Treatment Effects of Dexmedetomidine and Ketamine on Postoperative Analgesia after Cleft Palate Repair

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Abstract

Primary cleft palate repair may result in significant pain in the immediate postoperative period, which can lead to vigorous crying resulting in wound dehiscence and pulmonary complications. Effective pain control with opioids is the mainstay but administration on the floor has to be countered with the complications associated with their use, chiefly respiratory depression and sedation. We retrospectively examined the efficacies of intraoperative administration of intravenous (IV) dexmedetomidine (DEX) and ketamine (KET) to prevent early postoperative pain in children undergoing primary cleft palate repair and compared the results against relevant literature. The Texas Children's Hospital anesthesia database was queried to identify children undergoing a palatal surgery from December 2011 to December 2012. Inclusion criteria permitted completed primary palatal surgery without major complications and intraoperative administration of DEX or KET. The control group (CTRL) received no additional drug. A comprehensive literature review was performed. A total of 71 pediatric patients underwent palatal surgery during the study period with 46 patients qualifying for analysis. Although results were not significant, consistent trends were observed with regards to lower opioid requirements during the first 24 hours for both medications compared with the CTRL. KET also had shorter time to discharge. The literature review resulted in several studies supporting decreased postoperative pain end points for both DEX and KET. In our sample, DEX and KET reduced postoperative opioid requirements. KET seems to have the added benefit of a shorter hospital stay. These finding are supported in the literature. With further investigation, the addition of these drugs may serve to provide improved pain relief without over sedation in patients undergoing cleft palate repair.

Keywords
- dexmedetomidine
- ketamine
- cleft palate
- analgesia

Cleft palate abnormalities are among the most common craniofacial abnormalities in the pediatric population. The incidence of cleft palate alone is not easily assessed because cleft lip is concurrently present in many cases; however, the overall incidence of cleft palate is between 0.1 and 1.1 per 1,000 newborns.[1] Although there is no current consensus on

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the optimal timing and technique for surgical repair, all patients with cleft palate will have to be anesthetized and operated on to correct their abnormality. In the published literature, incidence of airway compromise can reach up to 18% in isolated cleft palate cases and increases in syndromic children.[1] The risk of postoperative airway obstruction necessitates formulation of an ideal perioperative anesthetic that results in adequate pain relief without respiratory depression. Furthermore, it is extremely favorable if such a medication could provide prolonged postoperative analgesia, thus decreasing the need for opioids and other analgesics that may contribute to respiratory depression. In addition to respiratory concerns, postoperative pain can lead to vigorous crying, which in turn increases the risk of wound dehiscence and pulmonary complications that may result in delayed discharge.[2] In this study, we present the results of a retrospective chart review of cleft palate repair cases from our own hospital and summarize the published literature describing the perioperative use of dexmedetomidine (DEX) and ketamine (KET) in children. The purpose of this article is to encourage and pave the way for future research in the quest to identify the optimal anesthetic for the pediatric population undergoing cleft palate repair.

Materials and Methods

Study Design

This is a retrospective chart analysis examining the effect of intraoperative use of intravenous (IV) DEX or IV KET on early postoperative pain and opioid requirements in children who underwent cleft palate repair. In addition, a literature review was performed focusing on the postoperative effects of DEX and KET in pediatric patients.

Retrospective Chart Review

The Institutional Review Board for Human Subject Research for Baylor College of Medicine and affiliated hospitals approved a retrospective chart review of patients undergoing a palatal surgery from December 2011 to December 2012. The Texas Children's Hospital anesthesia operating room database was queried to identify these patients. Surveyed data included age, gender, weight, American Society of Anesthesiologists (ASA) physical status, comorbidities, procedure type, operating surgeon, choice of intraoperative anesthetic drug, duration of surgery, postanesthesia care unit (PACU) length of stay, surgical complication, estimated blood loss (EBL), postoperative analgesic requirements including time and dosage and number of doses, airway compromise, oxygen use, and length of hospital stay. Patients were further reviewed for inclusion and exclusion criteria. Inclusion criteria for selection and analysis included patients undergoing primary palatal surgery by our two primary surgeons with no major perioperative complications, where either DEX or KET was administered intraoperatively. Major perioperative complications were defined as delayed extubation or complications requiring additional surgical intervention. Excluded patients had one or more of the following conditions: secondary palatal repair, intraoperative administration of both DEX and KET, were not operated on by one of our primary surgeons, or failed to meet inclusion criteria.

Descriptive statistics and two-sample *t*-tests were used for statistical analysis.

