Clinical Research

A randomized controlled trial of infraorbital block using ketamine 1% for intra- and postoperative analgesia in children for ambulatory cleft lip correction

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ABSTRACT

BACKGROUND In Indonesia, cleft lip correction surgery is often done as a social program in remote areas with limited resources. This study aimed to assess the effectiveness of ketamine, a cheaper and more accessible alternative, as a local analgesia in infraorbital block and to determine the possibility of ketamine as an alternative local analgesic drug for intraoperative and postoperative periods.

METHODS This was a randomized controlled trial in children aged 2 months to 5 years who underwent cleft lip correction surgery at Cipto Mangunkusumo Hospital in 2016. Subjects were randomly divided into two groups: ketamine and bupivacaine. Standard general anesthesia with endotracheal intubation was performed in each group. Bilateral intraoral infraorbital block was performed using ketamine 1% 0.5 ml or bupivacaine 0.25% 0.5 ml. Postoperative evaluation includes pain scores based on the face, leg, activity, cry, and consolability (FLACC) scale and analgesic duration.

RESULTS A total of 36 subjects were enrolled in this study, with 18 in each group. Both groups received the same total amount of fentanyl addition intraoperatively ($p = 1$). The postoperative FLACC pain scale scores between the two groups were not different, with $p>0.05$ in every measurement. The mean duration of postoperative analgesia in the ketamine group was longer than the bupivacaine group (15–13.49 hours, $p = 0.031$).

CONCLUSIONS Infraorbital block with 1% ketamine 0.5 mg/kg was similarly effective for intraoperative and postoperative analgesia but had a longer duration than that with 0.25% bupivacaine 0.5 ml in ambulatory cleft lip correction.

KEYWORDS cleft lip, ketamine, postoperative pain

Cleft lip is a common congenital abnormality that requires surgery for correction.[1] Cleft lip correction surgeries are usually ambulatory cases; therefore, modifications are done with anesthesia procedures so patients could recover quickly in a safe and comfortable state.[1,2] Cleft lip correction and other surgeries involving the lower eye lid, cheek, upper lip, and nostrils may cause intense intraoperative and postoperative pain in children.[1,2] Significant postoperative pain can cause harm as it disturbs the initiation of early oral intake and prolongs patients' recovery time. Proper pain management minimizes harm toward patients as it is correlated with a rapid recovery and early ambulation.[3]

Several studies have reported the use of infraorbital block combined with a general anesthesia as postoperative pain management in cleft lip correction surgery.[3–5] Currently, general anesthesia combined with an infraorbital block is the recommended anesthesia procedure for cleft lip correction surgery for patients

in both hospitals and remote areas. Infraorbital block procedure has two approaches (intraoral and extraoral) and is relatively easy to perform with minimal complications. Its effectiveness in managing postoperative pain is an advantage, considering that it overcomes the risk in cleft lip correction surgery.[2–4] In developing countries such as Indonesia, cleft lip correction is often performed as a social charity program in remote areas where medicine, equipment, and resources are limited. Furthermore, bupivacaine, the standard local analgesic agent for infraorbital neural block, is not readily available.

In several studies, ketamine in subanesthetic doses was shown to perform well in inhibiting pain caused by the activation of the *N*-methyl-d-aspartate (NMDA) receptor and decreasing the brain activity that responds to pain stimulation.[6,7] Therefore, ketamine appears as a promising analgesic modality in pain management strategy. The local analgesic mechanism of ketamine is still under debate as current studies are mostly in animals.[7] However, it is agreed that there is a similarity that ketamine also works by inhibiting sodium channel opening in the surface membrane of peripheral nerve cells, which eventually inhibits depolarization and decreases pain impulse conduction. Although it has not been widely accepted, ketamine as an alternative local anesthetic agent is cheaper and more readily available in remote areas but has not been widely accepted since only a few studies support it as a local analgesic agent. This study aimed to compare the effectiveness of infraorbital block using bupivacaine 0.25% with ketamine 1% for postoperative pain management in cleft lip correction surgeries.

