

Clonidine as an Adjuvant to Bupivacaine for Suprazygomatic Maxillary Nerve Blocks in Cleft Lip and Palate Repair: A Randomized, Prospective, Double-Blind Study

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Abstract

Objectives: Does clonidine, as adjuvant to bupivacaine for suprazygomatic maxillary nerve blocks, reduce emergence agitation in patients undergoing cleft lip and cleft palate surgery?

Design: Randomized, controlled, and double-blind study.

Setting: Guwahati Comprehensive Cleft Care Center, Guwahati (Assam, India).

Participants: A total of 124 patients; with a median age of 5 years in the clonidine group (CLG) and 7 years in the control group (CG), who underwent cleft lip or cleft palate surgery were included. Exclusion criteria included lack of consent from patients or their guardians, allergy to local anesthetics, coagulation disorders, local infection at the puncture site before performing the block, and language difficulties or cognitive disorders.

Interventions: Patients were randomized into 2 groups to receive bilateral suprazygomatic maxillary nerve blocks with either a bupivacaine/clonidine mixture for the CLG or bupivacaine alone in the CG.

Main Outcome Measure: The primary end point was the incidence of emergence agitation. Results: There was a statistically significant difference in the incidence of emergence agitation (30.2% in the CG compared to 15.2% in the CLG; difference of incidences: 15%, 95%CI: 0.1 – 30.1). The percentage of patients requiring intraoperative Fentanyl was lower in the CLG (10.6% compared to 26.4%; difference of incidences: 15.8%, 95%CI: 1.8 – 29). No other differences were observed. Further research in a more typically aged children population undergoing cleft surgery is needed.

Conclusions: The use of clonidine as an adjuvant to bupivacaine in maxillary nerve block reduces the incidence of emergence agitation and intraoperative opioid consumption without hemodynamic or sedative side effects in patients undergoing cleft lip and palate surgery.

Keywords

cleft surgery, double-blinded method, maxillary nerve block, clonidine, emergence agitation

Introduction

Cleft lip and cleft palate are the most common craniofacial abnormalities in children (Liau et al., 2010). Cleft surgery results in a profound sympathetic stimulation leading to hypertension, tachycardia, and bleeding. Postoperative pain can be severe, and many of these patients are at increased risk of opioid-induced respiratory depression (Roulleau et al., 2003; Augsornwan et al., 2011; Kulkarni et al., 2013; Reena and Abhijit, 2016). Emergence agitation (EA) is another common problem in these children, with an incidence between 10% and 80% after sevoflurane anesthesia (Welborn et al., 1996). Inadequate postoperative analgesia combined with vigorous crying may lead to surgical complications including wound dehiscence, bleeding, and respiratory compromise (Takemura et al., 2002; Antony and Sloan, 2002; Roulleau et al., 2003; Augsornwan et al., 2011). The anesthetic management of cleft surgery should ideally bound the intraoperative autonomic response and provide adequate analgesia without respiratory depression or EA. A combination of inhalation-based anesthesia and high-dose opioids has been described to block the autonomic response during surgical dissection; however, this technique may be associated with postoperative sedation and respiratory depression. Surgical infiltration with a local anesthetic and a vasoconstrictor promotes hemostasis and reduces the autonomic response intraoperatively but does not provide extended postoperative pain relief (Muthukumar et al., 2012; Kinsella et al., 2014). Sensory innervation of the lip and palate is provided by branches of the maxillary nerve (Hu et al., 2006; Hu et al., 2007; Somayaji and Rao, 2012). Suprazygomatic maxillary nerve blocks have been shown to be opioid-sparing after cleft lip and palate surgery (Chiono et al., 2014; Echaniz et al., 2019). The addition of an $\alpha - 2$ agonist might both prolong the analgesia after a regional nerve block (Cucchiari and Ganesh, 2007; Jindal et al., 2011) and reduce the incidence of EA. Clonidine has been administered orally, intravenously, and as an adjuvant in caudal blocks to reduce EA in children (Kulka et al., 2001; Bock et al., 2002; Malviya et al., 2006). The effect of clonidine as an adjuvant for the suprazygomatic maxillary block has never been evaluated. Intravenous dexmedetomidine has been shown to reduce the incidence of EA after pediatric cleft palate surgery (Surana et al., 2017). This prospective, randomized double-blind study evaluated the use of an intraoperative suprazygomatic maxillary nerve block with a bupivacaineclonidine mixture or with bupivacaine alone in a mixed pediatric-adult population undergoing cleft lip and palate surgery. The primary end point was the incidence of EA after sevoflurane anesthesia. Secondary end points included intraoperative and postoperative hemodynamics, pain scores, intraoperative and total opioid use, postanesthesia care unit (PACU) discharge times, and possible nerve block-related complications.