Literature Review

A broad search of the medical literature was performed using PubMed to query the Medline database up to March of 2013 (cutoff date, March 13, 2013) for articles about DEX or KET. The search was limited to clinical trials and review articles published in the English language except for one included article[3] in Chinese. Search terms included multiple combinations of DEX, KET, cleft palate repair, pain, perioperative pain, pediatrics, and children. The articles were reviewed for relevance based on title, abstract, and content. All articles that compared DEX or KET or both to any other anesthetic or analgesic regardless of the surgery performed or the significance of the results published were included.

Results

Retrospective Chart Review

The 71 initially identified charts were assessed to select those that met the study's inclusion criteria, which led to selection of 46 patients. Patients were allocated to different groups based on whether they received intraoperative DEX group or KET group or neither (control group [CTRL]). Of the 46 patients who qualified for the research, 24 patients were in the CTRL group, 14 in the DEX group, and 8 in the KET group. Demographic data are presented in ►**Table 1**.

Although not statistically significant, the patients in DEX group and KET group both had lower opioid requirements postoperatively measured by morphine equivalent/kilogram (Meq/kg) (►**Fig. 1**). The KET group had a 0.30 Meq/kg and DEX group had a 0.36 Meq/kg compared with 0.38 Meq/kg for the CTRL during the first 24 hour postsurgery. DEX had the

Table 1 Demographic data

Group	Number of patients	Average age (mo)	Gender (M; F)	ASA status (I; II; III)
DEX	14	18.3	5; 9	1; 10; 3
KET	8	13.4	3; 5	0; 4; 4
CTRL	24	12.5	14; 10	3; 19; 2

Abbreviations: ASA status, American Society of Anesthesiologists Physical Status Classification; CTRL, control group; DEX, dexmedetomidine group; F, female; KET, ketamine group; M, male.

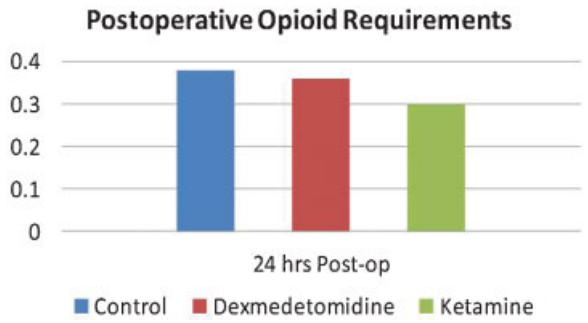


Figure 1 Cumulative 24-hour postoperative opioid requirements. The cumulative opioid requirements for the ketamine group (0.30 morphine equivalent/kilogram [Meq/kg]) and dexmedetomidine group (0.36 Meq/kg) compared with the control group (0.38 Meq/kg) with *p* values of 0.88 and 0.37 for dexmedetomidine and ketamine groups, respectively.

longest average time to discharge from both postanesthesia care unit (PACU) and hospital (►**Table 2**). KET had longer average PACU stay than the CTRL, yet a shorter overall hospital stay. Patients in the KET group were discharged after an average of 26.8 versus 27.8 hours for the CTRL group, although this difference was not statistically significant. EBL, average surgical duration, and surgical complications were comparable in all groups.

Literature Review

The combined literature searches yielded over 1,800 results. The abstracts or articles were reviewed and selected based on relevance to the effects of DEX and KET to postoperative analgesia and anesthetic effects on pediatric population resulting in selection of 41 articles. There were many overlapping articles within each search query. Articles with only caudal anesthesia were excluded. A summarized description of the relevant studies focused on head and neck surgeries can be found in ►**Table 3**.

Discussion

Primary cleft palate repair is known to cause significant pain in the immediate postoperative period. This may lead to vigorous crying causing wound dehiscence and pulmonary complications resulting in tardy recovery and late hospital discharge.[2] Because of this, effective pain control in this patient population is imperative. However, pain control should be accomplished without increasing the risk of respiratory depression, especially in children with increased risk of airway obstruction due to the coexistence of congenital anomalies. Currently, there is no consensus on how to best achieve this. In this study, we evaluated cleft palate repair cases from our own hospital and summarize the published literature about the perioperative use of DEX and KET in children.

