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A comparison of oral midazolam and nitrous oxide sedation for dental extractions in children

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Summary

The aim of the study was to compare oral midazolam and inhaled nitrous oxide as sedative agents during the management of children aged 5–10 years presenting for extraction of primary teeth under local anaesthetic. Subjects required two visits for the extraction of four primary teeth, one in each quadrant of the mouth, and were randomly allocated to be given nitrous oxide 30% in oxygen or oral midazolam 0.3 mg.kg^{-1} at the first visit, the other technique being used at the second visit. Vital signs, sedation levels and behavioural scores were recorded, and postoperative recall and satisfaction were reported by the patients. Thirty-five children, with a mean [range] age of 7.4 [5–10] years, completed the treatment. The mean dose of oral midazolam given was 8.6 [3.3–16.5] mg. The mean times taken to achieve the maximum level of sedation for midazolam and nitrous oxide sedation were 15.9 [2–30] min and 6.8 [2–10] min, respectively. Physiological parameters remained within acceptable clinical limits for both types of sedation. Oral midazolam was considered acceptable by 59% and was preferred by 36%. Oral midazolam sedation in 5 to 10-year-old children was shown to be as safe and effective as nitrous oxide in oxygen sedation for extraction of primary teeth but would not be the method of choice for all patients.

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The delivery of dental care to children can be very challenging. In such situations, the use of inhalational nitrous oxide sedation has proved to be very successful for the majority of patients [1–3]. However, when this is not effective, the only alternative management option may be general anaesthesia. Dental general anaesthesia is not without risk and in the UK the use of conscious sedation as an alternative has been encouraged [4]. Therefore, it is important to develop other sedation techniques acceptable to those patients who are not suitable or who fail to cope with nitrous oxide sedation. The oral administration of a drug is usually well accepted by children and indeed this route is used regularly for premedication before general anaesthesia. The drug most commonly used for premedication in children is midazolam [5–8]. Limited literature is available on the use of oral midazolam as a form of conscious sedation for paediatric dental patients. Researchers have used a dose range of 0.2–0.75 mg.kg^{-1} with varying results. The range with a good outcome and safety profile appears to be 0.2–0.5 mg.kg^{-1} [9–12]. The aim of the study was to compare the safety, effectiveness and acceptability of oral midazolam sedation with nitrous oxide sedation for the extraction of primary teeth under local anaesthesia children aged 5–10 years.

Methods

The study was designed as a prospective, randomised, controlled, crossover clinical trial and used a similar model to that of previous paediatric sedation trials conducted in our department [13, 14]. Approval was gained from the Newcastle and North Tyneside Ethics Committee and the study was carried out at the Newcastle Dental Hospital Sedation Department in the period 2003–4. Male and female patients aged 5–10 years, of ASA physical status I and II, who had been referred to the Department of Sedation for extraction of primary teeth under sedation and local analgesia were recruited. Suitable patients were those requiring the extraction of four primary teeth, one in each of the four quadrants of the

mouth. Each child was assessed as to their need and fitness for sedation. Only those who had failed to have the dental treatment carried out under local analgesia alone were recruited. Before recruiting subjects, a full verbal and written explanation of the study was given to the patient and the parent, and consent was gained from the parent.

The size of the sample necessary to detect a statistically significant difference was determined with a power calculation based on the results from studies carried out using the Houpt scale to evaluate behaviour [15, 16]. To achieve an 80% power to detect a difference between the two groups a sample size of 40 patients was required. Allocation to treatment groups was made by a dental nurse independent of the investigators, using computer-generated random numbers. Oral midazolam sedation (even number) or nitrous oxide inhalation sedation (odd number) was planned for the patient's first appointment. The other technique was used at the second appointment. Nitrous oxide sedation acted as the control, being the standard paediatric sedation technique in current use in the UK [17]. Dental extractions were carried out on opposite sides of the mouth at consecutive appointments, the order (right or left) being allocated randomly.