Material and Methods

This parallel, randomized, double-blind study was conducted in Assam, India, and it adheres to the principles of good clinical practice and the ethical principles in the Declaration of Helsinki. The study protocol was approved by the Operation Smile India Institutional Ethics Committee, Mumbai, India (Chairperson: Dr Rajeev Kapur) on March 19, 2014, with permission of Operation Smile International, and written informed consent was obtained for all patients before randomization.

We approached to consent all patients aged 6 months and older who were scheduled for cleft lip or cleft palate surgery under general anesthesia (GA) between September and October 2014. Exclusion criteria included lack of consent from patients or their parents, allergy to local anesthetics, coagulation disorders, local infection or lesion at the proposed puncture site before performing the block, language difficulties, or cognitive disorders.

Sedative premedication was not given to any of the patients. Standard ASA monitoring (ECG, pulse oximetry, noninvasive blood pressure [BP], capnography, and temperature) was used for all patients. Anesthesia was induced with sevoflurane (6% – 8% inspired in 100% oxygen) or intravenous propofol (2 – 5 mg · kg⁻¹) and fentanyl (1 – 2 μg · kg⁻¹) and it was maintained with sevoflurane 1.5% to 2.0% inspired in 100% oxygen. Airway was secured using an RAE tube.

Spontaneous ventilation was maintained and supported when necessary to maintain ETCO₂ between 30 and 35 mm Hg . Paracetamol either rectally ($40\text{mg} \cdot \text{kg}^{-1}$) after tracheal intubation or orally ($15\text{mg} \cdot \text{kg}^{-1}$) before anesthesia induction, and dexamethasone 0.1 to 0.2 $\text{mg} \cdot \text{kg}^{-1}$ (maximum 8 mg) were given as part of multimodal analgesia. Patients were randomized after anesthesia induction by a trained nurse not involved in the perioperative patient care and using a computerized randomized sequence in a 1: 1 ratio in 2 parallel arms to receive bilateral suprazygomatic maxillary nerve blocks with either a bupivacaine clonidine mixture (clonidine group [CLG]) or bupivacaine alone (control group [CG]). Following aseptic preparation of the skin, the suprazygomatic maxillary nerve blocks were performed by an independent anesthesiologist not involved in the intraoperative management nor in the postoperative patient care, using a 27 gauge 38 – mm needle according to the technique previously described by these authors (Echaniz et al., 2019). The needle was first inserted at the frontozygomatic angle, perpendicular to the skin, and advanced until the greater wing of the sphenoid was contacted. The needle was then partially withdrawn, reoriented in an anterior inferior direction (20° anterior and 10° inferior) and advanced 35 to 38 mm . Local anesthetic solution was injected following negative aspiration; $0.15 \text{ mL} \cdot \text{kg}^{-1}$ (maximum of 5 mL per side). The CG received bupivacaine 0.25% with epinephrine 1:200 K. Clonidine $3\mu\text{g} \cdot \text{kg}^{-1}$ (maximum $150\mu\text{g}$) was added to the anesthetic solution in the CLG. Lidocaine 1% with epinephrine 1: 200 K (maximum $5\text{mg} \cdot \text{kg}^{-1}$ of lidocaine) was infiltrated by the surgeon at the surgical area to improve surgical hemostasis for all cases. Surgical incision was delayed for 10 minutes after infiltration in order to differentiate increased BP and heart rate (HR) resulting from epinephrine or pain. Patient characteristics, type and duration of surgery, block-related complications, intraoperative hemodynamics, EA, and intra and postoperative opioid consumption were recorded.