DEX is a specific and selective α_2-adrenoreceptor agonist that was Food and Drug Administration (FDA) approved for adult use in December 1999.[2] It is well known for its short-term sedative effects which allows for easy postanesthesia arousal and decreased risk for respiratory depression,[2] hence, making its use favorable in patients with increased risk for respiratory arrest. In the literature, there are only two references that studied effect of DEX on cleft palate repair.[2,3] Obayah et al studied DEX effect when administered in combination with Bupivacaine for palatine nerve block versus Bupivacaine injections. There was a significant decrease in pain scores within the first 24 hour and time to first analgesic request postoperatively.[2] Xu et al compared four groups of DEX dosages with a CTRL, where saline was administered. The results proved that DEX administered at 1 µg/kg and a maintenance dose of 0.75 µg $\times$ kg^{1} $\times$ h^{1} had decreased extubation and discharge time.[3] In contrary, our study did not find a shortened discharge time with the addition of intraoperative DEX. Most of the trials conducted on efficacy of DEX for pediatric analgesia were on children undergoing tonsillectomy with or without adenoidectomy.[4–9] Other reported surgeries with DEX were spine,[10] strabismus,[11,12] and hypospadius[13] surgeries. Most results showed consistency in DEX's ability to decrease postoperative pain, agitation, and analgesic requirements.[2,4,6,7,9,11–15] Our study supports the finding of decreased analgesic requirements, but it was not proven to be significant. These findings are a result of DEX acting on adrenoceptors inhibiting the release of norepinephrine, ultimately terminating the propagation of pain signals.[16]

KET, an *N*-methyl-$_D$-aspartate receptor antagonist, is an IV anesthetic well known for its analgesic properties.[17,18] Many studies have studied the efficacy of KET in pediatric anesthesia; however, only few of those addressed the use of KET in cleft palate surgeries. In one trial, peritonsillar infiltration with KET proved to be significantly more effective in decreasing pain and crying in the first 24-hour postcleft palate repair when compared with Bupivacaine.[19] Most of the KET trials were done on children that underwent tonsillectomy or adenotonsillectomy.[20–37] Other surgeries were strabismus,[11] appendectomy,[38] Nuss procedure,[39] hernia repair, circumcision, and orchidopexy.[40] In some studies, KET did not prove to have higher efficacy in controlling postoperative pain in comparison to morphine,[20,23,27] magnesium sulfate,[22] placebo,[33,34,38,40] and tramadol.[23,33] In other trials, KET proved to decrease postoperative pain scores when compared

Table 2 Time to discharge

Average time to discharge (h)/group	DEX	KET	CTRL
PACU	4.5	3.9	3.7
Hospital	34.5	26.8	27.8

Abbreviations: CTRL, control group; DEX, dexmedetomidine group; h, hours; KET, ketamine group; PACU, postanesthesia care unit.

Table 3 Summary of head and neck literature review

Authors	Year	Design	*N*	Surgery	Route	Age	D	K	PC	OTHER	Pertinent results	Sig	Notes
Jha et al[19]	2013	RCT	50; 50	CPR	LI	21.4–26.8 mo		X		BPV	K < BPV in P/C at 24 h pp	X	
Mizrak et al[14]	2013	RCT	60; 60	AT	IV	8.7–9.8 y	X		X		D < PC in A/P/ANR	X	
Chen et al[11]	2013	RCT	84; 78	ST	IV	4.1–4.3 y	X	X	X		D < K < PC in P/V/A	X	
Xu et al[3]	2012	RCT	100; 100	CLPR	IV		X		X		Compared 5 groups of D with different doses; D at 1 μg/kg and a maintenance dose of 0.75 $\mu g \times kg^{1} \times h^{1}$ had decreased extubation and discharge time	X	Article in Chinese; data collected from English abstract
Meng et al[4]	2012	RCT	120; 120	TE	IV	5–14 y	X		X		D < PC in EA and P up to 10 min post-EX	X	D; two different doses
Ayatollahi et al[33]	2012	RCT	126; 126	TE	IV	5–12 y		X	X	T	T < K ∼ PC in P, hemodynamic parameters and time to start of liquid intake.* T group had longer time to analgesic demand POP.* K and PC similar in POP pain, analgesic demand, and time to begin liquid intake but K < PC in PS in hour 12 POP*	X*	K > T ∼ PC in hallucinations and negative behavior*
Mizrak et al[12]	2011	RCT	60; 60	ST	IV	4.5–11 y	X	X	X		D < PC in POP need for AN and A	X	
Zhuang et al[5]	2011	RCT	60; 60	AT	IV	4.5–5.0 y	X			M	D < M respiratory depression but less analgesia	X	Data for 1st h POP
Pestieau et al[6]	2011	RCT	101; 101	TE ± AD	IV	2–12 y	X			F	D < F for POP delay in 1st MR but D > F in TE & PACU LOS	X	D/F; two different doses
Elshammaa et al[31]	2011	RCT	60; 60	TE	IV	2–7 y		X		F	FK < K < F2 < F1 in PS POP	X	F 1 μg/kg (F1), F 2 μg/kg (F2)
Khademi et al[32]	2011	RCT	78; 78	AT	IV; LI	5–18 y		X	X		K and KL had lower PS and amount of AN needed POP vs. PC and PCL. KL < K in PS and amount of AN needed post op.	X	
Taheri et al[36]	2011	RCT	60	AT	IV	3–12 y		X		F	F > K in time to 1st AN intake POP*; K and F were comparable in PS and amount of AN required POP		

