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Comparison of transmucosal midazolam with inhalation sedation for dental extractions in children. A randomized, cross-over, clinical trial

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Background: The transmucosal route for conscious sedation in children has been reported widely in the field of medicine, but less so in dental patients. The aim of this study was to evaluate the efficacy and safety profile of midazolam (0.2 mg/kg) administered by the buccal transmucosal route, in comparison with nitrous oxide/oxygen inhalation sedation, for orthodontic extractions in 10–16-year-old dental patients.
Methods: Each patient attended for two visits and was randomly allocated to receive buccal midazolam (0.2 mg/kg) or nitrous oxide/oxygen titrated to 30%/70% at the first visit, the alternative being used at the second visit. The patients' vital signs, sedation levels and behavioural scores were recorded throughout. Postoperatively, side-effects, recall of the visit and satisfaction levels were recorded via questionnaire.
Results: Thirty-six patients, with a mean age of 12.9 years, completed both arms of the trial. The maximum level of sedation was achieved with buccal midazolam in a mean time of 14.42 min, compared with 7.05 min with inhalation sedation. The vital signs with both types of sedation remained within acceptable limits and the reported side-effects were of no clinical significance. Buccal midazolam was found to be acceptable by 65.7%. Only 28.6% of cases preferred this technique, the main disadvantage being the taste of the solution.
Conclusion: Buccal midazolam sedation (0.2 mg/kg) seems to be equally as safe and effective as nitrous oxide/oxygen for the extraction of premolar teeth in anxious children. However, further research is required to refine the midazolam vehicle to improve acceptability.

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Key words: Buccal transmucosal midazolam; children; conscious sedation; dentistry; nitrous oxide inhalation sedation.

THE transmucosal route for providing sedation in children has been reported widely in the field of medicine, but less so in dental patients. The advantage of the transmucosal drug route is the rapid absorption of the drug directly into the systemic circulation, from an area rich in blood supply, without the disadvantage of passing through the portal circulation (1, 2).

One possible method of transmucosal administration of midazolam is via the buccal route. It has been shown that absorption via the oral transmucosal route results in a high bioavailability because of the lack of hepatic first-pass effect (1). The pharmacokinetics of oral transmucosal (buccal/sublingual) midazolam suggest that this may be a fast and effective form of drug administration when providing conscious sedation in an outpatient setting.

The aim of this study was to evaluate the efficacy, safety profile and patient acceptability of midazolam (0.2 mg/kg) administered via the buccal transmucosal route, in comparison with nitrous oxide/oxygen inhalation sedation, for orthodontic extractions in 10–16-year-old paediatric dental patients.

Methods

The study design incorporated the same model as validated in three previous studies concerning paediatric dental sedation (3–5), and was a prospective, randomized, controlled, cross-over clinical trial. Ethical approval was obtained from Newcastle and North Tyneside Ethics Committee. A full verbal and written explanation of the study was given to the child and parent, and written consent was obtained for inclusion.

Subjects were recruited from children aged 10–16 years, ASA I and II, who had been referred for orthodontic extractions of four premolar teeth under sedation and local analgesia. Each child was specifically assessed as to his or her need and fitness for sedation. Children considered to be mouth breathers, those on central nervous system depressants and those sensitive to benzodiazepines were excluded from the trial. The period of recruitment, treatment and follow-up was 22 months from November 2002 to August 2004.

The sample size was calculated using a power calculation based on data obtained from the Spielberger State/Trait Anxiety Scale, one of the outcome measures employed in a study to assess patient anxiety (6). An estimate of the standard deviation was obtained by considering a previous study which used the Spielberger Scale. Kvale et al. (6) reported standard deviations of 11.6 and 12.6 in anxious and non-anxious groups, respectively. The calculation was based on achieving 80% power to detect a difference. A sample size of 40 patients was estimated to be necessary to detect a difference of 0.44 standard deviations, which was considered to be a substantial clinical effect. Patients were randomly allocated to treatment groups by a dental nurse independent of the investigator using a system of computerized random numbers. Blinding for the operator and patient was not possible in the trial as the two forms of sedation involved very different types of administration.

An experienced operator/sedationist who was a dentist, assisted by a trained dental sedation nurse, administered the sedation and carried out the dental extractions. All patients were asked to abstain from solids and liquids 2 h prior to their treatment visit. Baseline readings of the patients' blood pressure, pulse rate, arterial oxygen saturation and respiration rate, as well as their colour and level of responsiveness, were recorded. Monitoring was continued throughout the treatment visit.