The child is calm	1
The child is crying, but can be consoled	2
The child is crying, and cannot be consoled	3
The child is agitated and thrashing around	4

Figure 1. Watcha Scale. A child with a score of > 2 can be considered to have emergence delirium.

Fentanyl $0.5\mu\text{g} \cdot \text{kg}^{-1}$ intravenous (IV) was given to treat elevations in BP or HR ($>20\%$ above baseline) which was repeated after 5 minutes if hemodynamics did not improve. After 2 doses of Fentanyl, 50 to $100\mu\text{g} \cdot \text{kg}^{-1}$ of intravenous nalbuphine were administered if tachycardia or hypertension were persistent. After pharyngeal suctioning and recovery of airway-protective reflexes, patients were extubated awake in the operating room and transferred to PACU. Propofol $1\text{mg} \cdot \text{kg}^{-1}$ IV was given to treat EA immediately after extubation. Postoperative pain management was in charge of trained nurses and the pediatricians who were blinded to the study arms. Alternating doses of oral paracetamol ($15\text{mg} \cdot \text{kg}^{-1}$ every 8 hours) and ibuprofen ($10\text{mg} \cdot \text{kg}^{-1}$ every 8 hours) were given for postoperative analgesia. Intravenous nalbuphine ($50\mu\text{g} \cdot \text{kg}^{-1}$) was given every 15 minutes as rescue analgesia until pain score was $\leq 3/10$. The FLACC scale (Face, Legs, Activity, Cry, Consolability) was used to assess pain intensity in pediatric patients unable to report pain for themselves. In older patients, pain was assessed using a numerical scale from 0 to 10 or by visual analog scale, depending on patient characteristics. Trained nurses scored the child's level of agitation using the WATCHA Scale every 15 minutes, during the first 45 minutes post anesthesia. The Watcha Scale is a 4-point scale (Figure 1) with the highest overall sensitivity and specificity. A child with a score of > 2 can be considered to have EA or delirium (Bajwa et al., 2010). All other assessments were performed every 15 minutes

during the first hour, every 30 minutes until the patient was discharged from PACU, and every 4 hours during the first 24 hours postoperatively. Residual block-related complications were assessed at a 30 -day follow-up visit. Patients, nurses, and the clinical investigator were blinded to the type of anesthetic solution used during the procedure.

Statistic Analysis

The primary end point was the incidence of EA. Based on Ghai's study (Ghai et al., 2010), a 22.4% difference was estimated in the percentage of patients having agitation after sevoflurane anesthesia between the CLG and CG groups. Assuming a 2 -sided type I error protection of 0.05 and a power of 80%, a simple size of 42 patients per treatment group was needed for this study. Assuming a dropout rate of 20%, a total sample size of 104 patients (52 per treatment group was planned). Secondary end points included pain scores, perioperative opioid consumption, hemodynamic response, respiratory, and nerve block-related complications during the first 24 hours. Continuous data were expressed as mean and standard deviation, or median and interquartile range (IQR) where appropriate, and frequencies and percentages (%) for categorical data. A Pearson χ^2 test or Fisher exact test was used to analyze the possible relationship between qualitative variables. Student *t* test or Mann Whitney *U* test was used, as appropriate, to study the relationship between a quantitative variable and a dichotomous qualitative. Analysis was performed by intention-to-treat and per-protocol analysis. Values of $P < .05$ were considered significant. SPSS 14.0 statistical package (IBM Corp) was used for statistical analysis.

Results

This article adheres to the applicable CONSORT guidelines. Five of the 124 patients enrolled were excluded; one of them for postoperative bleeding and 4 due to incomplete documentation. Of the 119 patients analyzed, 66(55.5%) were in the CLG (37 cleft lip and 29 cleft palate) and 53 (44.5%) in the CG (28 cleft lip and 25 cleft palate; Figure 2). The median (IQR) age was 5 (16) years in the CLG and 7 (18) years in the CG, respectively, $P = .809$. In the CLG group, 66.6% of the patients were male compared to 39.6% in the CG, $P = .003$. There was a statistically significant difference in the incidence of EA (30.2% in the CG vs 15.2% in the CLG; difference of incidences: 15%, 95%CI: 0.1 to 30.1 ; Figure 3). In a subgroup analysis of patients 5 years old or younger, the incidence of EA was 52% in CG compared to 30.3% in CLG; difference of incidences: 21.7%(95%CI: -3.4 to 47) and this trend was independent of the type of surgery (37.5% vs 11.1% in patients with cleft palate; difference of incidences: 26.4%, 95% CI: -12.9 to 65.7 , and 58.8% vs 37.5% in patients with cleft lip; difference of incidences: 21.3%, 95%CI: -9 to 51.7 ; for CG and CLG, respectively). A subgroup analysis of patients aged ≤ 1 year has also been performed, and data are shown as additional information (Supplemental material).