Table 3 (*Continued*)

Authors	Year	Design	*N*	Surgery	Route	Age	D	K	PC	OTHER	Pertinent results	Sig	Notes
El Sonbaty et al[37]	2011	RCT	100	AT	LI	8.2–12.8 y		X		O	KB shorter average LOS in PACU vs. three other groups and K vs. O and MB*. Total HS shorter for KB vs. O and MB* and also shorter than K. Patients in KB had lower PS vs. K and O*, and MB as well.	X*	
Obayah et al[2]	2010	RCT	30; 30	CPR	PNB	11.7–12 mo	X			BPV	D + BPV group > BPV in time to 1st request for AN and PS < in D-BPV vs. BPV	X	Both groups received pre-op Dexamethasone
Patel et al[7]	2010	RCT	137; 122	TE and AD	IV	2–10 y	X			F	D < F in P/A/need for RM	X	
Olutoye et al[8]	2010	RCT	109; 109	TE and AD	IV	6.3–6.6 y	X			M	D > M in median time to 1st POP rescue AN and no of patients requiring > 1 rescue dose was less in D	X	D/M; two different doses
Inanoglu et al[30]	2009	RCT	90; 90	TE	IV	2–12 y		X	X	BPV	PC > B > KB in PS and AN amount administered POP; KB > BPV > PC in time to first analgesic	X	B < KB in PS only at 15 min POP
Canbay et al[27]	2008	RCT	60; 60	TE	LI	3–12 y		X	X	M	K ~ KM ~ M ~ < PC in PS and in AN consumption in 1st 24 h POP; K ~ KM ~ M ~ > PC in T of effective AN POP	X	four groups: K, M, KM, PC
Honarmand et al[28]	2008	RCT	75; 75	AT	LI	3–12 y		X	X		K5 ~ K1 ~ < PC in PS and in AN consumption in 1st 24 h POP; K5 ~ K1 did not require POP AN vs. 64% PC in 24 h POP; EXT K5 ~ K1 > PC		0.5 mg/kg (K5) or 1 mg/kg (K1)
Abu-Shahwan[29]	2008	RCT	84; 82	AT/TE	IV	2–12 y		X		M	KM required less AN than K*; KM and K comparable in PS and no. of patients reporting P	X*	two groups: K, K + morphine (KM)
Dal et al[25]	2007	RCT	90; 90	AT	IV	2–12 y		X	X		K < PC*; KL < PC*; K comparable with KL in P. PC > K > KL* in no of patients requiring rescue AN in PACU	X*	K > KL in extubation time*

(*Continued*)

Table 3 (*Continued*)

Authors	Year	Design	*N*	Surgery	Route	Age	D	K	PC	OTHER	Pertinent results	Sig	Notes
Erhan et al[26]	2007	RCT	60; 60	AT	LI	3–7 y		X	X		K < PC in P score, time to first AN need POP, and total amount of AN taken in first 8 h	X	
Batra et al[34]	2007	RCT	40	TE	IV			X	X		No difference between K and PC		K bolus 0.5 mg/kg then infusion 2 μg/Kg
DA Conceição et al[24]	2006	RCT	90; 90	TE	IV	5–7 y		X			CTRL > both K groups in no. of patients with P and higher degree of P; time to 1st AN dose CTRL > K group 1; K group 2 did not require POP AN	X	K group 1 0.5 mg/kg dose Preop K group 2 0.5 mg/kg dose POP
Guler et al[9]	2005	RCT	60; 60	AT	IV	3–7 y	X		X		D < PC in PS/AS, no. of severe coughs. D >PC in TTE/EXT	X	Patients who received MID for AX were excluded
Umuroğlu et al[23]	2004	RCT	60; 60	AT	IV	5–12 y		X	X	T, MH	PC* > K* > T > M* in % of patients requiring AN POP; time to first AN was less in PC* then K* < T* < M*	X*	Significant HR ↑ in K group POP
O'Flaherty and Lin[22]	2003	RCT	80; 80	TE	IV	3–12 y		X	X	MS	No difference among groups in P, AN in first 24 h, N/V, bleeding		MS, MS + K, K, PC
Elhakim et al[21]	2003	RCT	50;50	AT/TE	IV	5.1–5.7 y		X	X		K > PC in time to first AN administration POP; More patients in PC group required M POP, had higher PS in first 24 h with rest, drinking, and swallowing	X	Significantly shorter time to first food intake, better intake quality, and shorter duration of IV hydration in K
Aspinall and Mayor[20]	2001	RCT	50; 50	AT	IV	1–16 y		X		M	K and M groups were comparable and no added benefit for K		
Murray et al[35]	1987	RCT	40	TE	IV			X	X		K < PC in PS	X	