Both forms of sedation were administered by an experienced operator/sedationist, assisted by an appropriately trained dental sedation nurse. All patients were asked to starve for solids and liquids for 2 h before their treatment visit. In accordance with national guidelines [17], dental sedation is defined as 'conscious sedation' and as such the patients must always be able to maintain their own airway reflexes. For inhalational sedation, an MDM Quantiflex Inhalation Sedation unit (RA Medical Service, West Yorkshire, UK) was used to administer nitrous oxide in oxygen *via* a nasal mask in 10% increments to a final and maximum level of 30%, i.e. $F_{I}O_2 = 0.7$. Studies have shown that 30% nitrous oxide provides a suitable level of sedation for dental treatment and this level was therefore chosen for the control [1–3]. Nitrous oxide 30% was maintained throughout the dental procedure, with reassurance and distraction being provided by the clinician to enhance the sedative effect. On completion of the extractions, the nitrous oxide flow was terminated and 100% oxygen was administered for 3 min before the nasal mask was removed. The standard intravenous preparation of midazolam was given orally at a dose of 0.3 $mg.kg^{-1}$. As midazolam has a bitter taste, it was mixed with 30 ml of either sugar-free orange or blackcurrant cordial according to the patient's preference. The patient was then brought to a quiet area to wait for 20–30 min to allow the midazolam to take effect, and a sedation-trained nurse monitored the patient throughout this period. An adequate level of sedation to allow treatment to proceed was judged to be the point at which the patient showed a relaxed appearance, slurring and slowing of speech, a delayed response to commands, mild ptosis and a willingness to commence treatment but with the ability to communicate at all times. The patient's blood pressure, pulse rate, peripheral oxygen saturation and respiration rate, as well as their colour and level of responsiveness, were monitored during the onset of sedation, dental treatment and recovery.

Topical anaesthesia 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 adrenaline was then given in a standardised manner, i.e. maxillary primary teeth: buccal infiltration and palatal infiltration via the buccal papilla; mandibular primary teeth: buccal infiltration followed by lingual infiltration via the buccal papilla. Before tooth extraction, analgesia was tested using a dental probe placed into the gingiva buccally and lingually. When this was confirmed, the tooth was extracted using the appropriate forceps. On completion of treatment, the patient was transferred to a recovery area accompanied by a parent and supervised by a sedation nurse. The patient remained in recovery for at least 20 min after the start of nitrous oxide sedation and for at least 60 min after the administration of oral midazolam. At the end of the recovery period, the operator assessed the patient's fitness for discharge. Standard criteria for discharge were used: vital signs within normal limits, able to walk unaided, and full verbal communication. Post-operative sedation and surgical instructions were given to the parent before discharge.

To provide baseline readings before the administration of sedation, the child's weight, blood pressure, pulse, respiration rate and peripheral oxygen saturation were recorded on entering the dental surgery. After administration of the sedative, blood pressure, pulse rate, respiration rate and oxygen saturation were recorded every 2 min for the first 20 min and at 5-min intervals thereafter, and the treatment stage was noted, i.e. local anaesthesia, extraction, recovery and discharge. The level of sedation was recorded every 2 min for the first 20 min and every 5 min thereafter using the Classification of Emotional Status [18] (Table 1). Over-sedation was considered to be a loss of communication, respiratory

Table 1 Brietkopf and Buttner Classification of Emotional Status [18].

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

Table 2 Houpt Behaviour Rating Scale, sections 1–3 [15].

	Score
Rating for sleep	
Fully awake, alert	1
Drowsy, disorientated	2
Asleep	3
Rating for movement	
Violent movement interrupting treatment	1
Continuous movement making treatment difficult	2
Controllable movement that does not interfere with treatment	3
No movement	4
Rating for crying	
Hysterical crying that demands attention	1
Continuous, persistent crying that makes treatment difficult	2
Intermittent, mild crying that does not interfere with treatment	3
No crying	4

Table 3 Houpt Behaviour Rating Scale, section 4 [15].

