Intranasal Sufentanil/Midazolam Versus Ketamine/Midazolam for Analgesia/Sedation in the Pediatric Population Prior to Undergoing Multiple Dental Extractions Under General Anesthesia: A Prospective, Double-Blind, Randomized Comparison

J. A. Roelofse, PhD,* E. A. Shipton, FFA, FRCA, FANZCA, FFPMANZCA, D Med,† C. J. de la Harpe, BChD, BSc,‡ and R. J. Blignaut, PhD§

*Department of Anesthesiology, Faculty of Dentistry, University of Stellenbosch, †Department of Anesthesiology, Christchurch School of Medicine, University of Otago, and §Department of Statistics, University of the Western Cape

This article details a double-blind, randomized study evaluating the efficacy and safety of intranasal sufentanil and intranasal midazolam (S/M) when compared with intranasal ketamine and intranasal midazolam (K/M) for sedation and analgesia in pediatric patients undergoing dental surgery. Fifty healthy ASA status 1 children aged 5–7 years, weighing 15–20 kg, and having 6 or more teeth extracted, were randomly allocated to 2 groups of 25 patients each (n = 50). In the S/M group, 25 children received intranasal sufentanil 20 μg, and intranasal midazolam 0.3 mg/kg 20 minutes before the induction of anesthesia. In the K/M group, 25 children received intranasal ketamine 5 mg/kg and intranasal midazolam 0.3 mg/kg 20 minutes before the induction of anesthesia. Sevoflurane in nitrous oxide and oxygen was used for induction and maintenance of anesthesia. This study demonstrated the safety and efficacy of both methods with ease of administration, combined with a rapid onset of action. Both groups were equally sedated. A smooth mask induction of anesthesia was experienced in the majority of children. Effective postoperative analgesia for multiple dental extractions was provided. The intranasal administration of drugs for sedation and analgesia has some promising features in preschool children undergoing multiple dental extractions.

Key Words: Intranasal sedation and analgesia; Sufentanil; Ketamine; Midazolam; Pediatric dental surgery.

An increasing number of children are undergoing day-case surgery. Children from 3 to 5 years of age may experience significant emotional upset as a result of hospitalization, fear of separation from parents, and unfamiliar surroundings. Children in this age group may not be fully aware of the necessity of their surgical procedure. They are fearful of injections and cannot be easily reassured with an explanation. The primary clinical need in the pediatric population is for a well-tolerated, effective, and expedient analgesic agent that is safe to use. The intranasal administration of opioids may be an alternative route to intravenous, subcutaneous, oral transmucosal, oral, or rectal administration in some patients. Intranasal administration of lipophilic opioids has been shown to be an effective method of administration that is devoid of major side effects.[1]

Sufentanil is a potent mu opioid agonist used as a perioperative analgesic. Sufentanil is 5–10 times more potent and 2 times more lipophilic than fentanyl, with

Received March 11, 2004; accepted for publication July 8, 2004.

Address correspondence to Professor EA Shipton, Department of Anesthesiology, Christchurch School of Medicine, University of Otago, Private Bag 4345, Christchurch, New Zealand; shiptonea@xtra.co.nz.

Anesth Prog 51:114–121 2004

ISSN 0003-3006/04/$9.50
SSDI 0003-3006(04)

rapid absorption from the nasal mucosa.[2] In a recent double-blind, randomized, controlled study evaluating intranasally administered fentanyl for postoperative analgesia in pediatric patients, satisfactory analgesia was achieved and adverse effects were within an acceptable range.[3] Intranasal sufentanil (1.5–3.0 μg/kg) facilitates separation of children from parents and can provide postoperative analgesia.[4]

Midazolam is a benzodiazepine that is widely used as a sedative in conscious sedation or monitored anesthetic care. Rapid uptake and high bioavailability of intranasal midazolam has been demonstrated in healthy volunteers.[5] Both intranasal midazolam and sufentanil provide rapid, safe, and effective sedation in small children before anesthesia.[6] Ketamine is a phencyclidine anesthetic agent that provides analgesic activity at subanesthetic doses.[7] It is an N-methyl-D-aspartate receptor antagonist with opioid-receptor activity. Controlled studies and case reports on ketamine demonstrate efficacy in neuropathic and nociceptive pain.[7] Premedication with intranasal administration of S+ ketamine (1–2 mg/kg) and midazolam (0.2 mg/kg) provides good conditions for induction of anesthesia in preschool children with adverse effects within an acceptable range.[8]

There has, however, been no direct comparison of the combination of intranasal sufentanil/midazolam and ketamine/midazolam to determine which combination is preferable for sedation and perioperative analgesia in preschool children. The aim of this prospective, randomized, double-blind study is to evaluate the efficacy and safety of preoperative sedation and postoperative pain relief with intranasal sufentanil/midazolam when compared with intranasal ketamine/midazolam in children undergoing dental extractions under general anesthesia.

