

## Research Article

# Deep Sedation for Pediatric Dental Patients using Adjunct Remifentanyl Boluses

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**Keywords**

- Remifentanyl boluses
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**Abstract**

Remifentanyl has been widely described for a number of sedation procedures, but concerns of apnea and the relative costs may limit its use. In this study, we substituted remifentanyl boluses for fentanyl boluses in an established intravenous sedation protocol for oral surgery procedures. Remifentanyl sedation was evaluated through the Richmond Agitation Sedation Score (RASS). The dosing regimen produced a median RASS score corresponding to deep sedation for the duration of the procedure. Compared with the historical controls, the RASS was not statistically different. Time to discharge from the recovery room and incidence of airway obstruction was significantly greater in the historical group as compared to the remifentanyl group. The new remifentanyl protocol was found to be effective as evidenced by RASS. The use of remifentanyl bolus however proved more labor intensive, but appeared to have an acceptable safety profile compared with established standards for the areas of major concern, including apnea, chest wall rigidity, and hypotension. Finally, cost discrepancies between remifentanyl and fentanyl could be mitigated through dividing the remifentanyl vial between multiple patients. Overall, we concluded that remifentanyl bolus, while not superior in the modality, could prove an acceptable substitute during periods of shortage.

**ABBREVIATIONS**

RASS: Richmond Agitation Sedation Score

**INTRODUCTION**

Office based oral maxilla facial surgical procedures are often performed using deep sedation. Our pediatric anesthesiology department provides anesthesiology cover for a University pediatric dental and oral maxillofacial surgery office based sedation suite. We provide IV deep sedation to enable the oral surgeon to perform surgical office-based procedures for children without bringing the children to surgery and without concerns about the sedation. Routinely the sedation method used is similar to that used in adults OMFS patients, consisting of fentanyl, midazolam and propofol as needed [1]. Not unsurprisingly the doses required in children may often exceed those needed in adults.

During 2012 and 2013 there were significant sedation drug availability issues and our office based sedation suite experienced severe shortages of most of the commonly used agents. This forced us to modify our sedation regimens to continue to provide the needed dental care. At one point, the only opioid we were able to obtain from our supplier was remifentanyl. Remifentanyl has a

rapid onset and a short duration of action with a half-life of 5-8 minutes [2,3]. To avoid apnea and chest wall rigidity, remifentanyl is usually administered by infusion [4], however we did not have access to infusion pumps.

There are a few published reports on administering remifentanyl as a bolus technique. Using small doses of 0.25 to 0.5 mcg/kg remifentanyl, a rapid onset and offset of respiratory depression was noted in volunteers, without complications [5]. Small doses have been shown to have a clinical effect improving placement of a laryngeal mask airway [6,7] and provision of adequate pain relief during ESWL [8].

Remifentanyl was used as the alternate opioid during these periods of fentanyl shortages. Our usual sedation prescription was fentanyl 25-75 mcg, together with midazolam 2-4 mg and propofol 10 mg increments IV as needed. In order to assess the efficacy and safety of this new, regimen a QA process was initiated. We also have comparison data from previous data collection and research using the standard sedation regimen from 2010-2011.

The aim of this paper is to report our experience of using remifentanyl bolus sedation in pediatric patients from our QA analysis and compare the outcomes with historical data from our sedation clinic.

**MATERIALS AND METHODS**

A new remifentanyl based sedation regimen for pediatric (ages 5 to 17 years) deep sedation was implemented in our dental office due to drug shortages. An observer who was not involved in the clinical care of the children collected the QA data prospectively. This included patient demographics, drug dosing and times, cardio-respiratory parameters, quality of sedation and complications. The data collection occurred over a 3 month period in late 2012. After the data collection was complete and presented to our department QA committee, IRB approval was obtained for a retrospective review of this QA database as well as the sedation records from these procedures.

The sedation regimen included: midazolam 1-2 mg IV, followed by 4 doses of remifentanyl IV, each 2 minutes apart. The remifentanyl dose was 10-20 mcg, according to the child's weight (< 30 kg 10 mcg, > 30 kg 20 mcg). The remifentanyl was reconstituted using normal saline to a 10 mcg/ml solution. A second dose of midazolam was administered 5 minutes after the initial dose. Propofol was titrated to the appropriate depth of anesthesia with up to 2 additional remifentanyl boluses given if clinically indicated.