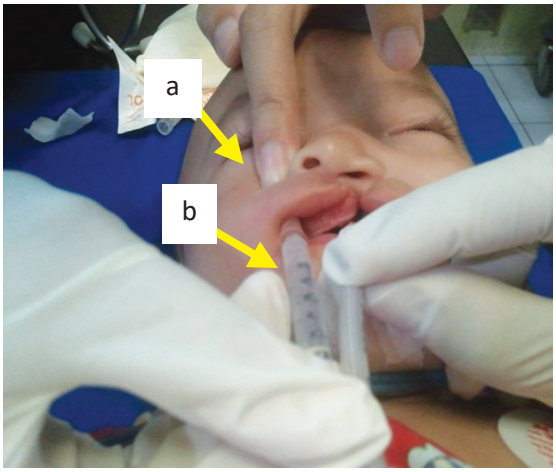

Figure 1. Infraorbital block using the intraoral approach. The procedures are: place the patient's head in a sniffing position by placing a roll below the shoulder; apply antiseptic using a cotton-tipped applicator to the oral mucosa of the gum line above the maxillary canine; locate the infraorbital foramen approximately 1 cm below the middle of infraorbital ridge using the index finger (a); insert a 3-cm 25G needle with 1 ml syringe filled with local anesthetic into the mucosa above the maxillary canine and directed superiorly toward the infraorbital foramen until it is palpated near the foramen (b); aspirate the syringe before injecting the local anesthetic; avoid injecting the anesthetic into the foramen

METHODS

This was an experimental study with a simple randomized, single-blinded clinical trial. The study was conducted in the operating room of Cipto Mangunkusumo Hospital, Jakarta in 2015 after being approved by the Health Research Ethics Committee of Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital (No: 305/H2.F1/ETIK/2014).

The inclusion criteria were children aged 2 months to 5 years who were classified as American Society of Anesthesiologists physical status I–II, had no other craniofacial abnormalities, and were consented by their parents. Exclusion criteria were children with a history of allergy to bupivacaine, ketamine, and or other anesthetic agents, which were used in sedation, and those undergoing surgical recorrection for a previous surgery. The drop-out criteria were the presence of blood during aspiration while performing the infraorbital block (which is a sign of intravenous penetration), severe intraoperative complications that require resuscitation intervention (cardiac arrest), bleeding that indicates a resurgery, and surgery duration of more than 2 hours.

The sample size was determined using unpaired two groups numerical comparative analytical formula in which 18 samples were calculated in each group. Pediatric patients with cleft lip who fulfilled the inclusion criteria were randomly divided into two groups using www.randomizer.org. All subjects were induced using sevoflurane, given 1 mcg/kg fentanyl, and intubated. We performed a bilateral infraorbital block in the bupivacaine group using bupivacaine 0.25% 0.5 ml for each side. Infraorbital block for the ketamine group was performed using 0.5 ml ketamine 1% for each side (ketamine 10% was diluted with NaCl.) The infraorbital block was performed using the intraoral approach (Figure 1).

For surgical purposes, the infiltration of adrenaline 1:200,000 in normal saline was performed