None of the patients older than 10 years had EA in the CLG compared to 10.7% in the CG (difference of incidences: 10.7%, 95%CI: -0.7 to 22). In the intraoperative period, there was a statistically significant difference in fentanyl use (10.6% in the CLG compared to 26.4% in the CG; difference of incidences: 15.8%, 95%CI: 1.8 - 29). There was a trend toward a difference in total perioperative opioid consumption (22.7% in the CLG compared to 37.7% in the CG; difference of incidences: 15%, 95%CI: -1.5 to 31.5). There were no differences between groups in the time to discharge readiness from PACU. Most of the patients were calm and cooperative or easily consolable in both groups during their ward admission. There were no other statistically significant differences (Table 1). Pain scores were less or equal to 3 during the first 24 hours in both groups, and there were no statistically significant differences between them. Subgroup analysis of the patients with cleft palate showed a statistically significant difference in total perioperative opioid consumption (48% in CG compared to 17.2% in CLG; difference of incidences: 30.8%, 95% CI: 6.8-54.7) and the intraoperative fentanyl consumption (40% in CG compared to 10.3% in CLG; difference of incidences: 29.7%, 95% CI: 7.5-51.8). In patients with cleft palate specifically, there was a trend toward a difference in EA (20% in CG compared to 3.4% in CLG; difference of incidences: 16.6%, 95%CI: -0.5 to 36.6). After cleft lip repair, 28.6% of the patients required extra analgesia during the perioperative period in CG compared to 27% in

CLG (difference of incidences: 1.6%, 95%CI : -20.5 to 23.6), and there was also a trend toward a difference in EA (39.3% in the CG compared to 24.3% in CLG; difference of incidences: 15%, 95%CI: -7.8 to 37.7). No other statistically significant differences between groups were found (Table 2). The percentage of patients not needing analgesic during intraoperative and postoperative periods is shown in Figure 4. No technical failures or block-related complications were reported.

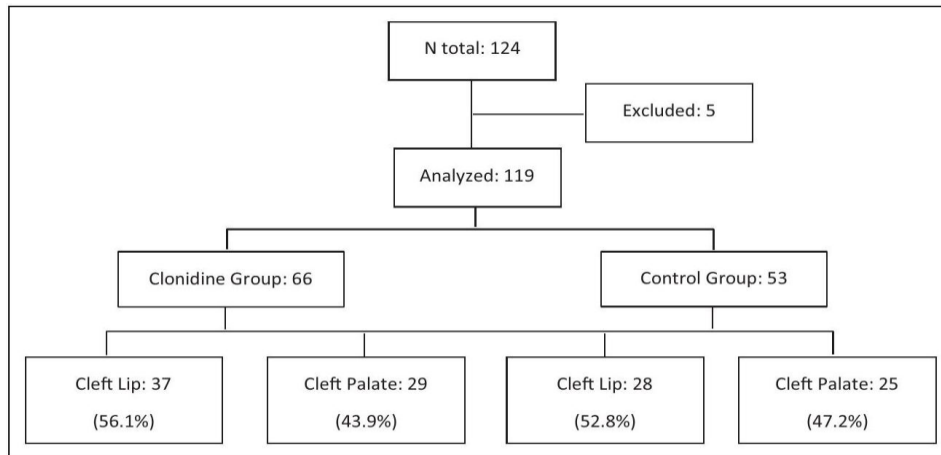


Figure 2. Flowchart of the study. Number of patients analyzed and their distribution according to the intervention group and type of cleft.