Sedation quality was assessed using the Richmond Agitation Sedation Score (RASS) every five minutes (Table 1) and an assessment by the surgeon (SAS) which was assessed at three points: 1) placement of the bite block whilst the patient is still able to cooperate, 2) placement of the local anesthesia and 3) the procedure itself (Table 2). On occasion we also had access to a BIS monitor.

Respiratory depression was evaluated using O<sub>2</sub> nasal cannula capnography. The data from the historical controls were cases sedated and operated on by the same surgeon / anesthesiologist combination.

Statistical analysis was performed using t-test, chi-square to compare demographics and outcomes between the study and control groups. One-way repeated measure ANOVA and Kruskal Wallis were used to evaluate changes over time for the cardio-respiratory parameters. P <0.05 was accepted.

**RESULTS AND DISCUSSION**

We reviewed the data from 32 children who received remifentanyl boluses as an adjunct to their deep sedation technique in 55 procedures. The mean age was 11.8 years (range 6 to 17 years) (Table 3).

The majority of the procedures were dental extractions of adult teeth (Table 4).

The sedation drugs and doses used are shown in Tables 5 & 6. The mean midazolam dose was 2.8 mg with a range of 2-4 mg as per protocol. There was a large variation in the requirements for propofol, 10 to 180 mg (Table 5). On average patients received about 1.4 mg/kg propofol. The mean total remifentanyl dose received was 95 mcg; the majority of the patients received 6 doses (Table 6).The multiple repeated dosing schedules required for the remifentanyl was completed satisfactorily as shown in Table 7. On average, the interval between starting the midazolam to commencing the operative procedure was 12 minutes. The

**Table 1:** Richmond Agitation Sedation Score (RASS).ca

SCORE	TERM
+4	Combative
+3	Restless
+2	Agitated
+1	Restless
0	Alert & Calm
-1	Drowsy
-2	Light Sedation
-3	Moderate Sedation
-4	Deep Sedation
-5	Unrouseable

**Table 2:** Surgeon Assessment Score.

SCORE	DESCRIPTION
0	Case Cancelled Due To Uncooperation
1	Aggressive
2	Movement, Patient Complains
3	Movement, Delay
4	Movement No Delay
5	Appropriate
6	Noisy Airway No Delay / Intevention
7	Intervention Before Airway Problem, Slight Delay
8	Intervention After Airway Problem, Moderate Delay
9	Oral Airway, Bag Mask Ventilation, Long Delay
10	Case Cancelled Due To Airway Issues

**Table 3:** Demographics.

	AGE	WEIGHT	GENDER
(n=32)	(years)	(kg)	Male / Female
Mean± SD	11.8 ± 2.8	51.7 ± 17.0	16 / 16
Range	6 to 17	22 to 82	-

The majority of the procedures were dental extractions of adult teeth (Table 2).  
Abbreviations: SD: Standard Deviation

**Table 4:** Procedures.

	NUMBER
Soft Tissue	2
Supernumerary Extraction	11
Deciduous Extraction	10
Adult Extraction	29
Exposure	2
Other	1
<b>Total Procedures</b>	<b>55</b>

operative procedure took about 15 minutes to complete (Table 8). Postoperatively, the time until discharge criteria were met was 35 minutes. The quality of the sedation is shown in Table 9. The median RASS while the bite block was placed was -2, which corresponds with light sedation. The median RASS scores for both local anesthesia placement and the procedure were consistent with deep sedation. The surgeon also assessed the sedation quality based upon the appropriateness of the sedation level and whether there was any interruption to surgery due to over or under sedation, using the Surgeon Assessment Score [SAS]. As with the RASS the median scores for the three time points during

**Table 5:** Sedation Doses.

	MID / KG	MID TOTAL	PROP / KG	NUMBER PROP BOLUSES	PROP TOTAL
	(mg/kg)	(mg)	(mg/kg)		(mg)
Mean± SD	0.06 ± 0.02	2.8 ± 1.0	1.4 ± 1.1	6.7 ± 4.3	66.6 ± 43.4
Range	0.03 to 0.09	2.0 to 4.0	0.2 to 4.4	1 to 18	10 to 180

Abbreviations: MID: Midazolam; PROP: Propofol

**Table 6:** Remifentanil Dosing.

	REMI DOSE	REMI TOTAL DOSE	NUMBER REMI BOLUSES	REMI TOTAL
	(mcg)	(mcg/kg)		(mcg)
Mean± SD	16.9 ± 4.7	2.0±	5.6 ± 0.7	95.0 ± 26.9
Range	10 to 20	1.0 to 4.3	4 to 6	40 to 120