METHODS

The University Ethics Committee approved the study, and the parents signed written consent forms. Fifty healthy ASA status 1 children, free of any nasopharyngeal or respiratory problems, aged 5–7 years, weighing 15–20 kg, and having 6 or more teeth extracted, were eligible for participation in the study. Exclusion criteria were as follows: the use of analgesics or central nervous system depressants over the previous 24 hours; the use of anticoagulants; hypersensitivity to opioids, benzodiazepines, and ketamine, or any other medication likely to interfere with the study drugs. At a presurgery visit, patients were evaluated for inclusion, and baseline assessments (including a medical history) were performed. Patients were randomly allocated before surgery according to a computer-generated randomization list to 1 of 2 treatment groups. Children were fasted for 8 hours beforehand with only sips of clear fluid allowed 3–4 hours preinduction. In the S/M group, 25 children received intranasal sufentanil 20 μg (50 μg/mL, via Go Medical^{R} nasal spray) and intranasal midazolam 0.3 mg/kg (5 mg/mL, via a tuberculin syringe in the other nostril) 20 minutes before the induction of anesthesia. In the K/M group, 25 children received intranasal ketamine 5 mg/kg (100 mg/mL, via Go Medical nasal spray) and intranasal midazolam 0.3 mg/kg (via a tuberculin syringe in the other nostril) 20 minutes before the induction of anesthesia. Sevoflurane in nitrous oxide and oxygen was used for induction and maintenance of anesthesia. The children were all intubated and a throat pack inserted to protect the airway. The children were allowed to breathe spontaneously. They underwent dental extractions. No local anesthesia was used. A blinded observer/researcher monitored parameters. The blinded observer/researcher remained with the child from prior to drug administration until discharge from the recovery room and was unable to tell which drug combination was being administered. Patients were also observed for adverse effects like nausea, vomiting, itching, and excessive sedation.

Monitoring consisted of a Dinamap adult/pediatric noninvasive blood-pressure monitor, an Ohmeda Biox III pulse oximeter for measuring oxygen saturation, and a continuous electrocardiogram and heart-rate monitor. Blood pressures (systolic, diastolic, mean), pulse and respiratory rates, and oxygen saturations were recorded at the following time intervals: before the start of sedation, 15 and 20 minutes after drug administration, and at 30, 60, 90, and 120 minutes postoperatively. The same anesthesiologist and the same dental surgeon carried out all the treatments and the independent observer/researcher made all the assessments. The independent observer/researcher assessed the following: the acceptability of the intranasal spray (observed scale: 1 = no defense action; 2 = defense action/weeping; 3 = refusing vehemently), the ease of mask induction (observed scale: 1 = no defense action; 2 = defense action/weeping; 3 = refusing vehemently), anxiety scores (observed scale: 1 = very anxious; 2 = alert, moderately anxious; 3 = calm, indifferent, not anxious; 4 = asleep), and sedation scores (according to Ramsay[9]: 1 = fully awake, orientated; 2 = drowsy; 3 = eyes closed, arousable to command; 4 = eyes closed, arousable to shoulder shaking; 5 = unarousable to shoulder-tip shaking).

Patients remained in the recovery room for 4 hours after surgery, where recovery was assessed according to the Aldrete postanesthetic recovery score[10]. Postoperative pain was assessed by the following: Oucher facial pain scale (0 = no pain, 100 = extreme pain), as eval-

Table 1. Demographic Profile and Baseline Vital Signs in the 2 Groups*

	Group S/M Mean ± SD	*Group K/M Mean ± SD*
Age (year)	5.87 ± 1.33	5.68 ± 1.31
Weight (kg)	17.80 ± 2.72	17.17 ± 3.09
Number of teeth	10.68 ± 3.77	10.63 ± 4.26
Heart rate (beats/min)	94.48 ± 26.22	105.16 ± 20.64
Duration of surgery	20.64 ± 6.60	19.96 ± 4.95
Gender		
Male	15	12
Female	10	13