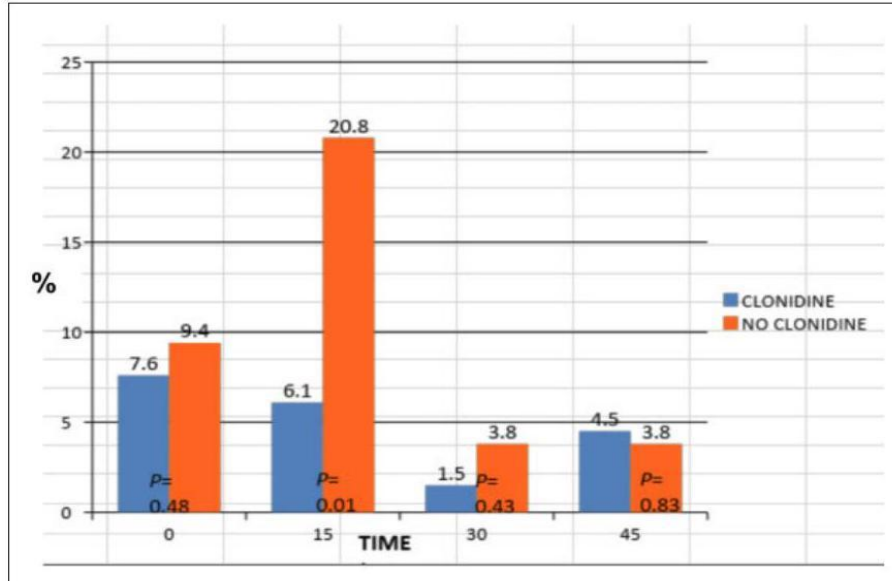


Figure 3. Percentage of patients having emergence agitation during early perioperative period. Incidence of emergence agitation during the first 45 minutes after extubation.

Discussion

Emergence agitation is a poorly understood phenomenon, and a variety of possible causes have been implicated such as sevoflurane, pain, anxiety, temperament, psychological immaturity,

genetic predisposition, and disorientation on rapid awakening (Vlajkovic and Sindjelic, 2007; Silva et al., 2008). Additionally, an imbalance of neurotransmitters such as dopamine, acetylcholine, and serotonin, or an anesthesia-related depression of inhibitory centers in the central nervous system has also been suggested as potential causes. Several studies have shown that administration of clonidine or dexmedetomidine significantly reduces the incidence of EA in children (Kulka et al., 2001; Bock et al., 2002; Ibacache et al., 2004; Guler et al., 2005; Peng and Zhang, 2015). Peng and Zhang (2015) reported an incidence of 15%EA in those who received continuous intravenous infusion of dexmedetomidine compared to 90% undergoing cleft palate repair in the CG. In our study, the overall incidence of EA was 15.2% and 30.2% ($P = .048$) for the CLG and CG, respectively. The lower incidence of EA in our study might reflect the benefit of our multimodal analgesia, including the use of regional anesthesia. Different mechanisms have been hypothesized to explain the beneficial effect of $\alpha - 2$ agonist agents in preventing EA. Clonidine is a mixed $\alpha - 1$ and $\alpha - 2$ adrenoceptor agonist with a predominant $\alpha - 2$ action. It reduces peripheral norepinephrine release and ultimately terminates the propagation of pain signals. However, studies evaluating the effect of clonidine or dexmedetomidine in patients who received GA for nonpainful procedures or for procedures under GA supplemented with nerve blocks also demonstrate a reduction in EA (Kulka et al., 2001; Bock et al., 2002; Ibacache et al., 2004; Malviya et al., 2006; Isik et al., 2006). Alpha-2 agonists also decrease the noradrenergic output from the locus coeruleus, thereby facilitating inhibitory neurons that play an important role in their sedative and anxiolytic effects (Tobias et al., 2003), and they appear to be analgesic and opioid-sparing as a component of anesthesia for cleft lip and palate repair. Xu et al. (2012) found that a loading dose of $1\mu\text{g} \cdot \text{kg}^{-1}$ followed by a maintenance dose of $0.75\mu\text{g} \cdot \text{kg}^{-1}$ had decreased pain scores and discharge time in patients undergoing cleft lip and palate surgery. Surana et al. (2017) demonstrated that a loading dose of $1\mu\text{g} \cdot \text{kg}^{-1}$ and an infusion of $0.5\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ reduced intraoperative opioid and volatile anesthesia requirements, and prolonged the time to first postoperative rescue analgesic with similar PACU discharge times.