Abbreviations: REMI: Remifentanil

**Table 7:** Mean Interval (minutes) between each remifentanil bolus dose.

Dose 1-2	Dose 2-3	Dose 3-4	Dose 4-5	Dose 5-6
2	2	3	6	5

**Table 8:** Procedure Times (minutes).

	SEDATION	PROCEDURE	PACU
Mean±	12 ± 4	15 ± 9	35 ± 8
Range	6 to 24	3 to 44	21 to 54

**Table 9:** Quality of Sedation.

ASSESSMENT	BITEBLOCK		LOCAL ANESTHETIC		PROCEDURE	
	RASS	SAS	RASS	SAS	RASS	SAS
Median	-2	5	-4	5	-4	5
Minimum	-4	5	-5	3	-5	2
Maximum	2	6	-1	7	2	8

Abbreviations: RASS: Richmond Agitation Sedation Score; SAS: Surgeon Assessment Score

**Table 10:** Complications.

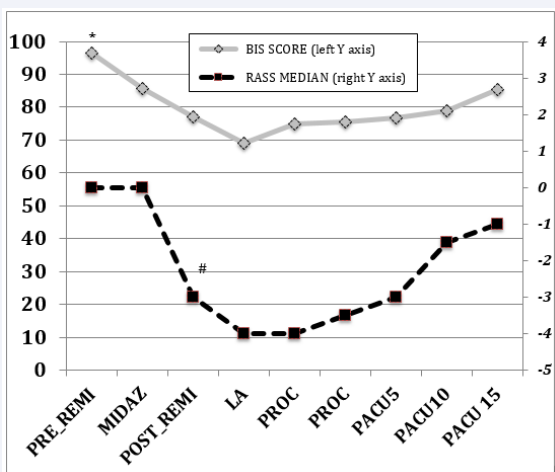
	Desaturation	Obstruction	Apnea	Hypotensive
	< 93 %	Intervention	Assist /Stimulation	Fluid Bolus
Number	6	4	1	1

the procedure were consistent with the appropriate level of sedation (score = 5). Some patients (n=8) had a BIS monitor used (when available) during the procedure; the results from the BIS score along with a comparison to the RASS are shown in Figure 1. The BIS scores observed were consistent with deep sedation, < 70. The RASS and the BIS scores track the depth of sedation in a similar manner.

There were no significant changes in the blood pressure during the procedure (Figure 2), and the heart rate increased slightly during the procedure before returning to baseline post procedure. The end tidal CO<sub>2</sub> increased after the remifentanil and remained elevated for the remainder of the procedure. There was no significant change in the oxygen saturation (Figure 3).

Complications are shown in Table 10. One patient required verbal stimulation for a respiratory rate of 6. Six patients de saturated to < 93% and 4 required an airway intervention for airway obstruction. There were no episodes of nausea / vomiting.

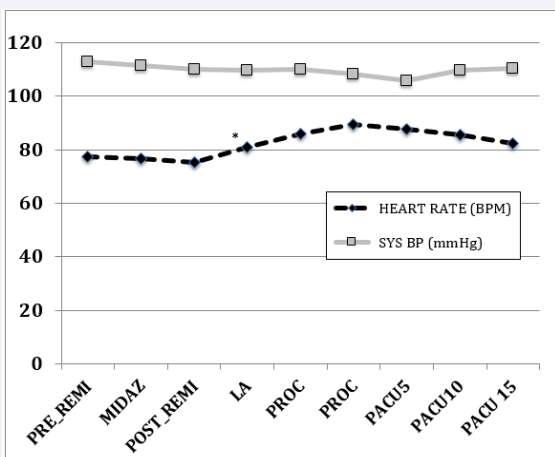
When compared with our historical control data (n=21), there were a few differences. Although the ages of the children in the two groups were similar, 9 and 11 years the duration of the procedures in 2010 were significantly greater (23 minutes) and required significantly more propofol (2.4 mg/kg) compared with the 2013 data. This was associated with a greater time to discharge from the recovery room 56 minutes. The RASS and SAS scores from the procedures however were not different. The incidence of airway complications in the historical group



**Figure 1** Depth of Sedation. The depth of sedation comparison of the median RASS and mean BIS. Both follow the same trends during the procedure.

\*  $p < 0.001$  All data points significantly different to baseline

#  $p < 0.001$  All data points after MIDAZ significantly different to baseline



**Figure 2** Cardiac Parameters (A) – Mean heart and systolic blood pressure during the procedure \*  $p < 0.001$  All data points after LA significantly different from baseline. There was no significant change in the oxygen saturation (Figure 3).

