Anaesthesia, 2002, **57**, pages 860–867

A randomised, controlled, crossover trial of oral midazolam and nitrous oxide for paediatric dental sedation

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Summary

A randomised, controlled, crossover trial was designed to assess the safety and effectiveness of oral midazolam sedation for orthodontic extractions. Forty-six ASA physical status I children aged 10–16 years were recruited. Each child required two treatment sessions. Sedation with either oral midazolam 0.5 mg.kg^{-1} or nitrous oxide in oxygen was used at the first visit, the alternative being used at the second visit. Blood pressure, heart rate, arterial oxygen saturation, and sedation and behavioural scores were recorded every 5 min. Anxiety levels and postoperative satisfaction were also recorded. Blood pressure, heart rate and arterial oxygen saturation in both groups were similar and within acceptable clinical limits. The median [range] lowest arterial oxygen saturation levels for subjects in the midazolam and nitrous oxide groups were 95 [90–100]% and 98 [93–100]%, respectively. The median [range] time to the maximum level of sedation in the midazolam group was 20 [5–65] min compared with 5 [5–10] min in the nitrous oxide group ($p < 0.001$). The median [range] duration of treatment was similar in both groups (midazolam group: 10 [5–30] min, nitrous oxide group: 10 [5–25] min). Seventy-four per cent of subjects were prepared to have oral midazolam sedation again, 54% preferring it. Oral midazolam appears to be a safe and acceptable form of sedation for 10–16-year-old paediatric dental patients.

Keywords *Surgery*: dental. *Hypnotics*: benzodiazepines; midazolam. *Anaesthetics*: gases; nitrous oxide. *Anaesthesia*: outpatient.

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Accepted: 30 March 2002

Conscious sedation is used extensively in dentistry to help anxious patients undergo dental treatment with minimal physiological and psychological stress. The General Dental Council [1] and the Royal College of Anaesthetists [2] have both encouraged the use of conscious sedation as a safe alternative to general anaesthesia for dental care. More recently, the Department of Health in the UK has further emphasised the need to use alternatives to general anaesthesia where appropriate [2]. The main type of sedation used for paediatric dental patients in the UK is an inhalational technique known as 'relative analgesia', which uses nitrous oxide in oxygen [4]. The technique has a proven safety record and is the mainstay of paediatric dental sedation in the UK [5–8].

However, nitrous oxide presents a potential hazard to clinical staff who are involved in providing inhalational sedation on a regular basis [9, 10]. There is evidence that chronic exposure to nitrous oxide gas can produce haematological, reproductive and neurological problems [11–14]. Although the use of scavenging equipment, good technique and well-ventilated surgeries have significantly decreased the level of staff exposure, there is inevitably some residual surgery pollution [10, 15]. The Health Services Advisory Committee has recently addressed the issue of occupational hazards and has recommended occupational exposure levels to nitrous oxide and other anaesthetic gases for staff involved [16]. Indeed, some experts predict that nitrous oxide will ultimately be banned as an anaesthetic sedation agent in order to eliminate completely the risk to clinical personnel [13].

With the need to provide alternatives to general anaesthesia for paediatric dental patients, and in the light of the potential problems associated with the use of nitrous oxide, and the fact that it is not accepted by some

paediatric dental patients, it is important to seek alternative sedation drugs for use in children. The use of oral sedation techniques may provide a useful alternative. Midazolam, the benzodiazepine with the most favourable pharmacological profile for this application, has been found to be an effective oral premedication before anaesthesia for surgical procedures [17–21]. It has a rapid onset and its relatively short half-life is associated with rapid recovery. It is therefore well suited to ambulatory surgery in dental practice [22, 23]. It has been suggested that oral midazolam sedation could provide an effective method of conscious sedation in paediatric dental patients, however, this has not been evaluated in the UK.

The aim of the study was to evaluate the safety, effectiveness and patient acceptability of oral midazolam sedation in paediatric dental patients undergoing orthodontic extractions of permanent teeth and to compare its use with that of nitrous oxide and oxygen sedation.

