine.²⁰ Since very

small doses of Bupivacaine have serious side effects, such as cardiac dysrhythmias and neurotoxicity,²¹ more studies are needed to standardize this technique as there is a greater risk of toxicity at an area highly vascularized like the face.

We did not use a peripheral nerve stimulator to locate the infra-orbital nerve as it is purely a sensory nerve; and also we did not use ultrasonography. It can, however, be easily blocked at the point where it emerges from the infra-orbital foramen. This foramen is either palpable or can be estimated from other palpable landmarks.¹² There are two well-known approaches to the infra-orbital nerve: intra-oral or extra-oral.¹² The intra-oral approach although is known to be as effective in producing upper-lip anesthesia as the percutaneous approach; but has also been associated with complications.⁷ Extra-oral approach for infra-orbital block was thus chosen in this study as it is technically easier and safer.

In infra-orbital nerve block for cleft lip repair, the addition of pethidine (0.25 mg.kg⁻¹) to bupivacaine significantly increased the time to first request for rescue analgesia from 18 h (14.2–20 IQR) to 29 h (24–36 IQR) ($p < 0.001$).⁷ Also, clonidine addition (1 µg.kg⁻¹) increased it from 516.8 to 624.2 min ($p < 0.015$).⁸ In contrast to these studies, the current study showed no differences between the two groups in the time to first request for rescue analgesia. In our study, two patients only in the Bupivacaine–Ketamine Group requested for rescue analgesia in the 1st 24 h postoperatively, (mean time to first request 6.00 ± 0.00 h) compared with 12 in the bupivacaine group (3.33 ± 1.5 h), ($p = 0.569$). This small patient number that requested for rescue analgesia in the Bupivacaine--Ketamine group did not enable us to draw our conclusion. A limitation to this study is that we

followed our patients for 24 h postoperatively. We think that a longer follow up period (e.g. 36 or 48 h) was recommended.

The time to first oral intake is an important parameter reflecting the dynamic effect of adequate pain relief. In this study, the time to first oral intake was significantly reduced in Group BK compared with Group B (27.33 ± 8.68 vs. 87.67 ± 15.41 min, $p < 0.001$) indicating an enhanced analgesia in patients received IONB with Bupivacaine–Ketamine.

In this study, we recorded reduced postoperative agitation scores in both groups. Moreover, there was a trend toward lower mean post-operative agitation scores in Group BK patients that reached a statistical significance at 45 min ($p < 0.04$) and in the 1st h ($p < 0.002$) postoperatively, compared with Group B patients. These results are in accordance with a recent study which demonstrated that IONB significantly reduced the incidence and duration of Emergence Agitation (EA) in children undergoing cleft lip repair under Sevoflurane anesthesia.²² Pain is widely recognized as a significant contributing factor in EA. Although EA can occur when pain was relieved adequately²³ or even following non-painful procedures (e.g. imaging procedures).²⁴ Effective analgesia with regional blockade, opioids, and non-steroidal anti-inflammatory drugs can prevent and treat EA in children.^{22,25} Many studies have demonstrated that infra-orbital nerve block provides satisfactory analgesia with lower complication rates and reduced rescue analgesic need in patients undergoing repair of cleft lip.^{5,6} Because pain itself is the source of agitation, some authors reported a positive correlation between EA and pain.^{22,25} Consistent with these data, this study recorded low postoperative agitation scores in both groups with further reduction in EA scores in Group BK patients denoting the efficacy of Ketamine addition in controlling postoperative pain.

There were no significant differences between the two groups in the overall incidence of postoperative adverse events ($p = 0.352$). Instead, in Group BK we had a quiet, sleeping child, with higher parent satisfaction and a relieved staff.

In summary, the addition of Ketamine to Bupivacaine has accentuated the analgesic efficacy of infra-orbital nerve block in patients undergoing cleft lip repair surgeries.

Trial registration

ClinicalTrials.gov Identifier: NCT02514980.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors would like to thank the residents in anesthesia and plastic surgery departments who helped completing this study.