* S/M indicates sufentanil/midazolam; K/M, ketamine/midazolam.

uated by the mother, the child, and the observer/researcher; word graphic rating scale, as evaluated by the observer/researcher (A = no pain, B = little pain, C = moderate pain, D = severe pain); and the modified Hannalah objective pain scale. The modified Hannalah objective pain scale[11] is a behavioral-cardiovascular checklist on which a percentage is calculated according to 6 parameters (systolic blood pressure, crying, movement, agitation, posture, and complaints of pain). The behavioral categories include crying, movement, agitation, posture, and complaints of pain (verbalization).

Any adverse reactions were noted. Children with any pain value over time more than 40 mm on a 100-mm visual analogue scale were classified as nonresponders, and those with any pain value over time of equal or less than 40 mm on a visual analogue scale as responders.

Statistical Analysis

All tests of the significance of differences were 2-tailed and a probability of .05 or less was accepted as significant. Various tests, such as the chi-square, Kruskal-Wallis, and the Wilcoxon rank index, were applied. All statistical modeling and significance testing was performed using the SAS statistical package (CMS version 5.18).

RESULTS

Patients in the 2 groups were similar with respect to age, height, weight, gender distribution, and length of surgery, and the number of teeth removed (Table 1). There were no significant differences ($P = .05$) in the physiological parameters, namely blood pressures (systolic, diastolic, mean arterial), heart rates, respiratory rates, and oxygen saturation between the 2 groups at the various time intervals measured (Table 2). With regard to the preoperative sedation and anxiety levels at the intervals post–drug administration, no significant differences were found between the 2 groups ($P = 0.05$) (Figures 1 and 2). Significantly more patients in the S/M group accepted the nasal premedication (chi-square test = 7.718, $P = .021$; Table 3). No significant differences were found in the ease of mask induction ($P = .05$; Table 4). No adverse effects like nausea, vomiting, itching, and excessive sedation were observed in either group. There were no significant differences seen between the 2 groups as far as postoperative recovery went ($P = .05$; Table 4). The Oucher facial pain scale showed the S/M group to experience less pain than those in the K/M group, although this was not statistically significant ($P > .05$) (Table 4). In the S/M group, 72% of children were responders as compared with 52% in the K/M group ($P > .05$; Figure 3). Using the word graphic rating scale and the modified Hannalah objective pain scale (Table 4 and Figures 4 and 5), no significant differences were found between the 2 groups at the various time intervals measured postoperatively ($P = .05$).

DISCUSSION

The intranasal route of administration shows promise. The intranasal route is one of the most permeable and highly vascularized sites for drug administration, ensuring rapid absorption into the systemic circulation and onset of therapeutic action.[12] In general, it has been potentially explored as an alternative route for drugs with poor bioavailability and for the delivery of biosensitive and high molecular-weight compounds such as proteins, peptides, steroids, and vaccines.[12] Direct systemic absorption bypasses the portal circulation (hepatic first-pass effect) and may increase the bioavailability of nasally absorbed drugs. Added absorption enhancers, such as cyclodextrins, phospholipids, bioadhesive powder systems, and chitosan, improve nasal delivery.[13] Intranasal delivery devices include drops[14] (eg, dripped in using a tuberculin syringe), sprays, aerosols,[15] and microsphere formulations.[16] Atomization of aqueous polymer solutions is a key step in the formulation of several pharmaceutical products.[17] For example, in pediatric dental patients, intranasal midazolam spray administered using an atomizer has been found to be safe.[18] Nasal drug delivery may be assessed by a variety of means, but high reliance is often placed on in vitro testing methodology (emitted dose, droplet or particle size distribution, spray pattern, and plume geometry).[19] Spray pattern and plume geometry define the shape of the expanding aerosol cloud, while droplet size determines the likelihood of deposition within the nasal cavity by inertial impaction. Aerosols are deposited mainly in the anterior