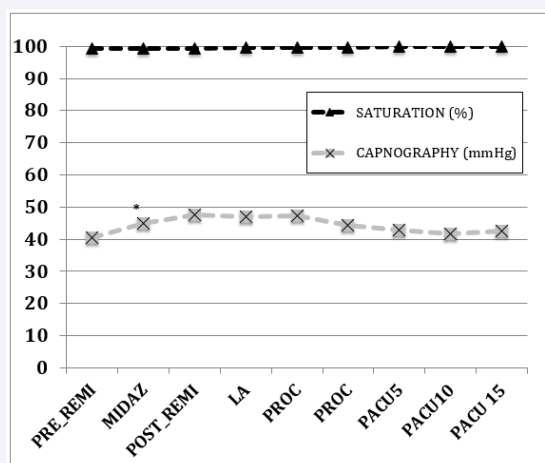
was significantly greater with respect to the incidence of airway obstruction ( $p < 0.01$ ) but not the episodes of de saturation.

The use of multiple boluses with remifentanyl was an attempt to simulate an infusion pump. We created remifentanyl kinetic plots (Figures 4A,4B,4C) to demonstrate the predicted remifentanyl blood levels when using our dosing regimen in contrast to using an infusion pump based on published [9] remifentanyl kinetic data (Table 11).

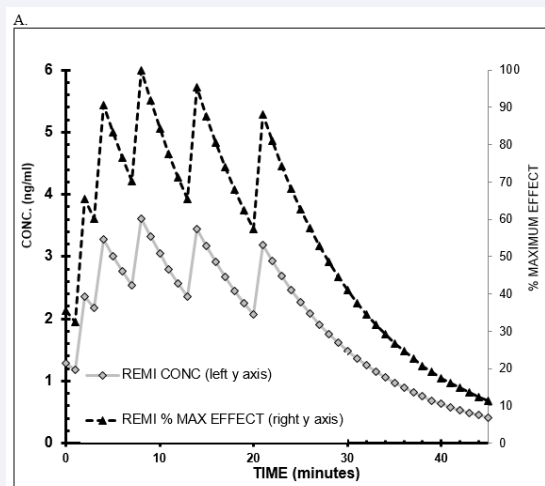
The multiple bolus technique (4A) achieves a blood level after 5 minutes, 80% of the maximum level achieved and maintained blood levels close to this for the next 15 minutes. A single infusion rate of remifentanyl (4B) yields increasing blood levels that gradually increases to the blood level similar to the multiple bolus

method, although the sedation level takes much longer to achieve a clinical effective level. If however a higher rate is used initially as a loading dose followed by a maintenance infusion rate [10], such as shown in Figure 4C, then this can provide a rapid increase to therapeutic level and maintain this level for the procedure.

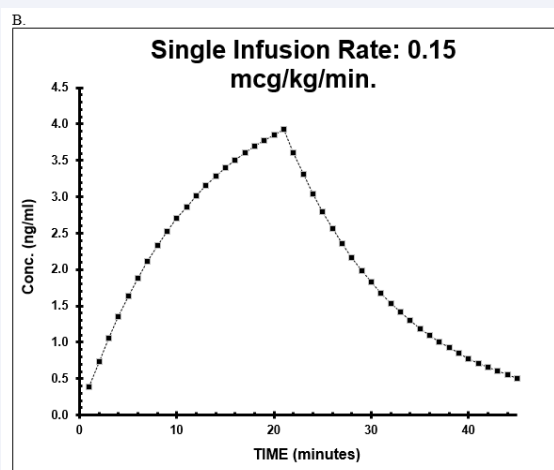
This retrospective review of the use of remifentanyl boluses as an adjunct to deep sedation demonstrated that remifentanyl is an effective technique for sedating children. These short office-based dental procedures require deep sedation and this is usually provided by a combination of benzodiazepines with opiates and propofol. The short duration of these procedures is consistent with the use of an ultra-short-acting opioid that facilitates a more