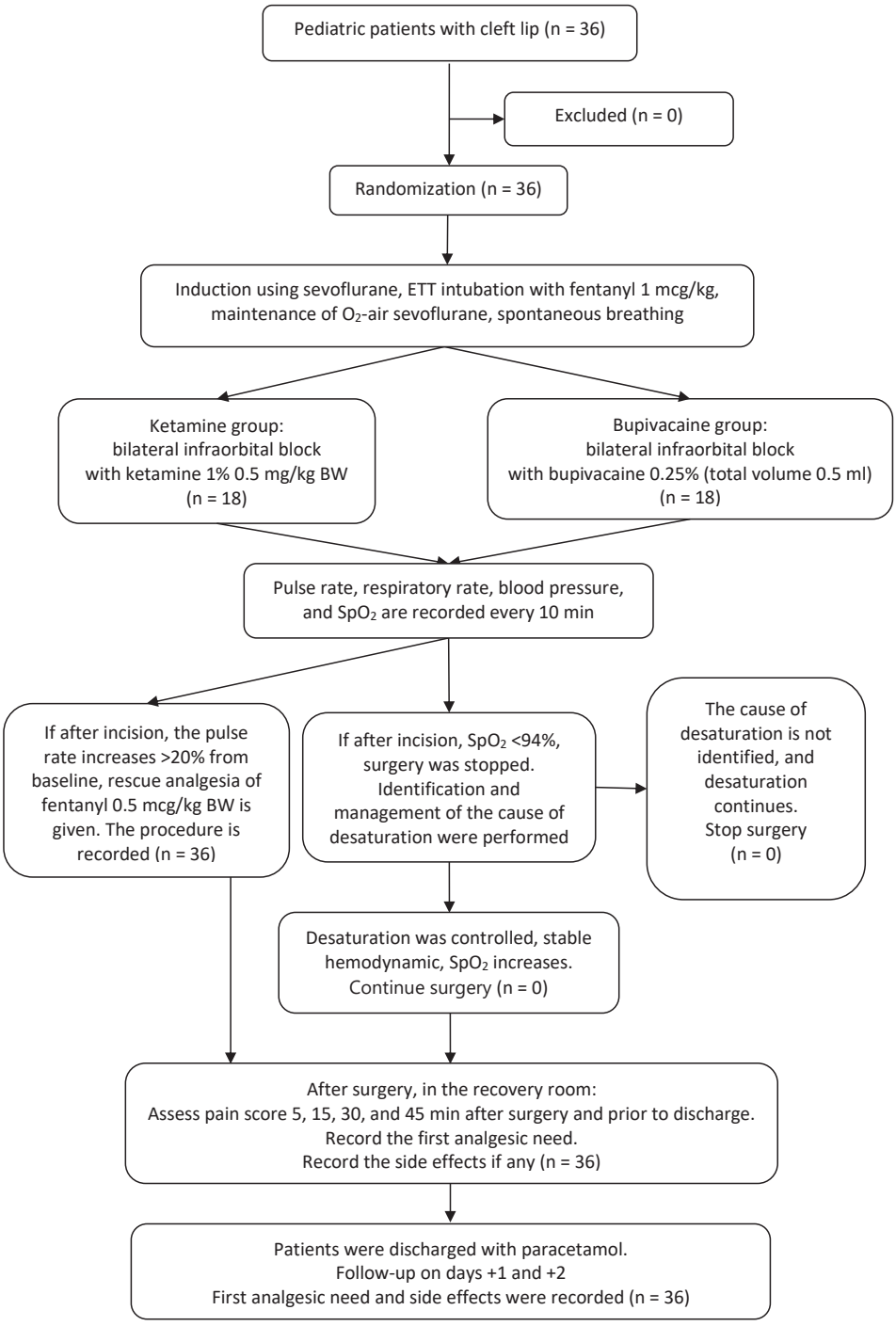

Figure 2. Study framework.
BW=body weight;
ETT=endotracheal tube

in the region of cleft repair. After surgery, the patients were evaluated in the recovery room using the face, leg, activity, cry, and consolability (FLACC) pain scoring system 5, 15, 30, and 45 min after surgery. The scoring was rated and documented by an author who was blinded to the procedure. Rescue analgesia was given if the FLACC score was ≥4 (recorded as the first analgesic need). After the subjects were discharged, we performed telephone follow-up on the next day to determine whether the subjects needed postoperative rescue analgesia of paracetamol syrup 15 mg/kg body weight (BW). Their mothers were informed to identify pain in children. If the children kept crying inconsolably, looked tense, or flexed their extremities, they were assumed as having pain and given rescue analgesia of paracetamol 15 mg/kg BW was given. We asked the parents to record the time when they give the analgesic drug to the patient. The time when the patients need the first analgesic agent reflected the duration of action of local anesthetic that has been

given in the study. The side effect was assessed when subjects were still in the recovery room and during follow-up on day +1 by telephone interview with their mothers. The side effects observed were nausea/vomiting, hallucination/agitation, hypersalivation, and bleeding/hematoma. An illustration of the study framework is depicted in Figure 2.

Data acquired were then analyzed using SPSS software version 20.0.0 (IBM Corp., USA). Analysis of pain scale was done using unpaired *t* and Mann–Whitney *U* tests for normally and not normally distributed data, respectively. Statistical analysis was determined to be significant when $p<0.05$.

RESULTS

This study was conducted on 36 subjects undergoing cleft lip correction surgery. A simple randomization was performed. The general (gender, age, and weight) and additional (cleft palate type) characteristics of the subjects in this study are presented in Table 1.