Table 1. Patient Characteristics, Opioid Consumption, and Perioperative Complications.

Parameters	Clonidine group (N = 66)	Control group (N = 53)	
Sex (male)	44 (66.6%)	21 (39.6%)	.003
Age			
Median in years (IQR)	5 (16)	7 (18)	.809
≤ 5 years	N = 33 (50%)	N = 25 (47.2%)	.759
Median in months (IQR)	15 (27)	12 (18)	.550
Surgery duration (minutes)			
Cleft type (lip)	37 (56.1%)	28 (52.8%)	.725
Extra opioids	15 (22.7%)	20 (37.7%)	.074
Fentanyl extra	7 (10.6%)	14 (26.4%)	.025
Nalbuphine extra OR	2 (3%)	4 (7.5%)	.263
Rescue propofol	10 (15.2%)	10 (18.9%)	.590
% Lowest BP OR, mean (SD)	19.06 (9.8)	17.1 (11)	.312
% Lowest HR OR, median (IQR)	11.5 (14)	9 (11)	.562
Nalbuphine PACU	10 (15.2%)	9 (17%)	.787

PONV	1 (1.5%)	1 (1.9%)	. 875
SpO ₂ < 95%	3 (4.5%)	5 (9.4%)	. 290
Length of PACU stay (min)	45 (30-60)	45 (30-45)	. 240
Watcha >2	10 (15.2%)	16 (30.2%)	. 048
Ward Nurses Observation			. 542
Calm/cooperative	53 (80%)	39 (73.6%)	
Easily consolable	11 (16.7%)	13 (24.5%)	
Mostly unhappy	2 (3%)	1 (1.9%)	

Abbreviations: BP, blood pressure; HR, heart rate; IQR, interquartile range; OR, operating room; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; SD, standard deviation.

Obayah et al. (2010) showed that dexmedetomidine added to bupivacaine for a palatine nerve block, significantly reduced pain scores and prolonged the time to first analgesic request when compared with bupivacaine injection alone. Jindal et al. (2011) showed that addition of clonidine to bupivacaine in bilateral infraorbital nerve block, significantly decreased the requirement of other anesthetic drugs and prolonged the duration of postoperative analgesia without any adverse effects in children undergoing cleft lip repair. We found a reduction in perioperative opioid consumption and incidence of EA in children undergoing cleft palate repair who received clonidine as adjuvant to bupivacaine. We did not find this same effect in patients who had cleft lip repair. Bilateral maxillary nerve blocks provide complete anesthesia for cleft lip surgery. In contrast, for cleft palate surgery, the glossopharyngeal and vagus nerve contributions to the sensory innervation of the soft palate and oropharynx, as well as the temporomandibular joint (TMJ) pain caused by the Dingman retractor is not covered by a maxillary nerve block. This suggests that the analgesic effect of clonidine might, at least partially, reduce the incidence of EA in patients undergoing cleft palate surgery. The duration of postoperative analgesia with bupivacaine ranges from 8 to 20 hours (Nicodemus et al., 1991; Prabhu et al., 1999). The addition of clonidine to local anesthetics for peripheral nerve blocks likely prolongs the duration of analgesia by inducing vasoconstriction, resulting in delayed systemic absorption of the local anesthetic. Clonidine may also bind to $\alpha - 2$ adrenergic receptors to modify neuronal excitability (Butterworth and Strichartz, 1993; Eisenach et al., 1996; Buckenmaier and Bleckner, 2005; Masuki et al., 2005) or may have a peripheral analgesic action by releasing enkephalinlike substances (Reuben et al., 1999). Cucchiari and Ganesh (2007) showed that the addition of clonidine to bupivacaine or ropivacaine can prolong the duration of peripheral nerve blocks in children independent of the type of local anesthetic used and operation performed. Our study was not specifically designed to evaluate the duration of the maxillary nerve block, but most of the patients did not require rescue opioids during the first 24 hours postoperatively in either group. Alpha-2 agonists are frequently utilized for their sedative properties. However, they may also cause excessive sleepiness or prolong emergence times and PACU discharge times. These side effects appear to be dose dependent and are more likely with caudal epidural or intravenous doses of $2\mu\text{g} \cdot \text{kg}^{-1}$ or greater (Klimscha et al., 1998; Sharpe et al., 2001; Malviya et al., 2006). Guler et al. (2005) found that $0.5\mu\text{g} \cdot \text{kg}^{-1}$ of intravenous dexmedetomidine significantly prolonged the times to emergence and extubation compared to the placebo group. Bergendahl et al. (2004) found excessive sleepiness following discharge in children who received $5\mu\text{g} \cdot \text{kg}^{-1}$ of rectal clonidine. We did not find any difference in PACU discharge times or postoperative oxygen saturation using $3\mu\text{g} \cdot \text{kg}^{-1}$ clonidine. Although $\alpha - 2$ agonists may cause bradycardia and hypotension, we found no significant difference in intraoperative hemodynamic variables between groups. Limitations in our study include comparing different postoperative pain scales for children and adults. However, these scales have all been previously validated and FLACC scores have