	Score
Rating for overall behaviour	
Aborted – no treatment rendered	1
Poor – treatment interrupted, only partial treatment completed	2
Fair – treatment interrupted but eventually all completed	3
Good – difficult, but all treatment performed	4
Very good, some limited crying or movement, e.g. during anaesthesia or mouth prop insertion	5
Excellent – no crying or movement	6

depression and eventual loss of consciousness. Behaviour during treatment was graded using the first three categories of the Houpt Behaviour Rating Scale [15] (Table 2). The outcome of the treatment session was recorded using the fourth category of the Houpt Behaviour Rating Scale [15] (Table 3). All patients were given a questionnaire at the end of each treatment visit and they were asked to complete it at home the following day. To obtain information about amnesia for the visit, the patients were asked if they could remember receiving the local anaesthetic, having the extraction and being in recovery. The postoperative questionnaire also asked the patients to grade how they felt about both types of sedation and they were asked to note what they liked best and least about the visit. After 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 parents were asked to comment on any adverse effects observed after treatment when their children returned home.

Data were entered onto a PC database using Minitab version 13 for WINDOWS (Minitab Ltd, Coventry, UK) and the analysis was carried out 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. Where data did not follow a normal distribution, the non-parametric Wilcoxon Sign Ranks test was used. The physiological data were analysed using ANOVA to compare the two forms of sedation at the different time points. Qualitative data from the patient satisfaction questionnaire were transcribed for evaluation.

Results

Forty-two patients were recruited for the trial, with 35 completing the planned treatment. Seven patients (16.7%) withdrew at various stages: three were unable to tolerate the oral midazolam; two were unable to tolerate the nasal mask; one requested inhalational sedation for both visits; one failed to attend the second visit. The mean [range] age was 7.4 [5–10] years, all but one were ASA physical status I and 19/35 were male. The mean [range] weight of the patients was 29.5 [17–55] kg and the mean [range] dose of midazolam administered was 8.6 [3.3–16.5] mg. It should be noted that in one case the child did not manage to swallow the full prescribed dose of midazolam and this accounts for the minimum drug dose of 3.3 mg. Heart rate, blood pressure, respiratory rate and peripheral oxygen saturation data at six different time points are given in Table 4. All vital signs remained within acceptable clinical limits with both forms of sedation.

The maximum sedation scores recorded for each type of sedation are illustrated in Fig. 1. The difference was found to be significant, with midazolam producing a greater level of sedation ($p < 0.001$, Wilcoxon Sign Rank Test). The durations of the various stages of the treatment are shown in Table 5. 'Crying' and 'movement' Houpt scores of 1 and 2 were considered to be disruptive behaviour. No disruptive behaviour was seen in children given nitrous oxide sedation. When oral midazolam was given, disruptive crying was seen in 3/35 (8.6%) patients and disruptive movement in 5/35 (14.3%) patients. These findings did not reach statistical significance ($p = 0.253$ and $p = 0.063$, respectively (McNemar test)). Side-effects on returning home were reported by a similar number of patients for each type of sedation: 7/35 (20%) after oral midazolam and 8/35 (23%) after nitrous oxide/oxygen. These included drowsiness and headache, and were reported to be self-limiting with no intervention required.

Feedback on recall was received from 32 patients in the midazolam group and 31 patients in the nitrous oxide group and is illustrated in Fig. 2. More children failed to recall the extractions and being in recovery when given midazolam than when given nitrous oxide. When the data were analysed using the McNemar test, the differences were found to be significant ($p = 0.031$ for both

Table 4 Cardiovascular and respiratory parameters recorded during midazolam and nitrous oxide sedation. Values are mean [range], or median [range] for peripheral oxygen saturation.