Nitrous oxide/oxygen was administered using an MDM Quantiflex Inhalation Sedation Unit (RA Medical Service, Steeton, West Yorkshire, UK). The gases were titrated at a rate of 10% nitrous oxide every minute to 30% nitrous oxide/70% oxygen. An average level of 30% nitrous oxide provides a suitable level of sedation for dental treatment, and this level was therefore chosen (7–9). The level of 30% nitrous oxide was maintained throughout the dental procedure, with reassurance and distraction being provided by the clinician to enhance the sedative effect. At the end of treatment, 100% oxygen was administered for at least 3 min before removing the nasal mask.

A specially prepared formulation of midazolam, EPISTAT (Special Product Ltd., Woking, Surrey, UK), was used for buccal administration. It presents as a syrup of 10 mg/ml and is supplied with a 1-ml syringe. Using a dose of 0.2 mg/kg (0.02 ml/kg), the solution was placed in equal amounts in the right and left buccal sulci, and the patient was asked to hold it there without swallowing. A dose of 0.2 mg/kg was selected as this has been shown to be effective in previous studies of transmucosal midazolam in children (2, 10, 11). After a period of 10 min, the patient was asked if he or she was ready to start treatment. If the answer was yes, the clinician commenced treatment. If the child answered no or was unsure, the clinician waited until consent was given to proceed. An adequate level of sedation to allow treatment to proceed was considered as the point at which the patient appeared relaxed, demonstrated slurring/slowing of speech and a delayed response to commands, mild ptosis and ultimately willingness for treatment to be carried out.

Topical anaesthetic in the form of benzocaine gel (20%) was applied to the dried mucosa next to the tooth for 2 min. Lidocaine 2% with 1 : 80,000 epinephrine local analgesic was then administered in a standard technique to anaesthetize the appropriate teeth. When total analgesia had been achieved, the teeth were extracted.

On completion of treatment, the patient, accompanied by a parent, was escorted to the recovery area. Monitoring continued throughout the recovery period with the patient remaining for at least 20 min following the commencement of inhalation sedation and for at least 60 min after the administration of buccal midazolam. Standard criteria for discharge were used: vital signs within normal limits, able to walk unaided and full verbal communication. At the end of the recovery period, the operator assessed the patient's fitness to return home and post-operative verbal and written instructions were provided.

The child's weight, blood pressure, pulse, respiration rate and oxygen saturation were recorded before dental surgery to provide baseline measurements. Following administration of the sedative, the blood pressure, pulse rate, respiration rate and oxygen saturation were recorded every 2 min up to 20 min and at 5-min intervals thereafter, and the treatment stage was noted (local anaesthetic, extraction, recovery, discharge).

An assessment of pre- and post-operative levels of anxiety in each child was determined using the Children's Fear Survey Schedule Dental Subscale (12).

This scale consists of 15 questions relating to anxiety about different elements of dental treatment, with total scores ranging from 15 to 75. Scores equal to or exceeding 29 have been associated with high dental anxiety (13). General state anxiety was measured using the Spielberger State Anxiety Inventory (14). This questionnaire has 20 questions about general levels of anxiety and calmness. Each question has four possible answers, with total scores ranging from 20 to 80; scores equal to or exceeding 52 have been associated with high state anxiety (6). The children were asked to complete both forms in the waiting room immediately before treatment and again on the following day at home.

The level of sedation was recorded every 2 min up to 20 min and every 5 min thereafter using the Classification of Emotional Status (15) (Table 1). Over-sedation was considered as a loss of communication, respiratory depression and eventual loss of consciousness. Behaviour during treatment was graded using the first three categories of the Houpt Behaviour Rating Scale (16). The outcome of the treatment session was recorded using the fourth category of the Houpt Behaviour Rating Scale (16).

All patients were given a questionnaire at the end of each treatment visit and asked to complete it at home on the following day. In order to obtain information regarding amnesia of the visit, the patients were asked if they could remember receiving the local anesthetic, having the extraction and being in recovery. The post-operative questionnaire asked the patients to grade how they found and felt about each type of sedation, and to note what they liked best and least. Following the second visit, the patients were asked to comment on their preferred form of sedation and the reason for their choice. After each visit, the parent was asked to comment on any adverse effects observed following treatment when the child returned home. Data were analysed using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL). A paired *t*-test was used to analyse continuous data, including time factors and anxiety levels. When the data did not follow a normal distribution, the non-parametric Wilcoxon sign rank test was used. Physiological data were analysed using analysis of variance (ANOVA) to compare the two forms of sedation at the different time points. Qualitative data from the patient satisfaction questionnaire were transcribed for evaluation.