Methods

The study was designed as a prospective, randomised, controlled, crossover trial and had the approval of Newcastle and North Tyneside Local Research Ethics Committee. Forty-six patients, aged 10–16 years, ASA physical status I or II, referred to the Department of Sedation at Newcastle Dental Hospital for orthodontic extraction of at least four teeth (premolars or canines), were recruited. Each patient required bilateral, identical extractions on opposite sides of the mouth. A full verbal explanation of the study and a written information sheet detailing the procedures involved were given to both child and parent. If both the child and the parent agreed with participation in the study, then the parent was asked to sign a consent form. If the child did not consent to take part, he or she was not included in the study but was instead treated in a routine manner. Using computer-generated random numbers, patients were allocated to receive either oral midazolam sedation (even number) or nitrous oxide sedation (odd number) at their first appointment. The alternative technique was used at their second appointment. Nitrous oxide sedation acted as the control, being the standard paediatric sedation technique in current use in the UK. Dental extractions were carried out on opposite sides of the mouth at consecutive appointments, the order (right or left) being allocated randomly.

An experienced operator/sedationist (a dentist trained in sedation techniques and holding the University of Newcastle Diploma in Conscious Sedation), working under the supervision of a consultant in dental sedation, was responsible for administering the sedation. The operator/sedationist also monitored the patient's clinical status throughout each session, assisted by an appropriately trained dental sedation nurse. All patients were instructed to starve for 2 hours before their treatment appointment.

A Quantiflex MDM relative analgesia machine (Matrix Medical Inc, Buffalo, NY, USA) was used to administer nitrous oxide via a nasal mask. The nitrous oxide was given in increments of 10% to a final dose of nitrous oxide 30% in oxygen, whilst the clinician provided reassurance and positive reinforcement. A maximum dose of 30% nitrous oxide was chosen, as studies have shown that levels of 20–30% nitrous oxide provide an adequate level of sedation without the risk of over-sedation [25]. Once the level of 30% nitrous oxide had been reached, it was continued throughout the subsequent dental treatment. Upon completion of the treatment, the nitrous oxide was switched off and 100% oxygen was administered for 3 min before the nasal mask was removed.

Oral midazolam 0.5 $mg.kg^{-1}$ was given; this dose has been shown to produce good anxiolysis when used as premedication [21, 24]. As midazolam has a bitter taste, it was mixed with 30 ml of sugar-free orange cordial in water. The drug was administered 45 min before treatment to ensure an adequate level of sedation, and the patient was monitored in a recovery area under the supervision of the parent and a sedation nurse.

Patients were monitored using pulse oximetry throughout the period of sedation, dental treatment and recovery. Clinical signs that were monitored included pulse, respiration rate, colour and level of responsiveness.

Benzocaine 20% was applied to the gingivae for 2 min and then lidocaine 2% with epinephrine 1 : 80 000 was injected in a standard technique for each quadrant, i.e. upper premolar or canine: buccal infiltration and palatal infiltration via the buccal papilla; lower premolar or canine: buccal infiltration followed by lingual infiltration via the buccal papilla. Once analgesia had been achieved, the two teeth were extracted.

Once dental treatment was complete, the patients were transferred to the recovery area and were allowed to recover for at least 20 min. They were supervised in the recovery room by the parents and a sedation nurse. The criteria for discharge were: vital signs within normal limits; able to walk unaided; full verbal communication. At the end of that period, the operator assessed the patient's fitness for discharge. Full written and verbal postoperative instructions were provided.

The parameters given below were measured in order to evaluate the technique.

Physiological status

Baseline weight, blood pressure, pulse rate, respiration rate and oxygen saturation were recorded immediately

before the administration of sedation. Once the sedative had been administered, the pulse rate, respiration rate and oxygen saturation were monitored continuously throughout treatment, and the data were recorded every 5 min.

Level of sedation and emotional status

The sedation level was recorded every 5 min using the classification of emotional status designed by Brietkopf & Buttner [26] (Table 1). The criteria for over-sedation included loss of communication, respiratory depression and eventual loss of consciousness.

Behaviour during treatment

The Frankl Behaviour Rating Scale [27] was used to grade the child's behaviour during treatment (Table 2).

Outcome of treatment

The Houpt Behaviour Rating Scale [27] was used to record the overall behaviour and outcome of treatment (Table 3).

Anxiety score

General anxiety and dental anxiety were recorded before each treatment session. Spielberger's State Anxiety Inventory [28] was used to score general anxiety (Appendix 1). The scale for this inventory ranges from 20 (minimum anxiety) to 80 (maximum anxiety). The Children's Fear Survey Schedule, dental subscale [29], was used to score dental anxiety (Appendix 2). The range of this scale is 15 (minimum dental anxiety) to 75 (maximum anxiety).

