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A partially blinded randomised controlled trial of patient-maintained propofol sedation and operator controlled midazolam sedation in third molar extractions

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Summary

Patient-maintained sedation using propofol has recently been shown to be effective for dental surgery. We compared this new technique to the established technique of operator administered midazolam. The two groups were compared before, during and after sedation. The two primary outcomes were time until discharge and oxygen saturation. Vital signs, anxiety and psychomotor skills were also compared. State anxiety was reduced to a greater extent in the propofol group (mean difference 10 (SD 4) mm; $p = 0.010$. Propofol patients recovered quicker (mean difference 7 (SD 1.4) min; $p = 0.001$). Propofol patients had a smaller reduction in arterial oxygen saturation (mean difference 0.8 (SD 0.3)%; $p = 0.030$), and a reduced increase in heart rate (mean difference 9 (SD 2) beats.min^{-1}; $p < 0.001$). Both techniques were well tolerated and safe. Propofol sedation offered superior anxiolysis, quicker recovery, less amnesia and less depression of simple psychomotor function.

Keywords *Anaesthetics*; propofol. *Anaesthesia, dental.*

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Increased financial, clinical and patient demand for daycase procedures and shorter hospital stays has led to an increased role for sedation rather than general anaesthesia. Sedation has generated a great deal of political interest in healthcare in general, and dentistry in particular. In 2000, a working group jointly chaired by the Chief Medical Officer and the Chief Dental Officer published 'A Conscious Decision' which discouraged the use of general anaesthesia and endorsed the need for more conscious sedation [1]. In 2001, the Academy of UK Medical Royal Colleges published a report highlighting the need for increased training, audit, clinical governance and research to improve the safety of current sedation practice; in particular, formal collaborative research projects were recommended [2].

Dentistry and anxiety have always been inextricably linked. The most recent Adult Dental Health Survey in the UK showed around 41% of dentate adults were irregular dental attenders and one of the principal reasons was fear of dental treatment [3]. Dentistry, in particular third molar extractions, provides a common and relatively reproducible surgical stimulus [4]. This has accordingly become a popular experimental model for studying sedation techniques.

As in most other fields of conscious sedation, dental patients in the United Kingdom currently receive incremental doses of intravenous benzodiazepine [5–7]. Morbidity and mortality data are currently difficult to find. The most comprehensive data have come from an audit of 14 000 patients receiving upper gastrointestinal endoscopy, where morbidity was reported as up to 1 in 200, and mortality as up to 1 in 2000 procedures [8, 9]. A more recent survey has found continued fatal complications despite new guidelines and education [6].

Propofol is a short-acting intravenous anaesthetic agent introduced into the United Kingdom in 1986. It is primarily used for intravenous anaesthetic induction, but increasingly for maintenance of anaesthesia by intravenous infusion. Its pharmacokinetics are tri-exponential, and so, are complicated; hence delivery by infusion is facilitated by target controlled infusion [10]. This delivers propofol to provide steady plasma concentrations, which are remarkably equivalent to those predicted [11]; this has proved very popular with anaesthetists.

Propofol has been used by anaesthetists for sedation since 1987 [12], and has subsequently been successfully used by low-dose target controlled infusion [13]. More recently, it has been used in patient-controlled sedation with small bolus doses [4, 12, 14, 15]. Its pharmacokinetic disposition is so rapid that peaks and troughs in plasma concentration are likely by this method. Patient-maintained sedation has been used to describe a system where the patient controls their plasma concentration of propofol by means of a patient control handset connected to a target controlled infusion pump. This has proved effective in various clinical situations including third molar extraction in dentistry [5, 16–19].

The object of this study was to compare the efficacy, safety, recovery and satisfaction of patients using patient-maintained sedation with propofol with the current standard of operator controlled sedation with midazolam during third molar extraction.