Table 2. Physiological Parameters in the 2 Groups*

	Mean ± SD							
	Baseline	*15 minutes postdrug*	*20 minutes postdrug*	*30 minutes postop*	*60 minutes postop*	*90 minutes postop*	*120 minutes postop*	*P value P = .05*
Heart rate (beats/min) S/M group	94.48 ± 26.22	95.00 ± 15.86	97.17 ± 17.88	115.68 ± 21.78	113.16 ± 21.29	103.32 ± 21.43	102.44 ± 19.22	*P* = not significant
Heart rate (beats/min) K/M group	105.16 ± 20.64	104.21 ± 18.97	104.68 ± 22.70	114.44 ± 25.26	111.80 ± 22.03	107.44 ± 17.30	107.36 ± 14.83	
Systolic BP (mm Hg) S/M group	112.80 ± 12.10	104.84 ± 10.28	100.08 ± 13.87	122.16 ± 17.64	120.80 ± 20.04	120.84 ± 16.30	115.48 ± 15.18	*P* = not significant
Systolic BP (mm Hg) K/M group	118.36 ± 16.83	112.76 ± 14.91	112.24 ± 18.13	120.24 ± 17.43	122.00 ± 15.53	121.68 ± 16.50	119.84 ± 11.08	
Diastolic BP (mm Hg) S/M group	67.08 ± 13.60	60.48 ± 14.37	57.24 ± 12.89	77.20 ± 15.87	72.56 ± 16.30	75.36 ± 15.79	71.00 ± 15.31	*P* = not significant
Diastolic BP (mm Hg) K/M group	70.16 ± 16.81	68.20 ± 13.29	69.36 ± 16.38	78.76 ± 14.45	78.84 ± 14.44	82.84 ± 20.38	76.00 ± 10.33	
Mean BP (mm Hg) S/M group	82.72 ± 13.47	76.60 ± 12.47	71.36 ± 12.69	92.52 ± 15.85	88.35 ± 19.16	90.57 ± 16.37	87.85 ± 14.68	*P* = not significant
Mean BP (mm Hg) K/M group	89.32 ± 16.27	82.56 ± 14.95	86.24 ± 16.24	93.48 ± 17.51	93.16 ± 13.24	93.20 ± 16.68	90.24 ± 13.17	
Respiratory rate (breath/min) S/M group	23.00 ± 3.54	22.56 ± 3.49	21.13 ± 4.84	23.65 ± 4.81	23.50 ± 4.05	22.92 ± 3.19	22.92 ± 3.44	*P* = not significant
Respiratory rate (breath/min) K/M group	23.56 ± 2.74	23.20 ± 3.06	21.57 ± 3.67	23.38 ± 3.80	23.13 ± 2.97	21.79 ± 2.32	22.00 ± 2.50	
SpO_2 (%) S/M group	97.72 ± 1.99	97.36 ± 1.60	97.24 ± 1.45	97.04 ± 1.70	97.60 ± 1.26	97.92 ± 1.35	97.76 ± 1.20	*P* = not significant
SpO_2 (%) K/M group	97.36 ± 1.52	97.24 ± 1.58	97.36 ± 1.32	97.44 ± 2.02	97.80 ± 1.66	97.88 ± 1.42	97.84 ± 1.86	*P* = not significant

* S/M indicates sufentanil/midazolam; K/M, ketamine/midazolam.

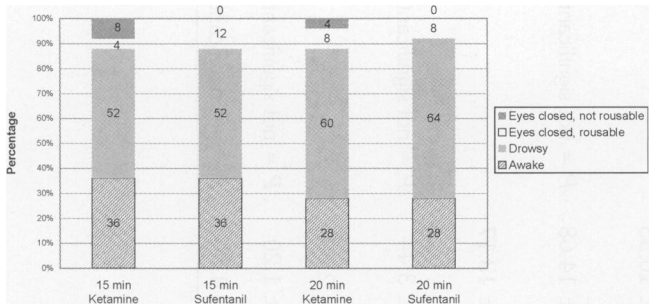

Figure 1. Sedation score: 15 and 20 minutes post–drug administration.

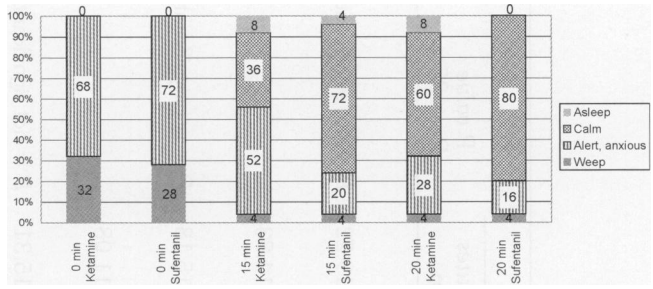

Figure 2. Anxiety scale: baseline, 15, and 20 minutes post–drug administration.

and turbinate regions, with little passing beyond the nasopharyngeal region.[15] Spray droplets are deposited in spots of the middle and posterior portions of the turbinate region as well.