Table 1 Brietkopf and Buttner Classification of Emotional Status [26].

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

Table 2 Frankl Behaviour Rating Score [27].

Score	Description
1	Refusal/distress
2	Unco-operative/reluctant
3	Co-operative/reserved
4	Interested/enjoyed

Table 3 Houpt Behaviour Rating Scale [27].

Score	Description
1	Aborted: no treatment rendered
2	Poor: treatment interrupted, only partial treatment was completed
3	Fair: treatment interrupted but eventually completed
4	Good: difficult but all treatment was performed
5	Very good: some limited crying or movement
6	Excellent: no crying or movement

Patient preference

After each session, the parent was given a questionnaire to be completed at home. The questionnaire asked the child to grade how well they liked the sedation, how they felt about the sedation and, after the second appointment, which type of sedation they preferred. The parent was also asked to record postoperative adverse effects and their perception of how well the child coped with each type of sedation.

Data were entered into a PC database and analysed using MINITAB software. Measurements of physiological status, emotion and behaviour all have scales consisting of ordinal or nominal data, and they were analysed using paired *t*-tests, Mann–Whitney *U*-tests or Chi-squared tests as appropriate. Data from the patient satisfaction questionnaire were transcribed for qualitative data and the paired *t*-test was used for quantitative data.

Results

Forty-six subjects in total were recruited to the study, but only 44 completed all their treatment. The mean [range] age of the subjects was 12.5 [10–16] years; 16 were male and 30 female; all were classifiable as ASA physical status I.

The median [range] values for the lowest arterial oxygen saturation recorded were 98 [93–100]% for the nitrous oxide group and 95 [90–100]% for the midazolam group. Using the Mann–Whitney *U*-test, the difference in these values was found to be statistically significant ($p < 0.001$, 95% CI: −3.99, −1.99). However, the range of values for the midazolam group was within acceptable and safe limits for conscious sedation (90−100%). The mean (SD) respiration rate for the nitrous oxide group was 15.8 (2.9) breath.min^{-1} and for the midazolam group was 15.5 (2.5) breath.min^{-1}. The difference was not found to be statistically significant ($p = 0.09$, 95% CI: –0.74, 0.06).

The median [range] time to maximum level of sedation in the nitrous oxide group was 5 [5–10] min, compared to 20 [5–65] min in the midazolam group. The difference was found to be highly significant ($p < 0.001$, 95% CI: 15.00, 14.99). However, there was no significant difference in the maximum duration of dental treatment, i.e. from administration of local anaesthetic to completion of dental extractions, between the two groups, with a

median [range] of 10 [5–25] min for the nitrous oxide group and 10 [5–30] min for the midazolam group. The maximum time spent in recovery was significantly different between the two groups, with median [range] values of 20 [20–25] min and 42.5 [15–90] min for nitrous oxide and midazolam groups, respectively. The difference between these times, using the Mann–Whitney *U*-test, was found to be significant ($p < 0.001$, 95% CI: 15.00, 25.00). The total appointment time (time from entering surgery to discharge home) was significantly greater for the midazolam group ($p < 0.001$, 95% CI: 60.00, 70.00), with the median [range] total appointment times being 35 [30–50] min and 100 [70–140] min for the nitrous oxide and midazolam groups, respectively.

The maximum levels of sedation recorded are illustrated in Fig. 1. As expected, patients in the midazolam group demonstrated higher sedation levels. However, no patient became over-sedated.

The Houpt scale was used to record overall behaviour and outcome of treatment. The results are illustrated in Fig. 2. The overall behaviour score in the two groups was similar, and only one procedure in each group had to be aborted because of loss of co-operation.

The patients' views of the treatments are illustrated in Figs 3 and 4. The majority of subjects in both groups found the treatment *very pleasant* or *pleasant*. Relating these results to the type of sedation used at the first visit, it is evident that regardless of whether the patient had midazolam or nitrous oxide at the first visit, they were all less positive about the type of sedation given at their second visit. Similar results were obtained when the patients were asked how they felt about their treatment. However, at the second visit, regardless of the type of sedation administered, there were more patients who felt *anxious* or *very anxious.*

The patients were asked if they could remember having the local anaesthetic, extraction of the teeth and being in recovery. Chi-squared analysis was used for the comparisons. Forty children in the nitrous oxide group could remember having the local anaesthetic compared with seven in the midazolam group. The difference was found to be highly significant ($p < 0.001$). In the nitrous oxide group, 40 patients remembered having their teeth extracted compared with 10 in the midazolam group ($p < 0.001$). Forty children in the nitrous oxide group and 23 in the midazolam group could remember being in the recovery area ($p < 0.01$). These results are illustrated in Fig. 5.

