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

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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 (36.67 ± 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.

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Introduction

Cleft lip and palate (CLP) is one of the most common surgical abnormalities requiring surgical treatment in early years of life.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{4} Unilateral or bilateral infra-orbital nerve block has been performed with a very high success rate.\textsuperscript{5,6} Various adjuvant to local anesthetics have been studied to improve the duration of the block.\textsuperscript{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.\textsuperscript{9} Ketamine is widely used as an adjunct to analgesics during the perioperative period.\textsuperscript{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 clinicaltrial.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, thombocytopenia, 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. Auffed 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. 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 25G 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, 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. 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). 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). Statistical analysis

The primary endpoint of this study was the postoperative FLACC Scale scores. Based on previous studies, a target
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–Wilks test. Continuous data were reported as mean ± 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.

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

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.

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

Lower mean postoperative Agitation scale 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.

Figure 3 Postoperative Agitation scale scores in the two studied groups. Lower mean postoperative Agitation scale 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.

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.

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

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.7,8,16,23 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,19 0.5 mL of 0.5% Bupivacaine in each side15 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).6 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 24h postoperatively, (mean time to first request 6.00 ± 0.0 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 INOB 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 INOB 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.22,23 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.3–6 Because pain itself is the source of agitation, some authors reported a positive correlation between EA and pain.22,23 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**


Ketamine in IONB