Intranasal administration of sedatives and opioid analgesics provides a mechanism for more rapid drug absorption and more rapid onset of pain relief compared with oral dosing.[20] Although the pharmacokinetics of intranasal sufentanil have not been worked out, lipophilic agents with a low molecular weight produce plasma levels similar to those achieved by the intravenous route.[3] While previous work has demonstrated the efficacy and safety of preanesthetic sedation of children with intranasal sufentanil or midazolam, there has been no direct comparison of a combination of sufentanil/midazolam and intranasal ketamine/midazolam to determine which drug combination is preferable for sedation and postoperative pain relief in preschool children. The Go Medical nasal spray is a portable 0.18-mL patient-controlled analgesic device that is a hand-activated spray. It incorporates a 3-minute fill time (during which another full dose cannot be delivered). The spray is delivered in small-droplet form (80 μm). It is simple to use.

In this study, patients had similar weight distributions in both groups (S/M group, mean = 17.8 kg; K/M group, mean = 17.17 kg). As drugs are administered according to weight, bias according to this variable was not introduced. The presurgery behavior was reflected in the baseline anxiety scale (Figure 2), in the preanesthetic sedation (in which both groups were equally calm, drowsy, and peaceful), as well as in an uneventful and smooth mask induction of anesthesia in the majority of children.

Despite the potentially additive effects that a benzodiazepine with an opioid may have on respiratory depression, no such event was detected. Preanesthetic and postanesthetic oxygen-saturation levels were the same for both groups, at mean values of 97–98%. The study demonstrated that the drug combinations chosen had no negative effects on behavior during the perioperative period. There was an absence of adverse effects (such as nausea and respiratory depression), and no abnormal physiological responses during the perioperative period.

Dental practitioners specifically referred these patients for extractions. Single dental extractions are not usually associated with severe pain. Increasing pain is usually associated with multiple extractions.[21–23] For inclusion in the cohort, it was a prerequisite that 6 or more extractions were to be performed. Ninety-two percent of patients had received no previous dental surgery. Sufficient pain was therefore present to demonstrate the analgesic properties of the drug combinations used. Although measuring pain and pain relief can be difficult in the pediatric patient, the pain assessment methods used have all been validated.[24–26] The Oucher facial pain scale is validated for use in children, as is a visual scale that children readily understand.[27] Seventy-two percent of children in the S/M group (vs 52% in the K/M group) were responders. The Oucher facial pain scale showed the S/M group to experience less pain than those in the K/M group. Even though the S/M group showed improved clinical analgesia, this was not statistically significant ($P > .05$). The analgesia provided was effective and reliable for pain due to multiple dental extractions. Using the modified Hannalah objective pain scale (Table 5 and Figure 5) as a behavioral-cardiovascular checklist, no significant differences were found between the 2 groups at the various time intervals measured postoperatively ($P = .05$). As the children had received no local anesthesia, no significant differences reflected on the combination of drugs that were used.

Intranasal pharmacokinetic studies in volunteers are reported for fentanyl, alfentanil, sufentanil, butorpha-

Table 3. Acceptance of Intranasal Spray*

	Good	*Moderate*	*Poor*	*Total*
Group K/M	4	9	12	25
Group S/M	7	15	3	25
Total	11	24	15	50

* K/M indicates ketamine/midazolam; S/M indicates sufentanil/midazolam. $P = .021$.

Table 4. Mask Acceptance Score, Recovery Room Score, and Pain Measures*

	Mean ± SD			
S/M group, mask induction acceptance score	42.40 ± 2.92			
K/M group, mask induction acceptance score	39.69 ± 7.49			
Time	*30 minutes*	*60 minutes*	*90 minutes*	*120 minutes*
S/M group, recovery room score	78.40 ± 15.46	81.60 ± 8.50		81.67 ± 6.37
K/M group recovery room score	74.80 ± 13.88	80.00 ± 7.64		79.58 ± 10.42
S/M group, sum of Hannalah scale (%)	29.00 ± 25.36	21.33 ± 24.66	11.33 ± 13.58	10.33 ± 12.33
K/M group, sum of Hannalah scale (%)	26.00 ± 22.35	14.33 ± 14.74	10.67 ± 13.29	9.33 ± 12.80
	Child	*Mother*	*Researcher*	
S/M group, oucher sum	86.40 ± 85.82	86.00 ± 85.63	84.00 ± 83.22	
K/M group, oucher sum	115.20 ± 89.36	115.60 ± 88.98	114.00 ± 90.00	