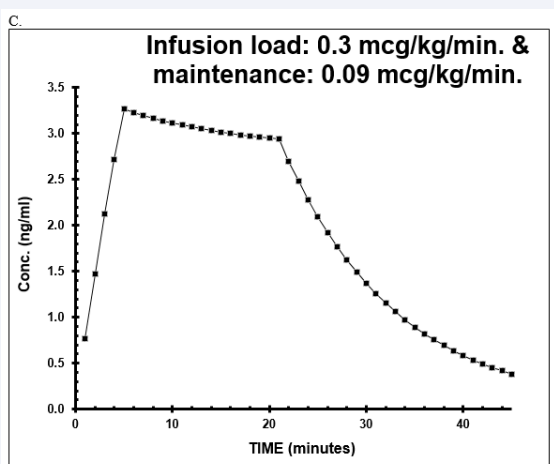
**Figure 3** Respiratory Parameters. The mean oxygen saturation and ETCO2 during the procedure. \* $p < 0.001$  Data points from MIDAZ to PACU 5 significantly different from baseline.



**Figure 4a** Pharmacokinetic Modeling of Remifentanyl. A-Pharmacokinetic modeling of remifentanyl for a 20 kg child receiving 10 mcg remifentanyl boluses as described in this review. Using the pharmacokinetic parameters shown in Table 11. The blood concentration reaches 80% of the peak level within 5 minutes and is maintained near this level for the duration of the procedure. Total dose of remifentanyl 60 mcg.



**Figure 4b** Pharmacokinetic Modeling of Remifentanyl. B-Remifentanyl 0.15 mcg/kg/minute infusion for 21 minutes, demonstrating a slower increase to a similar peak remifentanyl conc. When compared to the bolus method. Total dose of remifentanyl 63 mcg.



**Figure 4c** Pharmacokinetic Modeling of Remifentanyl. C-Using a loading infusion rate for 5 minutes and then a maintenance rate for 16 minutes. Remifentanyl conc similar to the bolus method. Total dose of remifentanyl 59 mcg.

**Table 11:** Remifentanyl Pharmacokinetics.

<b>Weight (kg)</b>	20
<b>Volume Distribution (l/kg)</b>	0.39
<b>Clearance (l/hour)</b>	2
<b>K-elimination</b>	5.13
<b>Half Life (minutes)</b>	8.4

From the range of pharmacokinetic parameters for remifentanyl reported in reference 9

rapid discharge from the office, as the effects of remifentanyl last less than 10 minutes after the last dose [11].

There are several pivotal concerns that should be addressed when considering a new sedation regimen. The first concern is

whether the technique was effective? In this review, all of the cases were successfully completed with sedation assessments and BIS monitoring confirming that an appropriate level of deep sedation was provided. BIS monitoring was used on 25% of the children; the changes in the BIS followed the same pattern as the RASS. The lowest BIS score noted in this study was 62, although our experience during office based deep sedation procedures have yielded BIS values in the 50's. The potency of the remifentanyl may have resulted in a reduced requirement for propofol and as such less effect on the BIS [12,13]. A rapid recovery was also noted.

All children are monitored for at least 20 minutes' post procedure to ensure rebound sedation does not occur after the intense surgical stimulation has ceased. The brief duration of remifentanyl should also reduce this potential risk. The efficacy, depth of sedation and quick recovery were similar to those reported when a remifentanyl/propofol deep sedation technique was used for muscle biopsy in children [14].

Also propofol and remifentanyl has been shown in pediatric dental patients to provide a more effective sedation with a more rapid recovery when compared to ketamine propofol technique [15]. This supports the possible significance our earlier discharge noted in our study group when compared to our historical comparative data.

In a comparison of repeat boluses of remifentanyl with an infusion of remifentanyl for ESWL, with a propofol infusion for sedation / analgesia, the bolus only remifentanyl technique achieved as effective sedation as the infusion method, [8] as well as an earlier discharge time.

The second main concern is the safety of a multiple bolus remifentanyl technique. We utilized a small repeated dosing schedule to reduce the risk of apnea or rigidity. Remifentanyl used as an adjunct and given as a load infusion followed by maintenance infusion has been described as effective and safe for pediatric bronchoscopy patients. These patients share similar airway concerns to our pediatric dental patients. The intermittent dosing although labor intensive provides similar benefits to this infusion practice [16]. When considering the pharmacokinetic simulations (Figure 4), this method appeared to be equivalent to a load and maintenance infusion rate technique, which is often the recommended method for infusion-based sedation. The blood levels remained stable during the operative part of the procedure with the repeated boluses and did not peak excessively, limiting the risk of hypopnea and apnea. A study by Eger et al., using adult volunteers found that respiratory events were common when remifentanyl doses of about 1 mcg/kg or greater were used [17]. The few apnea episodes noted were of a short duration and were easily managed. Using a similar kinetics plot simulation as we have shown in Figure 4, they also showed that the remifentanyl would be almost completely eliminated about 15 minutes after the last dose.