been shown to be comparable to 0 to 10 number rating scales across different settings and different populations (Voepel-Lewis et al., 2010). An additional limitation is that nalbuphine could have been inappropriately given for EA. This limitation is commonly reported due to difficulties in differentiating pain from EA in young children. Another limitation is that our patient population is older than the recommended age for these types of surgeries. This limitation reflects that a high degree of inequity in access to surgery exists between regions, with a delayed access to cleft surgery, particularly in low- and lower middle-income countries (Cubitt et al., 2014; Carlson et al., 2016). Unfortunately, the number of patients ≤ 1 is small and this sample is not sufficiently powered to detect a difference between groups. However, $\alpha - 2$ adrenergic receptor agonists have been used for cleft surgery without increasing complications (Jindal et al., 2011; Kayyal et al., 2014; Peng and Zhang, 2015; Surana et al., 2017). A final limitation is that we did not include an intravenous CLG in our study. However, Bock et al. (2002) previously demonstrated that $3\mu\text{g} \cdot \text{kg}^{-1}$ clonidine given either caudally or intravenously significantly reduced EA after sevoflurane anesthesia. In this prospective, randomized, double-blind study, we demonstrated that $3\mu\text{g} \cdot \text{kg}^{-1}$ of clonidine administered as an adjuvant to bupivacaine in suprazygomatic maxillary nerve blocks significantly reduced the incidence of EA in children after cleft lip and palate repair. Secondly, the addition of clonidine appears to reduce the need for perioperative opioids (principally intraoperatively) without altering hemodynamic parameters or affecting PACU discharge or postoperative sedation. Further studies should explore the dose of clonidine administered or compare clonidine to perineural dexmedetomidine as a component of the suprazygomatic maxillary nerve block in a similar population.

Table 2. Patient Characteristics, Perioperative Opioid Consumption, and Postoperative Complications. ^a

Parameters	Lip (N = 65)			Palate (N = 54)		
	Clonidine (N = 37)	Control (N = 28)	P	Clonidine (N = 29)	Control (N = 25)	P
Sex (male)	30 (81.1%)	11 (39.3%)	.001	14 (48.3%)	10 (40%)	.542
Age						
≤ 5 years	N = 24 (64.9%)	N = 17 (60.7%)		N = 9 (31%)	N = 8 (32%)	
Median months (IQR)	11 (22)	8 (10)	.531 ^b	33.44 (15.14)	29.25 (10.78)	.526
>5 years	N = 13 (35.1%)	N = 11 (39.3%)		N = 20 (69%)	N = 17 (68%)	
Mean years (SD)	17.31 (8.88)	16.64 (11.38)	.873	17.45 (5.99)	16.65 (6.42)	.697
Surgery duration (minutes)						
Median (IQR)	68 (42)	65 (47)	.647 ^b	90 (45)	80 (27)	.424 ^b
Fentanyl extra	4 (10.8)	4 (14.3)	.717	3 (10.3)	10 (40)	.011
Nalphy OR	1 (2.7)	0 (0)	1	1 (3.4)	4 (16)	.170
Rescue PPF	7 (18.9)	6 (21.4%)	.802	3 (10.3)	4 (16)	.692
Nalphy PACU	8 (21.6)	6 (21.4)	.985	2 (6.9)	3 (12)	.653
Extra opioids	10 (27)	8 (28.6)	.890	5 (17.2)	12 (48)	.015
Watcha > 2 PACU	9 (24.3)	11 (39.3)	.196	1 (3.4)	5 (20)	.054