There was no effect of appointment number on the changes in anxiety score. However, the mean [range] state anxiety score for those having midazolam at the first visit was 47 [23–73] compared with 40 [20–68] for the second visit (Fig. 6). Using a paired *t*-test, the difference was found to be statistically significant ($p < 0.001$, 95% CI: 3.71, 10.29). When nitrous oxide was administered first, the mean [range] state anxiety score was 44 [20–67] at the first visit and 35 [20–64] at the second visit ($p < 0.01$, 95% CI: 2.55, 14.17) (Fig. 7). The mean [range] dental

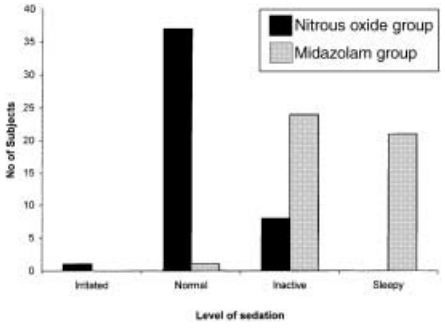

Figure 1 Maximum levels of sedation (Brietkopf and Buttner classification [26]).

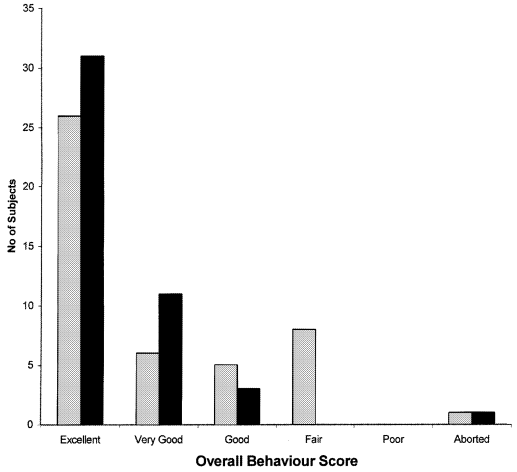

Figure 2 Overall Behaviour score (Houpt Behaviour Rating scale [27]). Groups as for Figure 1.

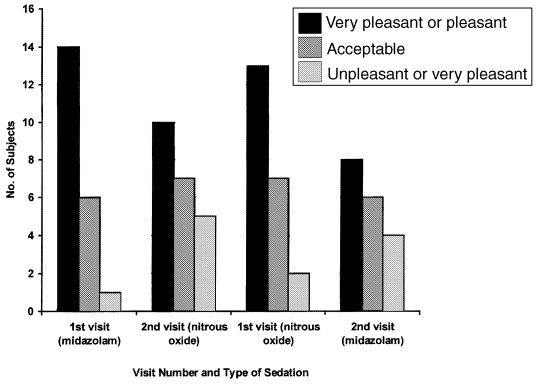

Figure 3 Patients' opinions of treatment.

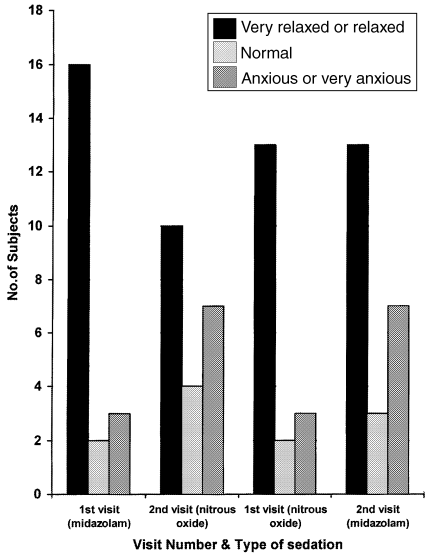

Figure 4 Feelings experienced during treatment.

anxiety score when midazolam was used first was 32 [17–61], compared with 30 [15–59] at the second visit ($p < 0.5$, 95% CI: −0.69, 3.56) (Fig. 8). When nitrous oxide was used first, the mean [range] Dental Anxiety Score was recorded as 30 [15–46], and at the second visit was 26 [15–43] (Fig. 9). The difference, using a paired *t*-test, was found to be significant ($p < 0.001$, 95% CI: 2.25, 7.14).