Table 1

Breitkopf and Buttner classification of emotional status (15).

Score	Description
1	Irritated: awake, restless, crying
2	Normal: awake, calm
3	Inactive: tired, hardly moving
4	Sleepy: drowsy, without reaction but rousable

Results

Fifty-five patients were invited to take part in the study and 45 agreed. Of those recruited, 36 completed both arms of the trial and the results are based on this number of subjects. The mean age (range) was 12.9 years (10–15 years), with 10 male and 26 female patients. Of the nine who withdrew, four who had received inhalation sedation at their first visit requested this form of management for their second visit as they felt confident with this technique. One patient could not tolerate the taste of buccal midazolam, two became uncooperative with inhalation sedation and two became uncooperative with buccal sedation [this paragraph has been reported according to the Consolidated Standards of Reporting Trials (CONSORT) principle].

The mean weight (range) of the patients was 50.9 kg (34–91 kg) and the mean dose (range) of midazolam administered was 10.0 mg (6.8–18.2 mg). All vital signs remained within acceptable clinical limits with both forms of sedation. The maximum sedation scores recorded for each type of sedation were similar, with all 36 patients in the midazolam group scoring 3 (tired), compared with 35 in the inhalation sedation group. The time periods for various stages of the appointment are illustrated in (Table 2). For 'crying' and 'movement', Houpt scores of 1 and 2 were considered as disruptive behaviour. No children demonstrated disruptive behaviour in either

Table 2

Time periods of different stages of the visit.

	Mean (range) time period (min)		
	Time to maximum sedation level	Extraction procedure	Duration of visit
Buccal midazolam	14.4 (2–20)	10.1 (4–18)	64.7 (60–90)
Nitrous oxide	7.1 (2–10)	8.0 (4–16)	34.1 (28–44)
Significance	$P < 0.001$	$P < 0.001$	$P < 0.001$
	CI 6.4–8.4	CI 1.3–3.5	CI 28.1–33.5
	SD 3.0	SD 3.1	SD 8.0

CI, confidence interval; SD, standard deviation.

group, and no significant difference in overall behaviour was noted. Side-effects on returning home were reported by a similar number of patients for each type of sedation [16 (44%) following buccal midazolam and 14 (38.9%) following nitrous oxide/oxygen], and included sleepiness, headache and slight nausea. There was no significant difference between the two groups and the symptoms were considered to be minimal.

Thirty-five patients in the midazolam group and 36 patients in the nitrous oxide group responded to the questions on recall; the results are illustrated in Fig. 1. More children in the midazolam group failed to remember receiving the local anaesthetic compared with those in the nitrous oxide group; however, the difference was not significant ($P = 0.289$, McNemar test). Although greater amnesia of the extractions was reported with midazolam, there was no significant difference between the two sedation groups ($P = 0.29$, McNemar test). Opinions regarding future sedation and preferences were obtained from 35 patients who had received buccal midazolam and 36 who had received nitrous oxide/oxygen. Twenty-three (65.7%) were prepared to have buccal midazolam again, compared with 32 (88.9%) who were willing to have nitrous oxide/oxygen again ($P = 0.77$, McNemar test). Nitrous oxide/oxygen sedation was preferred by 20 (57.1%), buccal midazolam by 10 (28.6%) and no preference was expressed by five (14.3% of patients) ($P = 0.1$, Fisher's exact test). There was no significant association with the order of administration of the sedation techniques ($P = 0.058$, Fisher's exact test).