References

1. Tremlett M. Anaesthesia for cleft lip and palate surgery. *Curr Anaesth Crit Care*. 2004;15:309–16.
2. Reena Bandyopadhyay KH, Paul A. Postoperative analgesia for cleft lip and palate repair in children. *J Anaesthesiol Clin Pharmacol*. 2016;32:5–11.
3. Bosenberg A. Benefits of regional anesthesia in children. *Pediatr Anaesth*. 2012;22:10–8.
4. Suresh S, Voronov P. Head and neck blocks in children: an anatomical and procedural review. *Paediatr Anaesth*. 2006;16:910–8.
5. Rajamani A, Kamat VJ, Rajavel VP, et al. A comparison of bilateral infraorbital nerve block with intravenous fentanyl for analgesia following cleft lip repair in children. *Pediatr Anaesth*. 2007;17:133–9.
6. Takmaz SA, Uysal HY, Uysal A, et al. Bilateral extraoral, infraorbital nerve block for postoperative pain relief after cleft lip repair in pediatric patients: A randomized, double-blind controlled study. *Ann Plast Surg*. 2009;63:59–62.
7. Jonnavithula N, Durga P, Kulkarni DK, et al. Bilateral intra-oral, infra-orbital nerve block for postoperative analgesia following cleft lip repair in paediatric patients: comparison of bupivacaine vs bupivacaine–pethidine combination. *Anaesthesia*. 2007;62:581–5.
8. Jindal P, Khurana G, Divedi S, et al. Intra and postoperative outcome of adding clonidine to bupivacaine in infraorbital nerve block for young children undergoing cleft lip surgery. *Saudi J Anaesth*. 2011;5:289–94.
9. Elia N, Tramer MR. Ketamine and postoperative pain – a quantitative systematic review of randomized trials. *Pain*. 2005;113:61–70.
10. Vadivelu N, Schermer E, Kodumudi V, et al. Role of ketamine for analgesia in adults and children. *J Anaesthesiol Clin Pharmacol*. 2016;32:298–306.
11. Abdel-Ghaffar HS, Kalefa MA, Imbaby AS. Efficacy of ketamine as an adjunct to lidocaine in intravenous regional anesthesia. *Reg Anesth Pain Med*. 2014;39:418–22.
12. Bösenberg AT, Kimble FW. Infraorbital nerve block in neonates for cleft lip repair: Anatomical study and clinical application. *Br J Anaesth*. 1995;74:506–8.
13. Willis MH, Merkel SI, Voepel-Lewis T, et al. FLACC behavioral pain assessment scale: a comparison with the child's self-report. *Pediatr Nurs*. 2003;29:195–8.
14. Aono J, Ueda W, Mamiya K. Greater incidence of delirium during recovery from sevoflurane in preschool boys. *Anesthesiology*. 1997;87:1298–300.
15. Di Tomasso RA, Willard M. The development of a patient satisfaction questionnaire in the ambulatory setting. *Fam Med*. 1991;23:127–31.
16. Fenlon SM. Anaesthesia for plastic surgery in children. *Curr Anaesth Crit Care*. 2002;13:87–91.
17. Ahuja S, Datta A, Krishna A, et al. Infraorbital nerve block for relief of postoperative pain following cleft lip surgery in infants. *Anaesthesia*. 1994;49:441–4.
18. Mayer MN, Bennaceur S, Barrier G, et al. Infraorbital block in early primary cheiloplasty. *Rev Stomatol Chir Maxillofac*. 1997;98:246–7.
19. Bouattour L, Smaoui M, Belhaj S, et al. Infraorbital nerve block for cleft lip surgery. *Anesthesiology*. 2007;24:100.
20. Mariano ER, Watson D, Loland VJ, et al. Bilateral infraorbital nerve blocks decrease postoperative pain but do not reduce time to discharge following outpatient nasal surgery. *Can J Anesth*. 2009;56:584–9.
21. de Ladeira PR, Alonso N. Protocols in cleft lip and palate treatment: systematic review. *Plast Surg Int*. 2012;2012:562892.
22. Wang H, Liu G, Fu W, et al. The effect of infraorbital nerve block on emergence agitation in children undergoing cleft lip surgery under general anesthesia with sevoflurane. *Pediatr Anaesth*. 2015;25:906–10.
23. Aouad MT, Kanazi GE, Siddik-Sayyid SM, et al. Preoperative caudal block prevents emergence agitation in children

- following sevoflurane anesthesia. *Acta Anaesthesiol Scand.* 2005;49:300–4.
24. Dalens BJ, Pinard AM, Létoumeau DR, et al. Prevention of emergence agitation after sevoflurane anesthesia for pediatric cerebral magnetic resonance imaging by some doses of ketamine or nalbuphine administered just before discontinuing anesthesia. *Anesth Analg.* 2006;102:1056–61.
25. Bortone L, Bertolizio G, Engelhardt T, et al. The effect of fentanyl and clonidine on early postoperative negative behavior in children: a double-blind placebo controlled trial. *Paediatr Anaesth.* 2014;24:614–9.