* S/M indicates subfentanil/midazolam; K/M, ketamine/midazolam.

nol, oxycodone, and buprenorphine.[27] Mean times for achieving maximum serum concentrations vary from 5 to 50 minutes, while mean figures for bioavailability vary from 46 to 71%.[28] Fentanyl, pethidine (meperidine), and butorphanol have been studied for postoperative pain. Mean onset times vary from 12 to 22 minutes and times to peak effect from 24 to 60 minutes.[28] There is considerable interindividual variation in pharmacokinetics and clinical outcome.[28] This may partly be due to lack of optimization of nasal formulations. Patient-controlled intranasal opioid analgesia may be an effective alternative to intravenous patient-controlled analgesia.[28] Adverse effects are mainly those related to the opioids themselves rather than being due to nasal administration.[28] Fewer patients with intranasal patient-controlled analgesia suffer opioid adverse effects, such as episodes of vomiting, when compared with intravenous patient-controlled analgesia.[1]

The use of oral midazolam as a premedicant in pediatric dentistry preceded the use of the intranasal route and still needs to be compared with it.[29] Using intranasal midazolam in healthy volunteers, the mean (± SD) peak plasma concentration of midazolam of 71 (±25) ng/mL is reached after 14 (±5) minutes.[5] Mean bioavailability following intranasal administration is 0.83 ± 0.19.[5] It has an elimination half-life of 4 hours. Intranasal midazolam (0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg) has been used in conscious sedation of young pediatric dental patients.[30] There is a rapid onset of sedation, with the maximal effect occurring between 8 and 15 minutes.[30] This sedation lasts for 25–40 minutes.[30] All 3 doses of intranasal midazolam are effective in modifying the behavior of the uncooperative-child patient to accept dental treatment.[30] Another recent study showed that, for premedication in young children, intranasal midazolam (0.3 mg/kg) achieves maximum sedation and anxiolysis at 20 minutes.[31] Patient mask acceptance is good in the majority of children (more than 75%).[31] It does, however, cause significant nasal irritation. Most parents are satisfied with its use for premedication.

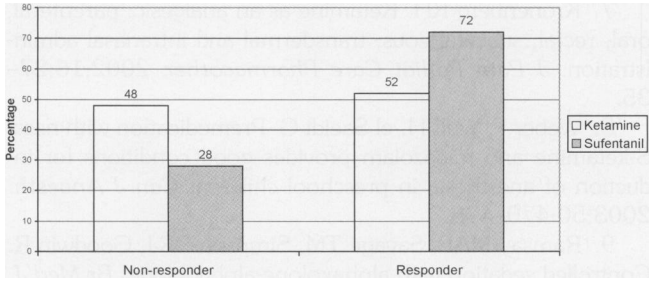

Figure 3. Oucher score categories for observer/researcher.

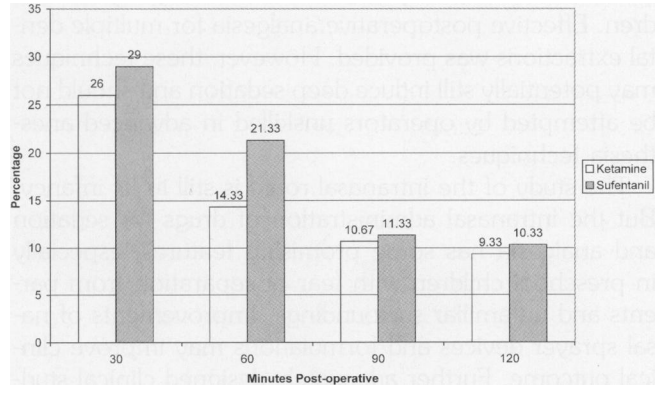

Figure 4. Word graphic rating scale for observer/researcher.