All subjects were asked if they would be prepared to have the same form of sedation again, and which method they preferred. Of those who responded to this question, 33 (75%) said they would have nitrous oxide again and 29 (74%) said they would have midazolam again. Twenty-two (54%) subjects preferred midazolam sedation, 18 (44%) preferred nitrous oxide sedation and 1 (2%) had no preference.

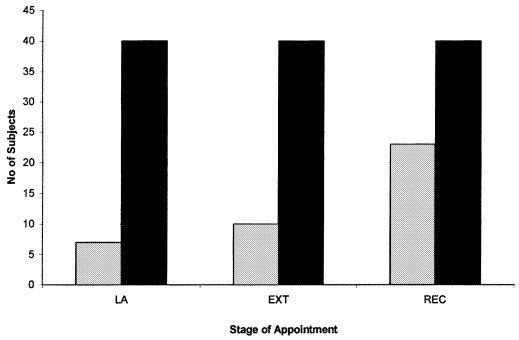

Figure 5 Positive recall of the appointment. Groups as for Figure 1. LA, remembered local anaesthetic injection; EXT, remembered tooth extraction; REC, remembered being in recovery.

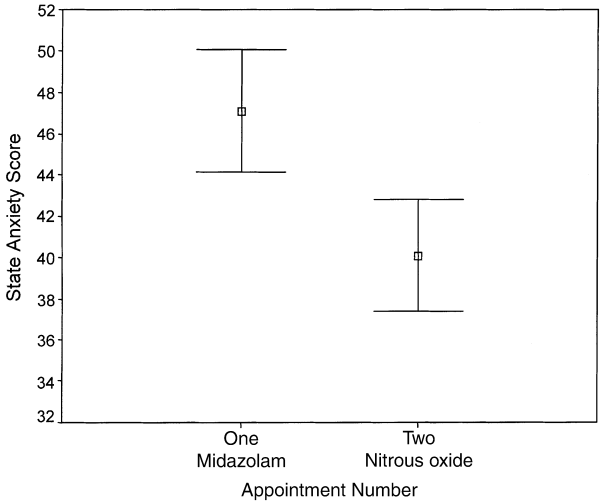

Figure 6 Change in State Anxiety Score [28]. The box represents the mean, error bars indicate SEM. For these subjects, midazolam was used at the first appointment, nitrous oxide was used at the second appointment.

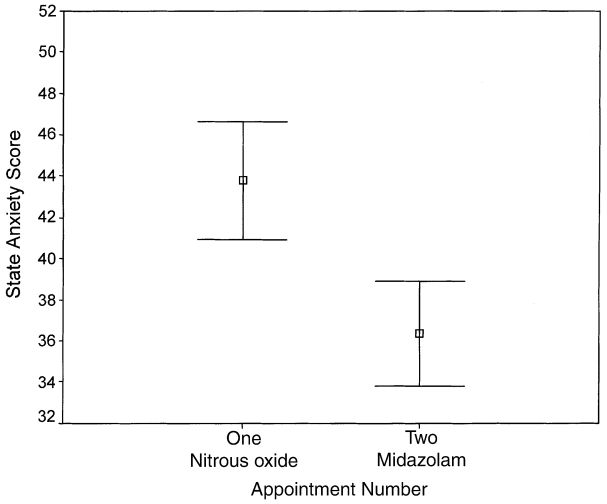

Figure 7 Change in State Anxiety Score [28]. The box represents the mean, error bars indicate SEM. For these subjects, nitrous oxide was used at the first appointment, midazolam was used at the second appointment.

Discussion

Relative analgesia sedation with nitrous oxide is the mainstay of conscious sedation services for children receiving dental treatment in the UK [4]. However, evidence suggests that nitrous oxide may pose a potential risk to clinical personnel who are providing this form of sedation on a regular basis [9–14]. Indeed, there is a possibility that nitrous oxide may be banned altogether