After infraorbital block was performed, hemodynamic assessment was taken during the procedure. If an increase of 20% from baseline in pulse rate and blood pressure was found, subjects were assumed as having pain and were given rescue analgesia of intraoperative fentanyl 0.5 mcg/kg. Two subjects in both the bupivacaine and ketamine groups received rescue an analgesia and an additional fentanyl intraoperatively ($p = 1$). After the surgery was performed and the subject regained consciousness, postoperative pain was assessed in the recovery room using the FLACC score system. Pain scoring was conducted 5, 15, 30, and 45 min after patients regained consciousness from general anesthesia.

Table 1. Characteristics of the subjects

Characteristics	Ketamine (N = 18)	Bupivacaine (N = 18)	Total (N = 36)
Male sex, n (%)	8 (44)	12 (67)	20 (56)
Weight (kg), mean (SD)*	6 (1.39)	5.8 (1.29)	5.9 (1.33)
Age (months), mean (SD)*	5.4 (2.77)	4.4 (1.72)	4.9 (2.33)
Type of cleft lip, n (%)			
Complete bilateral	3 (16.7)	8 (44.4)	11 (30.6)
Complete unilateral	3 (16.7)	2 (11.1)	5 (13.9)
Incomplete unilateral	12 (66.3)	8 (44.4)	20 (55.6)

SD=standard deviation
*Shapiro–Wilk normality test

Table 2. Comparison of FLACC pain scores (N = 36)

FLACC	Ketamine, median (min–max)	Bupivacaine, median (min–max)	*p*
5 min	3 (2–4)	3 (3–4)	0.324
15 min	3 (2–3)	2 (2–3)	0.189
30 min	2 (1–3)	2 (1–3)	0.714
45 min	2 (1–2)	2 (1–2)	0.074

FLACC=the face, leg, activity, cry, and consolability

Both the bupivacaine and ketamine groups observed cases of FLACC pain score of <4, which is considered mild pain and did not require postoperative rescue analgesia. The Mann–Whitney *U* test was used to compare the pain scores of both groups, and no significant difference was observed (Table 2).

The bupivacaine group had a shorter postoperative analgesic duration (12.39 ± 2.82 hours) than the ketamine group (15.00 ± 4.05 hours). This difference, which was calculated using unpaired *t*-test, was statistically significant, with a *p*-value of 0.031.

During the observation, all subjects from both groups did not exhibit any side effects, such as nausea/vomiting, hallucination/agitation, hypersalivation, and bleeding/hematoma.

DISCUSSION

In this study, we demonstrated that bilateral infraorbital block using ketamine 1% is comparable with bupivacaine 0.25% for postoperative pain management in cleft lip correction surgery. Both groups required less additional fentanyl. The FLACC score showed only mild pain in both groups, and the ketamine group showed a significantly longer analgesic duration. Pain is defined as a sensory experience and emotional discomfort correlated with tissue injuries. From this definition, we can conclude that there is a connection between objective (physiologic aspect) and subjective (emotional and mentality aspect) factors. From the physiologic aspect, the age of the study subjects was between 2 and 12 months, which was categorized as infants. This could minimize the bias of subjective factors, such as educational degree, culture, situation meaning, and cognitive activities toward pain perception.

To assess a postoperative pain in this study, we observed the additional administration of

intraoperative fentanyl, postoperative FLACC pain score, and postoperative analgesic duration. During the observation, we found that two subjects of each group needed an additional fentanyl after incision. However, the comparison of both results did not show any significant differences. The additional intraoperative fentanyl, which was reported as pain after incision, might be caused by the late onset of infraorbital block that was performed before the intervention.

The onset of local analgesia depends on its lipid solubility and dissociation constant (pKa). The hydrophilicity of local analgesia comes from their structural domain, which is an aqueous solution, and local analgesia exists in ionized and nonionized forms. The ratio of ionized and nonionized forms is predicted on the pKa. Local analgesia with pKa whose pH is closer to the physiologic pH (pH 7.4) will have a local analgesic concentration with more nonionized form, which makes it easier to penetrate the cell membrane, hence decreasing the onset time. Bupivacaine has pKa of 8.1 and has an onset of 15–20 min, whereas ketamine has pKa of 7.5 and has a faster onset.[8]

Postoperative analgesic effectiveness has been observed by assessing the pain scale objectively on subjects. However, in this study, the FLACC score was preferred because the subjects were in their preverbal ages (2 months to 2 years) and were unable to communicate the pain.[9] The FLACC scoring system that is a behavioral pain tool associated with pain in preverbal children and adults with a cognitive impairment has an excellent reliability and validity.[9,10] The FLACC score is used as a standard of care for pain assessment in patients aged 1 month to 5 years in our institution; hence, the staff of pediatric pain services were more familiar with this scoring system. To ensure the validity of score, one experienced anesthesiologist was assigned to score all subjects. Pain assessment was done in the recovery room 5, 15, 30, and 45 min after patients regained consciousness (Table 2). The FLACC scores in both groups were <4 or were categorized as mild pain and did not require any postoperative rescue analgesia. The result of the comparison between the two groups did not show any significant differences (Table 2).