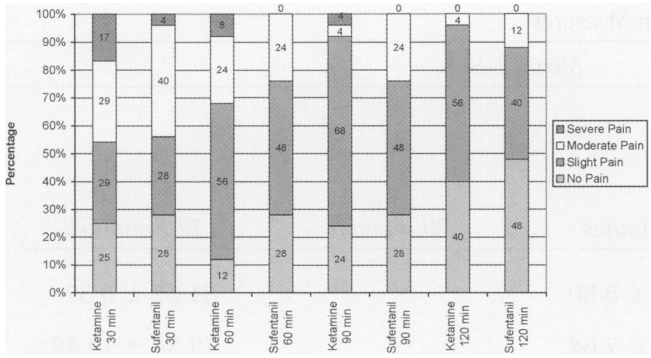

Figure 5. Modified Hannalah objective pain scale: for observer/researcher.

In children, intranasal administration of low doses of ketamine produce plasma concentrations associated with analgesia.[32] Intranasal ketamine permits pleasant and rapid separation of children from their parents, cooperative acceptance of monitoring and of mask inhalation induction, and does not cause prolonged postanesthetic recovery or delayed discharge home.[33] The bioavailability of the nasal spray is approximately 45%. The area under the curve (0 to 6 hours) of its metabolite, norketamine, is low (approximately 100 ng/mL) in both enantiomers.[34] Most reports demonstrate no or mild psychotomimetic effects when ketamine is dosed at subanesthetic doses.[7] This is further reduced by the use of the S-enantiomer of ketamine.[35]

This study directly compared a combination of sufentanil/midazolam with intranasal ketamine/midazolam to determine which drug combination is preferable for sedation and postoperative pain relief in preschool children. This is, to our knowledge, the first time that a randomized double-blind study has been used in this way. This study demonstrated the safety and efficacy of both methods. Key features were the ease of administration, combined with rapid onset of action. Both groups were equally sedated. A smooth mask induction of anesthesia was experienced in the majority of children. Effective postoperative analgesia for multiple dental extractions was provided. However, these techniques may potentially still induce deep sedation and should not be attempted by operators unskilled in advanced anesthesia techniques.

The study of the intranasal route is still in its infancy. But the intranasal administration of drugs for sedation and analgesia has some promising features, especially in preschool children with fear of separation from parents and unfamiliar surroundings. Improvements of nasal sprayer devices and formulations may improve clinical outcome. Further adequately designed clinical studies are needed.

Table 5. Modified Hannalah Objective Pain Scale

Observation	*Criteria*	*Points*
Blood Pressure	± 10% preop	0
	>20% preop	1
	>30% preop	2
Crying	Not crying	0
	Crying but responds to tender loving care	1
	Crying and does not respond to tender loving care	2
Movement	None	0
	Restless	1
	Thrashing	2
Agitation	Patient asleep or calm	0
	Mild	1
	Hysterical	2
Posture	No special posture	0
	Flexing limbs	1
	Holding mouth	2
Complaints of pain	Asleep or states no pain	0
	Cannot localize	1
	Can localize	2

REFERENCES

1. Ward M, Minto G, Alexander-Williams JM. A comparison of patient-controlled analgesia administered by the intravenous or intranasal route during the early postoperative period. *Anaesthesia.* 2002;57:48–52.

2. Helmers JH, Noorduin H, Van Peer A, et al. Comparison of intravenous and intranasal sufentanil absorption and sedation. *Can J Anaesth.* 1989;36:494–497.

3. Manjushree R, Lahiri A, Ghosh BR, et al. Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients. *Can J Anaesth.* 2002;49(2):190–193.

4. Henderson JM, Brodsky DA, Fisher DM, et al. Pre-induction of anesthesia in pediatric patients with nasally administered sufentanil. *Anesthesiology.* 1988;68:671–675.

5. Knoester PD, Jonker DM, Van Der Hoeven RT, et al. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. *Br J Clin Pharmacol.* 2002;53:501–507.

6. Zedie N, Amory DW, Wagner BK, O'Hara DA. Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. *Clin Pharmacol Ther.* 1996;59:341–348.

7. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother.* 2002;16:27–35.

8. Weber F, Wulf H, el Saeidi G. Premedication with nasal S-ketamine and midazolam provides good conditions for induction of anesthesia in preschool children. *Can J Anaesth.* 2003;50:470–475.

9. Ramsay MAE, Savage TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxolone-alphadolone. *Br Med J.* 1974;2:656.

10. Aldrete A. Post-anaesthetic recovery score. *Anesth Analg.* 1970;49:924–933.

11. Norden J, Hannallah, Getson P, Kellihir G, Walker N. Reliability of an objective pain scale in children. *Anesth Analg.* 1991;72:S199.

12. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. *Drug Discov Today.* 2002;15:7:967–975.

13. Davis SS, Illum L. Absorption enhancers for nasal drug delivery. *Clin Pharmacokinet.* 2003;42:1107–1128.

14. Shapira J, Holan G, Botzer E, et al. The effectiveness of midazolam and hydroxyzine as sedative agents for young pediatric dental patients. *ASDC J Dent Child.* 1996;63:421–425.

15. Cheng YS, Holmes TD, Gao J, et al. Characterization of nasal spray pumps and deposition pattern in a replica of the human nasal airway. *J Aerosol Med.* 2001;14:267–280.

16. Hascicek C, Gonul N, Erk N. Mucoadhesive microspheres containing gentamicin sulfate for nasal administration: preparation and in vitro characterization. *Farmaco.* 2003;58: 11–16.

17. Petersen FJ, Worts O, Schaefer T, Sojka PE. Design and atomization properties for an inside-out type effervescent atomizer. *Drug Dev Ind Pharm.* 2004;30:319–326.

18. Dallman JA, Ignelzi MA, Briskie DM. Comparing the safety, efficacy and recovery of intranasal midazolam vs. oral chloral hydrate and promethazine. *Pediatr Dent.* 2001;23: 424–430.

19. Newman SP, Pitcairn GR, Dalby RN. Drug delivery to the nasal cavity: in vitro and in vivo assessment. *Crit Rev Ther Drug Carrier Syst.* 2004;21:21–66.

20. Fitzgibbon D, Morgan D, Dockter D, Barry C, Kharasch ED. Initial pharmacokinetic, safety and efficacy evaluation of nasal morphine gluconate for breakthrough pain in cancer patients. *Pain.* 2003;106:309–315.

21. Roelofse JA, Payne KA. Oral tramadol: analgesic efficacy in children following multiple dental extractions. *Eur J Anaesthesiol.* 1999;16:441–447.

22. Acs G, Moore PA, Shusterman S, Needleman HL. The extent of trauma and postextraction pain in children. *Pediatr Dent.* 1988;10:210–214.

23. Moore PA, Acs G, Hargreaves JA. Postextraction pain relief in children: a clinical trial of liquid analgesics. *Int J Clin Pharmacol Ther Toxicol.* 1985;23:573–577.

24. Perrott DA, Goodenough B, Champion GD. Children's ratings of the intensity and unpleasantness of post-operative pain using facial expression scales. *Eur J Pain.* 2004;8:119–127.

25. Roelofse JA, Payne KA. Oral tramadol: analgesic efficacy in children following multiple dental extractions. *Eur J Anaesthesiol.* 1999;16:441–447.

26. Paik HJ, Ahn YM. Measurement of acute pain after eye surgery in children. *Korean J Ophthalmol.* 2002;16:103–109.

27. Goodenough B, Addicoat L, Champion GD. Pain in 4 to 6 year old children receiving intramuscular injections: a comparison of the faces pain scale with other self report and behavioural measures. *Clin J Pain.* 1997;13:60–73.

28. Dale O, Hjortkjaer R, Kharasch ED. Nasal administration of opioids for pain management in adults. *Acta Anaesthesiol Scand.* 2002;46:759–770.

29. Jensen B, Matsson L. Oral versus rectal midazolam as a pre-anaesthetic sedative in children receiving dental treatment under general anaesthesia. *Acta Paediatr.* 2002;91: 920–925.

30. al-Rakaf H, Bello LL, Turkustani A, Adenubi JO. Intranasal midazolam in conscious sedation of young paediatric dental patients. *Int J Paediatr Dent.* 2001;11:33–40.

31. Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. *Paediatr Anaesth.* 2002;12:685–689.

32. Malinovsky JM, Servin F, Cozian A, et al. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. *Br J Anaesth.* 1996;77:203–207.

33. Diaz JH. Intranasal ketamine preinduction of paediatric outpatients. *Paediatr Anaesth.* 1997;7:273–278.

34. Yanagihara Y, Ohtani M, Kariya S, et al. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharm Drug Dispos.* 2003;24:37–43.

35. Engelhardt W. Recovery and psychomimetic reactions following S-(+)-ketamine. *Anaesthetist.* 1997;46(suppl 1): S38–S42.