	Midazolam sedation	Nitrous oxide sedation
Baseline		
Mean arterial blood pressure; mmHg	77.9 [63.3–93.3]	77.3 [62–113]
Heart rate; beats.min^{-1}	82.2 [53–107]	83.7 [58–123]
Respiratory rate; bpm	19.6 [16–24]	20.0 [16–24]
Peripheral oxygen saturation; %	98 [95–100]	99 [96–100]
At maximum sedation		
Mean arterial blood pressure; mmHg	75.5 [58–92.6]	75.7 [63–100]
Heart rate; beats.min^{-1}	81.6 [64–104]	79.8 [56–122]
Respiratory rate; bpm	19.4 [16–22]	20.0 [16–22]
Peripheral oxygen saturation; %	98 [95–100]	100 [97–100]
At injection of local anaesthetic		
Mean arterial blood pressure; mmHg	75.9 [62–100.6]	75.7 [63.3–92.3]
Heart rate; beats.min^{-1}	83.2 [60–111]	82.2 [57–113]
Respiratory rate; bpm	19.8 [16–22]	19.8 [16–24]
Peripheral oxygen saturation; %	99 [96–100]	100 [98–100]
At tooth extraction		
Mean arterial blood pressure; mmHg	74.9 [63–89.3]	76.7 [59.6–93]
Heart rate; beats.min^{-1}	93.5 [66–118]	85.4 [63–109]
Respiratory rate; bpm	19.6 [16–22]	19.9 [16–24]
Peripheral oxygen saturation; %	99 [96–100]	100 [98–100]
On entering recovery room		
Mean arterial blood pressure; mmHg	74.0 [60.3–86.6]	76.7 [59.6–93]
Heart rate; beats.min^{-1}	90.1 [57–113]	81.5 [57–106]
Respiratory rate; bpm	19.4 [16–22]	19.8 [16–24]
Peripheral oxygen saturation; %	99 [95–100]	100 [96–100]
At discharge		
Mean arterial blood pressure; mmHg	75.9 [57.6–97.6]	76.8 [62–95.6]
Heart rate; beats.min^{-1}	87.6 [71–109]	84.8 [59–123]
Respiratory rate; bpm	19.2 [16–20]	20.0 [14–26]
Peripheral oxygen saturation; %	98 [95–100]	98 [96–100]

treatment stages). Opinions regarding future sedation and preferences were received from 32 patients who had been given oral midazolam and 31 who had been given nitrous oxide, and the results are illustrated in Fig. 3. No difference between the two techniques was found for the choice of future sedation ($p = 0.5$, McNemar test) or preference ($p = 0.063$, McNemar test). The order of administration of sedation technique had no influence on preference (Fig. 4) ($p = 0.332$, Fisher's Exact test). The main reasons for preferring oral midazolam were: 'I felt more relaxed' and 'not having the mask' and for inhalational sedation were: 'I didn't like taste of the drink' and 'it was faster'.

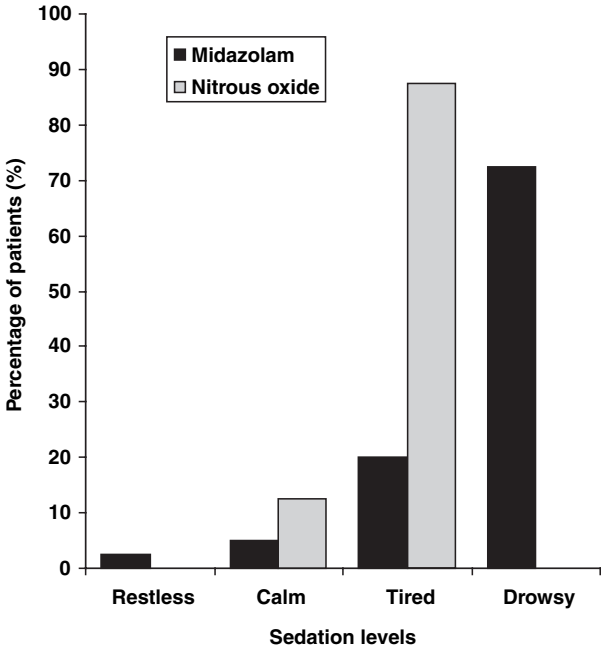

Figure 1 Maximum sedation levels for patients undergoing midazolam and nitrous oxide sedation.

Table 5 Time to maximum sedation and durations of extraction and total visit. Values are mean [range].