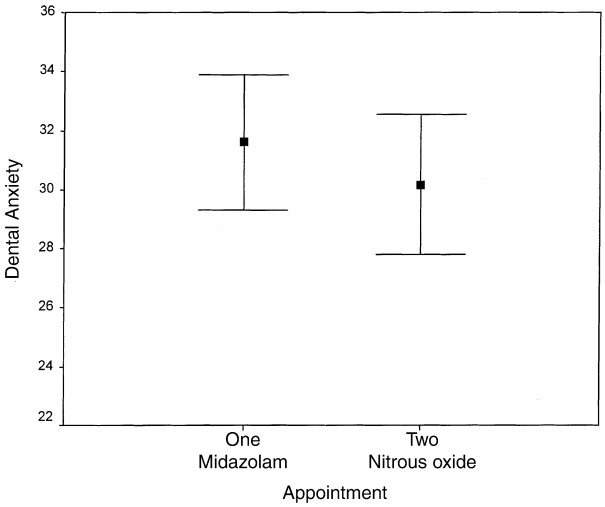

Figure 8 Change in Children's Fear Survey Schedule – Dental Sub-scale Score [29]. The box represents the mean, error bars indicate SEM. For these subjects, midazolam was used at the first appointment, nitrous oxide was used at the second appointment.

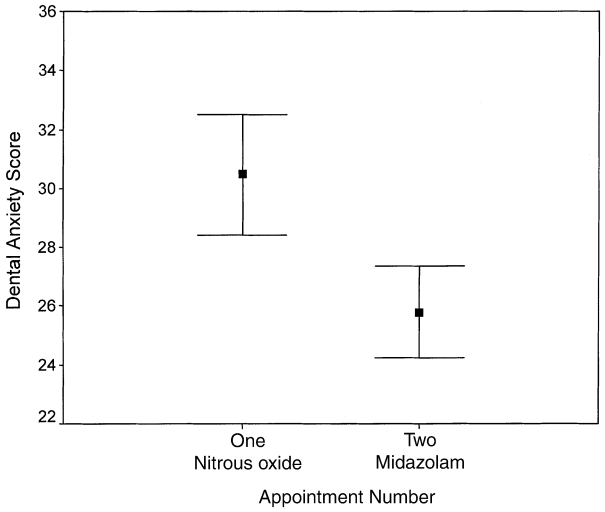

Figure 9 Change in Children's Fear Survey Schedule – Dental Sub-scale Score [29]. The box represents the mean, error bars indicate SEM. For these subjects, nitrous oxide was used at the first appointment, midazolam was used at the second appointment.

for medical use [13]. It is for these reasons that research into other safe and effective sedation techniques for paediatric dental patients is important.

Benzodiazepines are used extensively in adults but little work has been carried out in the UK to assess their use in children. The main side-effect of benzodiazepines is respiratory depression, and oxygen saturation monitoring is therefore essential. Patients undergoing sedation should always have an oxygen saturation ≥ 90% [14]. In this study, the range of values of arterial oxygen saturation for the midazolam group (90–100%) and the mean respiratory rate were within clinically safe limits for this age group, suggesting that from a physiological point of view, it appears to be a safe technique. The results observed with regard to the level of sedation indicated that that all children remained conscious throughout their care with both forms of sedation, and no children were over-sedated. These findings are consistent with other studies in which oral midazolam sedation was used in similar patients [19, 24].

When using different sedation techniques, it is important to consider the time factor for both the patient and the clinician. One of the arguments against oral midazolam sedation for dental treatment has been the long onset time. In a dose-related study of oral midazolam sedation in children, McMillan *et al.* [19] reported that the time taken to reach maximum sedation when using midazolam 0.5 $mg.kg^{-1}$ was 15–30 min. The results obtained in our study are in agreement with this and would suggest that this period might be shorter than was originally anticipated and that the onset time is acceptable to clinicians and patients.

It is important to consider how efficiently the dentist's time is used during the visit. This should ideally be confined to the time spent in the surgery. Administration of nitrous oxide sedation is carried out by the dentist, and therefore uses more clinician time than oral midazolam. However, the actual time taken to carry out the dental treatment did not differ between the groups receiving the two different sedation methods.

Studies have shown that oral midazolam improves patient co-operation during treatment [25, 30]. Shapira *et al.* [31], in a study of midazolam sedation in children, reported high behaviour scores throughout treatment, and in our study, the majority of patients exhibited good to excellent overall behaviour. Paradoxical reactions, including disinhibition with midazolam, have been reported by other researchers [19, 25], but these are uncommon. Only one treatment session with midazolam in the current study had to be aborted due to the patient showing disinhibition associated with the drug. This supports the evidence that such adverse responses to midazolam are rare. As would be expected, because of the known anterograde amnesic effects of midazolam [32], fewer patients under midazolam sedation could recall the various elements of their treatment. This can be particularly beneficial when unpleasant procedures such as extractions are being carried out.