We did not note any nausea or vomiting, this was attributed to the rapid offset of the remifentanyl, after a brief 20-minute dosing period. However, it has been reported that a remifentanyl based sedation regimen can cause nausea [18] and may require pre-emptive ondansetron to reduce this risk [19].



A major concern with remifentanyl boluses is the issue of apnea or respiratory arrest [20]. In the ESWL study, the incidence of oxygen de saturation (< 90%) with the infusion-based technique was actually twice that of the bolus arm [8]. The incidence of airway issues after bolus remifentanyl in this study is similar to that reported in the ESWL study [8]. Some contend that with an infusion, respiratory depression develops more slowly, allowing the CO<sub>2</sub> to increase and maintain a degree of respiratory drive that reduces the risk of apnea developing. However, if a large enough bolus of remifentanyl is given, sudden apnea could occur, the CO<sub>2</sub> would increase, the remifentanyl levels would then decrease and the child will resume start breathing at a remifentanyl level that is greater than that which caused the apnea because of hypercapnic stimulation on the respiratory center. This means that apnea with remifentanyl boluses should be short-lived and easier to manage, although the airway remains unprotected during oral surgery, which itself is not optimal. Accordingly, we used small repeated boluses of remifentanyl to minimize the risk of this occurring.

The combination of remifentanyl and propofol has been used to facilitate placement of a laryngeal mask airway due to the effective depression of pharyngeal reflexes [5,6]. Remifentanyl improved the placement of the LMA with propofol in a dose-dependent manner. This could be associated with an increased risk of airway obstruction due to poor pharyngeal tone. We did not demonstrate any airway complications when we compared these data with historical controls. In addition, 1 mcg/kg remifentanyl boluses at exudation did not increase the risk of respiratory depression or airway issues in a population of patients who were deeply sedated as they begin to wake up from anesthesia [21].

Hypotension and bradycardia may occur concurrently, when a propofol/remifentanyl combination is used. The decreases in both blood pressure and heart rate from baseline were similar, 25%. There were no substantive decrease in blood pressure and the heart rate actually increased during the procedure, possibly related to the use of lidocaine with epinephrine.

The dosing schedule we utilized is consistent with the speed of onset of the respiratory depression possible from remifentanyl boluses [2]. Allowing 2 minutes at least between doses provided a degree of safety concerning the apnea risk.

A third issue that must be considered is the cost of remifentanyl, which is substantially greater than that of fentanyl. A 1 mg vial of remifentanyl costs our clinic \$70 compared with \$2 for a 100 mcg vial of fentanyl. This 1 mg vial could treat 10 children at the doses we used, although this degree of economy is usually not possible. An infusion of remifentanyl is likely similar to the cost of our bolus technique and it requires the additional expense of an infusion pump. Our kinetic modeling did not identify any reduction in remifentanyl usage with the infusion technique, as the total dose of remifentanyl used was similar with the three methods we analyzed. However, the use of multiple boluses does add a degree of complexity to the sedation process and is labor intensive. This degree of active involvement with the sedation is paramount for the success of the bolus method.

There are several limitations to this review. First, the data were collected prospectively for the QA analysis, however the treatments were neither randomized nor blinded and used a

convenience sample of patients determined by our drug shortage situation. Second, the children in the comparator arm were not matched as closely as they should have been. The duration of the procedures in our control group affected our ability to compare the sedation methods. However, there was no evidence of an increased incidence of airway complication using remifentanyl. The surgeon assessment tool has not been validated; however its results were very similar to the expected depth of sedation as reflected by the RASS. Also the characteristics of the score are clinically based, reflecting practical assessments of both under sedation and especially over sedation that may be difficult to assess using a patient's behavior based score such as the RASS. With using a potent opiate, we wanted to ensure that we were able to accurately document over sedation for this QA review.

## CONCLUSION

In summary, we report our experience using remifentanyl boluses as part of a sedation regimen in children undergoing dental procedures. Although it is a labor intensive and expensive technique, the quality of sedation was appropriate and the discharge times were less than our historical comparison, consistent with the brief half-life of remifentanyl. We reported no complications that were related to the use of remifentanyl. Our QA review did not conclude that this technique was superior to our standard technique, but an appropriate replacement if warranted. The use of an infusion-based method may be easier to use with the same quick recovery benefits as suggested by this review.

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