Abbreviations: A, agitation; AD, adenoidectomy; AN, analgesia; ANR, analgesia requirement; AS, agitation score; AT, adenotonsillectomy; AX, anxiety; BPV, bupivacaine; C, crying; CLPR, cleft lip and palate repair; CPR, cleft palate repair; CTRL, control group; D, dexmedetomidine; EX, extubation; EXT, extubation time; F, fentanyl; FK, fentanyl-ketamine; HR, heart rate; HS, hospital stay; IV, intravenous; K, ketamine; KB, ketamine + bupivacaine; KL, local ketamine; KM, ketamine-morphine; LI, local infiltration; LOS, length of stay; M, morphine; MB, meperidine + bupivacaine; MH, morphine hydrochloride; MID, midazolam; MS, magnesium sulfate; N, nausea; O, oral meperidine; P, postoperative pain; PACU, post anesthesia care unit; PC, placebo; PCL, local placebo infiltration; POP, postoperatively; PNB, palatine nerve block; PS, pain scores; RCT, randomized clinical trial; RM, rescue morphine; ST, strabismus surgery; T, tramadol; TE, tonsillectomy; TTE, time to emergence; V, vomiting.
*Significant findings in study.

with placebo.[21,23,27,28,32,35] KET administered intravenously was more effective than that administered locally in decreasing postoperative pain intensity and demand for analgesia; however, local infiltration with KET had superior results in the first 6 to 24 hours postoperatively.[41] Our study, using IV KET, demonstrated decreased postoperative demand for analgesia during the first 24 hours postoperative, although it was not statistically significant.

DEX proved to be significantly more effective than KET in controlling postoperative pain in children undergoing strabismus surgery.[11] This observation was not supported in our study, as KET appeared superior to DEX in all categories surveyed. Despite all the current literature, there is no consensus on the efficacy of KET or DEX in decreasing early postoperative pain and analgesia requirement in children. However, trends toward both agents having these effects are gaining support. A review article by Tobias suggests that combining DEX and KET would result in counteraction of each other's adverse effects, hence limiting hypertension or hypotension, tachycardia or bradycardia, salivation, and emergence agitation.[42] One patient, excluded from the analysis of our study, received both agents and did not demonstrate any of these reported side effects. A combination of these agents may serve as a useful adjunct to traditional anesthetic management, however more investigation is required.

Because of the retrospective nature of the study, we were not able to control for anesthetic premedication, number of patients in each study group, or for possible confounding variables, such as, age, gender, ASA physical status, etc. In addition, there was no control on intraoperative anesthetic agents, dosages administered, timing of administration, and other analgesics given. The sample size was not large enough to conclude significance. Also with respect to the literature review done, it would have been ideal if the results were presented as a meta-analysis; however, because of variance in the outcomes examined as well as variation in choice of anesthetics, premedication, types of surgery, age, gender, ASA physical status, and other factors in the selected studies a meta-analysis was not feasible. However, the results of this combined chart and literature review call for the need to conduct prospective randomized controlled trials to assess the efficacy and effects of DEX and KET in children undergoing cleft palate repair. Such trials would clearly identify which medication would provide optimal relief of early postoperative pain with fewer side effects, eventually leading to an evidence-based superior benefit-to-risk ratio agent to be used in future cleft palate repairs.

Conclusion

In the literature, effects of DEX and KET on children have been studied. Combined with our results, both agents demonstrate promising results when used in pediatric patients undergoing cleft palate repair. The choice of perioperative analgesia in cleft palate repair surgery is very important especially for children with increased risk for airway obstruction and respiratory depression. It necessitates a synergism between the choice of premedication, intraoperative anesthetic, and postoperative analgesic. We believe that DEX, KET, or a combination of both could potentially resolve this concern by providing effective early postoperative analgesia without the risk of respiratory depression; however, there is a pressing need for prospective randomized trials to further test their effect on pediatric population undergoing cleft palate repair.

Financial Disclosures/Commercial Associations
None.

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