	Midazolam sedation	Nitrous oxide sedation	p value
Time to maximum sedation; min	15.9 [2–30]	6.8 [2–10]	$p < 0.001$
Duration of extraction; min	8.9 [4–18]	6.6 [4–14]	$p = 0.001$
Total duration of visit; min	74.8 [60–100]	33.2 [24–65]	$p < 0.001$

Discussion

It is not uncommon for a young child's first experience of dental treatment to involve extractions, a potentially traumatic experience. Many paediatric dental patients can be managed with behavioural management and local anaesthesia alone. However, pharmacological support is required for some in the form of conscious sedation. The use of oral medication in children is usually well accepted. However, this route of administration is not without its difficulties. The taste of the solution can often be a barrier and may result in the child rejecting the medication. In developing a technique for oral sedation, the drug preparation must be palatable and acceptable to the patient. Midazolam has a pH of 3.5–4.0 and therefore tastes very acidic. In this study, in an attempt to make the midazolam palatable, the children were given a choice of the flavour of

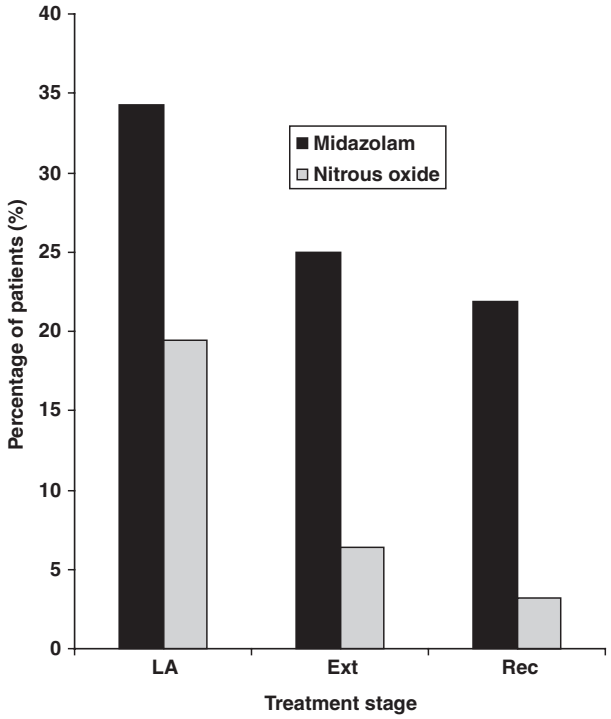

Figure 2 Percentage of patients recalling injection of local anaesthetic (LA), extraction of teeth (Ext) and being in the recovery room (Rec).

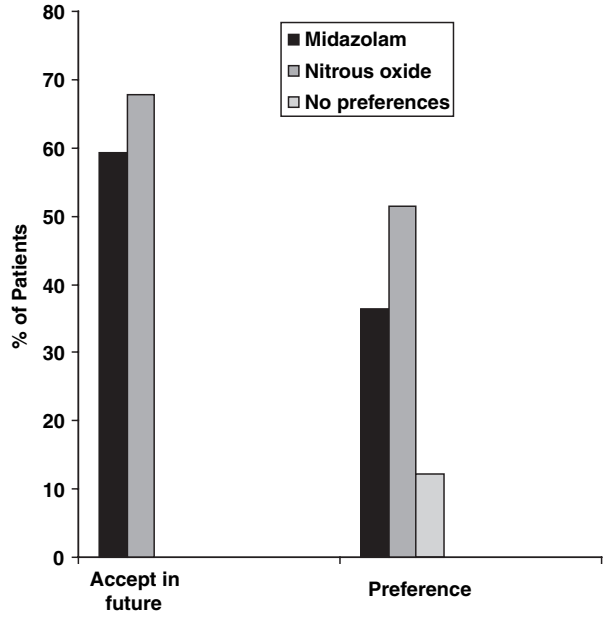

Figure 3 Percentage of patients identifying which technique they would accept in the future and indicating a preference for the technique used.

a cordial to be added to the drug, resulting in good compliance. Indeed, only one of the children was unable to tolerate the solution, resulting in their withdrawal from the trial. However, it is worth noting that 8/35 (23%) children commented on the taste as being one of the worst aspects of the oral midazolam. Other formulations may provide a more palatable preparation, such as Versed syrup, available only in the USA at present [19]. The addition of fruit flavoured Syrpalta Syrup has been shown to improve compliance [20]. It may also be possible to ask local hospital pharmacy units to prepare a palatable oral solution. However, in using such solutions one must be aware of the stability and therefore the shelf life of the drug, and the method of storage.