Methods

Participants

Approval was obtained from the institutional research and ethics committee. Inclusion criteria were any ASA 1 or 2 patients referred to the sedation unit at the University of Glasgow Dental School for removal of third molars with intravenous conscious sedation. Exclusion criteria were significant systemic disease (ASA 3–5), and specifically patients with epilepsy or severe respiratory disease; inability to use the handset; and patients with a history of drug addiction or current opioid use.

Study design and blinding

Study design was a randomised, partially blinded comparison of operator sedation using midazolam (OSM) with patient-maintained sedation with propofol (PMS). Patients were randomly assigned to receive either OSM or PMS; they could not be blinded owing to the nature of sedation delivery. The surgeon was not blinded to patient group, since he was the operator administering sedation; however, the recovery staff were fully blinded to the sedation technique.

Interventions

Following informed written consent to surgery and the study, 110 patients were recruited and randomly assigned to one of the two sedation groups. Randomisation was performed by an independent statistician, using a block randomisation system. All patients presenting for third molar surgery on the investigators' operation list were approached, and patients were allocated a sequential study number once recruited.

Conduct of sedation

Patients were screened pre-operatively for medical disease, and were advised not to eat for 2 h pre-operatively. All patients had intravenous access secured, and pulse oximetry, heart rate and non-invasive blood pressure monitoring were applied throughout the entire study period. An anaesthetist was present at all times, and full access to resuscitation equipment and drugs was available.

Group 1: Operator-controlled sedation with midazolam

These patients received an initial intravenous bolus of midazolam 2 mg, with 1-mg incremental boluses at 1-min intervals until the patient expressed a readiness to receive their local anaesthetic injection.

Group 2: Patient-maintained sedation with propofol

Propofol 1% was delivered to the patient using the PMS system using TCI technology (Appendix). This system was set to deliver an initial plasma concentration of 1.5 $\mu g.ml^{-1}$ of propofol. When the calculated effect-site concentration had reached 1.0 $\mu g.ml^{-1}$, the target plasma concentration was also set to 1.0 $\mu g\ ml^{-1}$ and the patient given control of the system (Fig. 1). The incremental steps were set at 0.2 $\mu g.ml^{-1}$, the lockout time at 2 min, the decrement time at 6 min and the maximum concentration at 3.0 $\mu g.ml^{-1}$.

The patients were allowed to titrate their sedation with propofol until they expressed a readiness to receive their local anaesthetic injection. In addition, this group were able to continue to titrate their sedation throughout the surgery.

Conduct of surgery and recovery

Both groups received standard dental local anaesthetic (2% lidocaine with 1 : 80 000 epinephrine) and the effectiveness of this was confirmed before the surgery was commenced. Surgery was performed in all patients by the same non-blinded surgeon (J.A.L.). At the end of the surgery the patients were allowed to recover for 5 min before being escorted to the recovery room, where they were allowed further time to recover. They were discharged into the care of a responsible adult by the

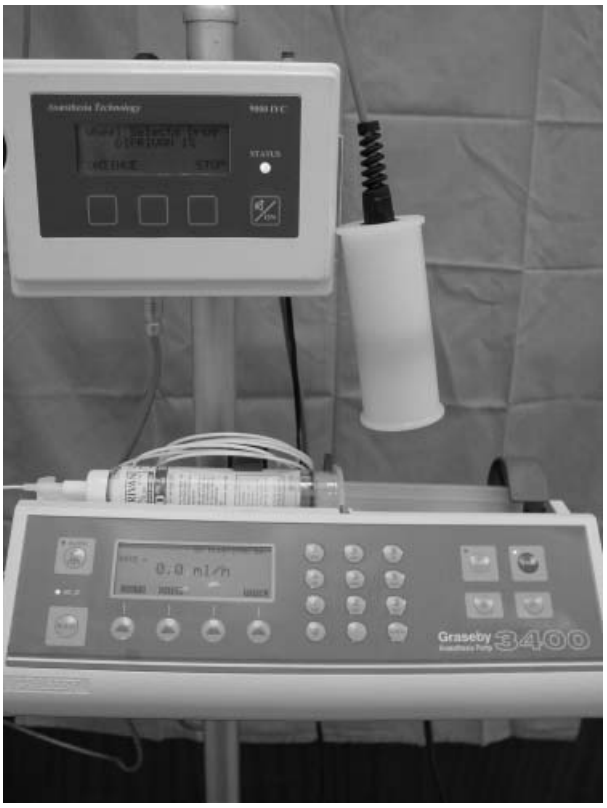

Figure 1 Patient-maintained sedation equipment including handset.