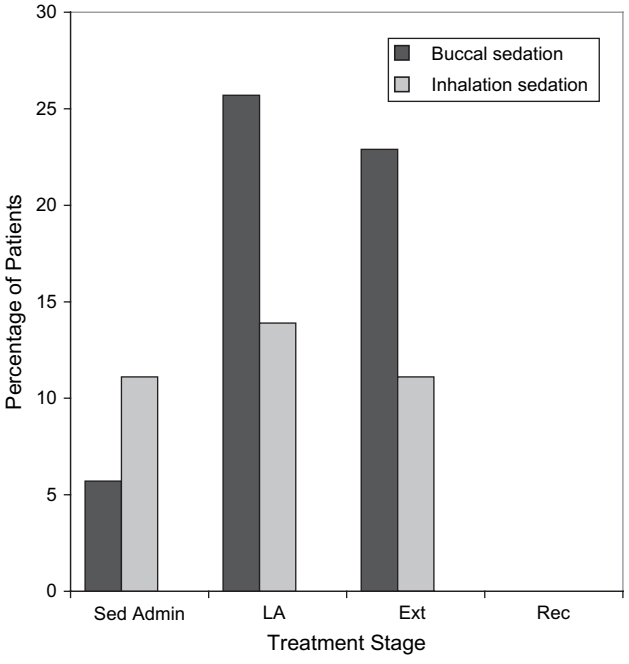

Fig. 1. Positive recall of the appointment. The results are presented as the number of subjects who remembered sedation (Sed Admin), local anaesthetic (LA), teeth extraction (Ext) and recovery (Rec).

The first pre-operative and final post-operative anxiety scores were compared to provide an indication of the overall treatment effect. The pre-operative state anxiety score on the Spielberger Scale for all subjects was 45.5 (20–73), and the mean post-operative score at the end of the study was 39.4 (20–66). Using a paired *t*-test, the difference was found to be significant: $P = 0.012$ [95% confidence interval (CI), 1.45–10.84; standard deviation (SD), 14.68]. For dental anxiety, the mean pre-operative score for all patients was 31.9 (15–61), with a mean post-operative score at the end of the study of 27.1 (15–52). The difference again was significant at $P < 0.001$ (95% CI, 2.43–7.22; SD, 7.5).

Discussion

Transmucosal administration of midazolam for paediatric sedation has been studied by the sublingual, nasal and rectal routes (10, 17–20), and has been shown to have a relatively high bioavailability compared with oral administration (20). A relatively new formulation of midazolam, EPISTAT, is now available for transmucosal administration via the buccal route, having been developed for the management of status epilepticus (21–23). To date, there have been no studies reported on the use of buccal midazolam for dental sedation.

It is essential when introducing new sedation drugs and/or techniques that these are as safe as those which form the mainstay of care. Respiratory depression is one of the most serious adverse effects attributed to midazolam. The results of this trial suggest that the arterial oxygen saturation levels recorded were clinically comparable for both types of sedation, and did not reach critical levels. Indeed, the lowest arterial oxygen saturation level recorded for the midazolam group was 94%, which compares with the results obtained by Scott et al. (23), who reported a minimum level of 93%. This study investigated the treatment of epileptic seizures, however, and direct comparison of the results may need to be considered with some caution.

Ideally, any new drug regime must exhibit limited post-operative problems. On returning home, minor problems were reported in both groups, including sleepiness, headache and nausea, but none

necessitated medical attention. In order to reduce the potential for post-operative complications, it is important to ensure that the patient has fully recovered and meets all the criteria for discharge prior to being allowed to travel home.

In the present trial, caution should be exercised when referring to the administration route and the amount of drug administered. Although the drug was placed in the buccal sulcus to allow for transmucosal absorption, after the first few cases it became apparent that an increase in salivation occurred. This resulted in the patient having difficulty holding the solution in the desired position, with small amounts of the drug being swallowed; therefore, the accuracy of the actual amount of drug absorbed by the buccal route alone is in question. This situation will need to be taken into consideration in future work, with a more accurate delivery system being developed.

Dental anxiety was demonstrated by the subjects on entering the trial, and it is encouraging to note that this decreased significantly throughout the study period. Although the data cannot be accurately attributed to any particular form of sedation, the result is similar to that reported in a study by Wilson et al. (4). Neither buccal midazolam nor nitrous oxide/oxygen sedation resulted in any child displaying disruptive behaviour. This is extremely promising, as one of the perceived problems when administering midazolam to children is the potential for disinhibition.

The technique of buccal sedation appeared to be acceptable to the majority of children; however, it was not the preferred sedation method. The reasons given for this were mainly dislike of the taste of midazolam and the increased salivation, making it difficult to retain the midazolam in the buccal sulcus. In order to make the technique more acceptable, the formulation used needs to be refined to improve the taste and to ensure that the transmucosal effect is working effectively with minimal oral ingestion. Collaboration with the research unit at the hospital pharmacy is being sought to develop a form of midazolam gel which can be applied more effectively.

Conclusion

The use of transmucosal midazolam via the buccal route appears to be as safe as inhalation sedation with nitrous oxide and oxygen in paediatric dental patients; however, patient acceptability was poor and further work is required to refine the technique if it is to be introduced into dental practice.

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