This was the first study of infraorbital block using only ketamine as the local anesthetic agent. However, the local anesthetic properties of ketamine are still debatable. Some studies have shown the effectiveness of ketamine as an intravenous regional anesthetic agent.[7] Ketamine, given orally as a gargle, throat swab, and peritonsillar injection, produced analgesia without any systemic symptoms.[11]

In this study, the subjects in the ketamine group showed mild postoperative pain (FLACC score <4). Ketamine administration by an infraorbital block in cleft lip correction surgery provides a postoperative analgesic effect. This result supports the theory that ketamine can be used as a local analgesia, despite it is commonly used in intravenous, intramuscular, intranasal, or topical routes. The comparison between the bupivacaine and ketamine groups was not statistically significant, which showed that neither of the drugs was a more superior postoperative analgesic agent. Ketamine can be considered an alternative for bupivacaine of infraorbital block with similar effectiveness.

Observing the postoperative analgesic duration was done to assess the effectiveness of postoperative analgesia. The mean analgesic durations of the ketamine and bupivacaine groups were 15 and 12.39 hours, respectively, showing that ketamine has a longer mean duration of action as postoperative analgesia than bupivacaine. This study demonstrated a significant duration of analgesic effects in the ketamine group. We could not find any previous study that showed the same result. However, a study by Grewal et al[12] showed that the analgesic effect of bilateral infraorbital block using bupivacaine 0.25% lasted for about 6 hours compared with the 12 hours of the bupivacaine group in this study.

There were no side effects observed in each group. This could be due to the low dose of ketamine used in this study, whereas the psychomimetic side effects (hypersalivation and hallucination) were dose dependent. By using low dose, the risk of side effects was minimal or almost none.[7] On the other hand, the result showed that the use of ketamine as a local anesthesia did not extend systematically.[13]

Ketamine's analgesic mechanism on the peripheral nerves has not been completely understood; however, this derivative of phenylcyclohexyl piperidine works in several different target receptors. This explains the analgesic effect can be obtained by the administration of ketamine through different routes (intravascular, topical, or local analgesia). Ketamine works as an NMDA receptor antagonist with a critical role in the nociceptive process. The analgesic effect of ketamine

can be produced from its activity as a mu-opioid receptor agonist and from its interaction with a voltage-sensitive sodium channel.[14] Ketamine's local analgesic effect in infraorbital block may also be caused by its effect on inhibiting the release of local proinflammatory substances during incision or dissection. This theory is in concordance with a previous study by Li et al[15] that the use of reported that ketamine was found to suppress inflammatory mediators, such as tumor necrosis factor-alpha, interleukin-6, nuclear factor-kappa B's activity, and toll like-receptor 4's expression in rat models in a state of injury.

In this study, we did not analyze the pain score based on the cleft anomaly types (unilateral or bilateral and complete or incomplete cleft) because the number of subjects was insufficient and not equal. The different anomaly types might cause different pain scores because they underwent various surgical techniques that will lead to different tissue injury levels. However, we performed bilateral infraorbital blocks that will work in each cleft type.[16]

In our center, all patients with cleft lip surgery were performed as an ambulatory surgery in accordance to the institution's standard of care. Postoperative data were achieved by conversations with parents or caregivers, prohibiting direct patient observations after they were discharged from the hospital. The study assessed the postoperative analgesic duration and side effects by asking the parents or caregivers at home who were taught to identify signs of pain and side effects of drugs using written materials that were given before discharge. However, this method still could not give objective results since parents' education level and understanding need to be considered.

In conclusion, ketamine has similar effects with bupivacaine for infraorbital block in managing postoperative pain on cleft lip correction; hence, it has a longer postoperative analgesic duration without systemic side effects. Therefore, ketamine can be considered an alternative of bupivacaine as a local analgesic agent in infraorbital block for cleft lip surgery.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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