Length of PACU stay (min)	45 (30-60)	45 (30-56)	.462	45 (45-60)	45 (30-45)	.343
PONV	0	0		1 (3.4)	1 (4)	1
SpO ₂ < 95%	3 (8.1)	3 (10.7)	1	0	2 (8)	.210

Abbreviations: IQR, interquartile range; OR, operating room; PACU, postanesthesia care unit; PPF, rescue propofol; PONV, postoperative nausea and vomiting; SD, standard deviation.

^a Subgroup analysis according to the intervention group. Extra opioids: Fentanyl and/or nalbuphine at any time.

^b Mann-Whitney U.

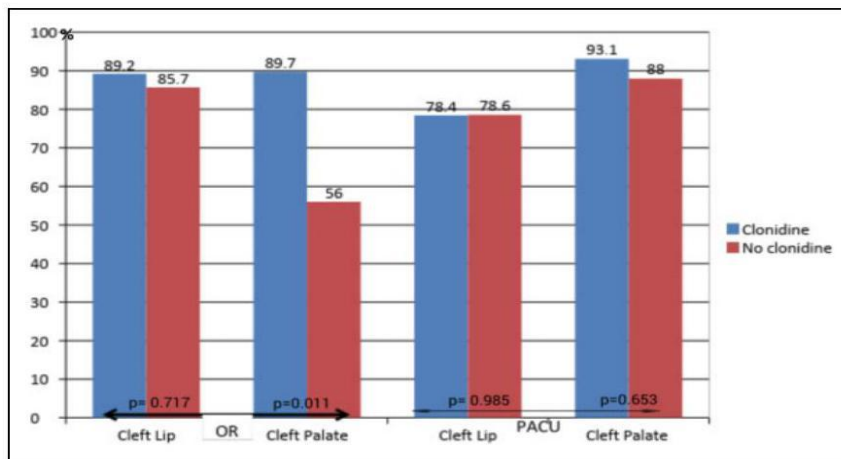


Figure 4. Percentage of patients not needing analgesia during intraoperative and postoperative periods. Subgroup analysis by type of surgery and intervention group.

Authors' Note

Presentation: Preliminary data for this study were presented as a poster presentation at the SPPM 4th Annual Meeting; March 2, 2017; Austin, TX, and at the ESRA-SPAIN 23rd Annual Meeting; September 27-29, 2017; Madrid, Spain. The abstract won the Bosenberg Regional Anesthesia Award at the 2017 meeting of SPA/AAP Pediatric Anesthesiology; March 3-5, 2017; Austin, TX. This study was carried out at Guwahati Comprehensive Cleft Care Center (Assam, India), located at the Mahendra Mohan Choudhury Hospital, Guwahati. This study was done in accordance with the principles of good clinical practice, and the ethical principles in the Declaration of Helsinki. Ethical approval for this study was provided by the Operation Smile India Institutional Ethics Committee, Mumbai, India (Chairperson: Dr Rajeev Kapur) on March 19, 2014, with permission of Operation Smile International. Written informed consent was obtained from all subjects, a legal surrogate, or the parents or legal guardians for minor subjects, before randomization. In this study, the incidence of EA, perioperative opioids consumption and side effects when clonidine is administered as an adjuvant to bupivacaine in suprazygomatic maxillary nerve block after cleft lip and cleft palate surgery are reported; these can be used to improve safety and outcomes in cleft surgery. The work is to be attributed to the Department of Surgery Vall d'Hebron Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain. Our study has been registered in ISRCTN register with study ID: ISRCTN13265788 (<http://www.isrctn.com/ISRCTN13265788>).

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Declaration of Conflicting Interests

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