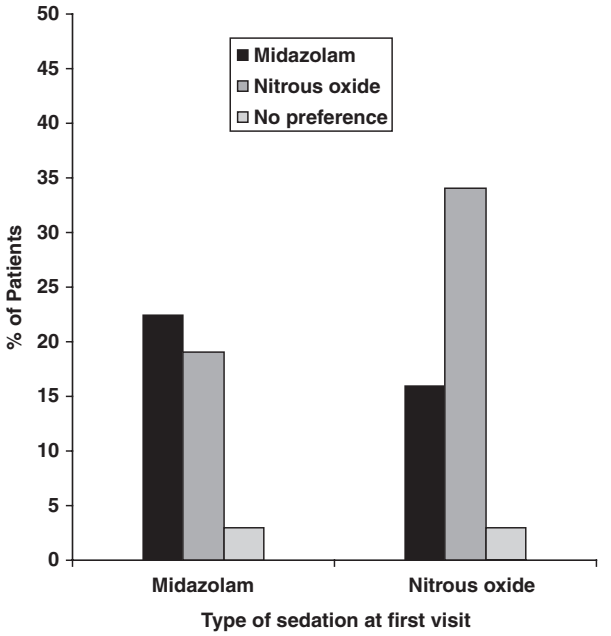

Figure 4 Percentage of patients expressing a preference for a technique related to which technique was used first.

For any drug to be appropriate for patient use it must have a satisfactory safety profile. With regard to physiological parameters and reported side-effects, both drugs used in this study showed acceptable profiles, findings consistent with other studies carried out in similar age groups [7, 9, 20, 21]. The main objection to the use of midazolam for conscious sedation in children is the risk of a paradoxical reaction. Although rare, these reactions can often be profound in young children, particularly when the drug has been administered orally [10, 11, 22]. In this study, 2/42 (5%) of the children demonstrated unco-operative behaviour after oral midazolam. This took the form of persistent crying and distress necessitating withdrawal from the trial. This incidence is similar to that reported in the literature and would appear to be less problematic than previously thought. However, it does serve to remind us that oral midazolam is not a universal panacea.

The time necessary to perform sedative and other procedures may influence their clinical practicality and often the patient's opinion of the care provided. The time to the maximum level of sedation, although greater for oral midazolam than nitrous oxide, was still clinically acceptable and compares well with previous studies [5, 9]. The greater preference for inhalational sedation in this study differs from that reported in a similar study conducted at our centre involving 10 to 16-year-olds [13], in which oral midazolam was the preferred sedation technique. The difference may relate to the level of maturity of the subjects and therefore their ability to cope with the more profound feelings of sedation. A higher dose of midazolam was used in the 10 to 16-year-old study, and this may have had a bearing on patient opinion. A study of dose-related effects in similar age groups would be of interest.

It interesting to note that there was a tendency to prefer the type of sedation administered at the first visit. This may be due to a level of confidence that results from the child having a positive experience with a particular treatment modality. Where this has been successful, patients may be reluctant to try a new and different technique. Comparing the different sedation techniques, twice as many children reported that the worst aspects of care were 'getting teeth out' and 'gums being frozen' when inhalational sedation was used, and this suggests that the amnesic property of midazolam is beneficial for some patients, particularly when more traumatic procedures are being carried out.

In conclusion, this study has demonstrated that oral midazolam 0.3 $mg.kg^{-1}$ is as effective as nitrous oxide in producing a satisfactory level of sedation for carrying out local anaesthetic extractions of primary teeth in healthy children. Although it would appear not to be the preferred technique, oral midazolam may be more appropriate for some individuals depending on their treatment requirements, level of anxiety and compliance with the treatment. Sedating young children requires a high level of knowledge of and skill with the particular technique chosen, and it is imperative that any clinician undertaking such treatment is fully competent to do so.

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