The general state anxiety levels reported amongst the subjects ranged from 20 to 73 at the first visit. Both types of sedation produced a decrease in general levels of anxiety. This is a similar finding to that of Varpio & Wellfeit [33], who found that anxious children treated with sedation tended to have decreased levels of anxiety at future visits.

However, there was a more marked difference in dental anxiety scores – a greater decrease being noted where the patient had had nitrous oxide at their first visit. This result may be a reflection of the amnesic effect of midazolam, so that the patient is unable to remember the dental treatment and therefore remains anxious about the actual dental procedure. Veerkamp *et al.* [34] found that dental anxiety was significantly decreased after the use of nitrous oxide sedation in child dental patients. However, in a study of the long-term anxiety-reducing effects of midazolam in adults [32], the researchers reported that there was no change in the level of dental anxiety one month after dental treatment under oral midazolam sedation.

The results obtained are very promising. However, some clinicians may argue that midazolam is not licensed for oral use. The use of licensed drugs for unlicensed applications is acceptable in paediatric practice where there is no suitable alternative, provided the consent of the parent has been obtained [35]. In prescribing such a drug, the practitioner must ensure that it offers benefits to the child and, in the case of midazolam, there is evidence to suggest that it is a useful anxiolytic [17, 19, 20, 24].

In conclusion, this study has shown that oral midazolam 0.5 $mg.kg^{-1}$ appears to be a safe sedative agent for use in 10–16-year-old healthy patients, producing no significant physiological changes and few side-effects. It is accepted by patients and produces good anxiolysis, which enables treatment to be carried out effectively. The amnesic effects may be of particular benefit to very anxious children who may be undergoing their first experience of dental extraction.

As oral midazolam cannot be titrated to the individual's response, anyone undertaking this technique must be competent in managing the over-sedated patient; they must be proficient in carrying out intravenous cannulation in case intravenous flumazenil needs to be given. It is also essential that the operator/sedationist be trained in providing paediatric life support, and that such a technique for dental patients be carried out in accordance with the General Dental Council's Guidelines [1].

Acknowledgments

We would like to express our thanks to the Dental Nurse Sedation Team at the unit for their clinical support throughout the study and to Mrs A Girdler, research nurse, for carrying out the data entry.

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Appendix 1

Spielberger's Stait Anxiety Inventory [28]
CHILD'S NAME:
TODAY'S DATE:

Please indicate, by circling the numbers, how your child feels about the following situations. Your child may answer the questions or you may respond on their behalf.

		Not at all	Some what	Moderately so	Very much so
1	I feel calm	1	2	3	4
2	I feel secure	1	2	3	4
3	I am tense	1	2	3	4
4	I feel strained	1	2	3	4
5	I feel at ease	1	2	3	4
6	I feel upset	1	2	3	4
7	I am presently worrying	1	2	3	4
8	I feel satisfied	1	2	3	4
9	I feel frightened	1	2	3	4
10	I feel comfortable	1	2	3	4
11	I feel self confident	1	2	3	4
12	I feel nervous	1	2	3	4
13	I am jittery	1	2	3	4
14	I feel indecisive	1	2	3	4
15	I am relaxed	1	2	3	4
16	I feel content	1	2	3	4
17	I am worried	1	2	3	4
18	I feel confused	1	2	3	4
19	I feel steady	1	2	3	4
20	I feel pleasant	1	2	3	4

Appendix 2

Children's Fear Survey Schedule [29]
CHILD'S NAME:
TODAY'S DATE:

Please indicate by ticking the boxes, how your child feels about the following situations. Your child may answer the questions or you may respond on their behalf.

	Situation	Not afraid at all	A little afraid	A fair amount afraid	Pretty much afraid	Very afraid
1	Dentists					
2	Doctors					
3	Injections					
4	Having someone examine your mouth					
5	Having to open your mouth					
6	Having a stranger talk to you					
7	Having someone look at you					
8	The dentist's drill					
9	The sight of the dentist's drill					
10	The noise of the dentist's drill					
11	Having somebody put instruments in your mouth					
12	Choking					
13	Having to go to hospital					
14	People in white uniforms					
15	Having the nurse clean your teeth					