recovery nurse, who was blinded to patient sedation group. Criteria for discharge were adequate arterial oxygen saturation breathing room air and an adequate modified Romberg's test.

Outcome measures

Control physiological measurements were taken prior to the study, and at 5-min intervals until transfer into recovery and on discharge. In addition, the maximum and minimum values obtained were recorded as these occurred. Control psychomotor assessment was made before sedation, after sedation and once assessed ready for discharge. Operator assessments were made at the end of the procedure, and patient satisfaction taken before discharge.

Physiological measurements

Heart rate, oxygen saturation and non-invasive blood pressure were recorded every 5 min and the minimum or maximum value was noted.

Anxiety, psychomotor function and memory

The patients' baseline tendency to anxiety (trait anxiety) was assessed by the state-trait anxiety inventory [20], and their actual current anxiety level (state anxiety) was assessed using a visual analogue anxiety scale (VAS). This was measured prior to sedation and during sedation before local anaesthesia was administered. Cognition, central processing and motor skills were assessed by the Digit Symbol Substitution test (DSST). In this test the patient must translate various symbols into a number ascribed to each symbol. They are allowed 30 s to accustom themselves to the task, which they then perform for 2 min. The number of substitutions and errors were recorded on three occasions; pre-operatively, while sedated and before discharge. Their memory was tested for two words and pictures shown to them before and after sedation. Recollection of local anaesthetic injection and tooth extraction were also recorded.

Operator assessment

There was a single operator for all patients, and he assessed all patients for ease of surgery, co-operation, and level of sedation using defined scoring systems [22, 27].

Patient satisfaction

Patients were asked if they were happy with the sedation they received, if they would have the same sedation again, and about their overall satisfaction with the procedure using predefined scales (Appendix).

Statistical analysis

The study was powered to detect a 3% difference in oxygen saturation at the 0.05 significance level with a power of 0.95. Data were analysed for two groups of unrelated samples using SPSS for WINDOWS (v10.0). Physiological data, visual analogue anxiety scores and digit symbol substitution were continuous normal data, and were analysed by two-tailed unpaired Student's *t*-test. Scoring systems were interval and non-normal data and were analysed by Mann–Whitney *U*-test. Dichotomous and categorical data were analysed by Chi-squared test, with exact tests used where appropriate.

Results

All 110 recruited patients (mean age 28 (SD 6.5) years, range 17–49 years) completed their treatment successfully and maintained a level of sedation which was adequate both for anxiety control and for completion of the treatment. Verbal contact was not lost with any patient at any time, in line with the established definition of conscious sedation.

Table 1 Pre-operative variables.

Variable	Midazolam Group Mean (SD)	Propofol Group Mean (SD)
Age; years	28 (6)	27 (7)
Sex; M/F	13/42	8/47
Trait anxiety	37 (8)	37 (8)
VAS anxiety; mm	48 (24)	52 (21)
Heart rate; beats.min^{-1}	92 (21)	97 (19)
Arterial oxygen saturation (%)	99.2 (1.0)	99.5 (0.8)
Systolic blood pressure; mmHg	136 (14)	135 (14)
Diastolic blood pressure; mmHg	81 (10)	79 (9)
DSST – total	74 (13)	71 (16)
DSST – errors	2 (11)	1 (2)

The two sedation groups were comparable for all pre-operative variables (Table 1).

Mean doses administered

The mean calculated plasma and effect-site levels of propofol at various points in the surgery are shown in Table 2. The mean dose in the midazolam group was 6.7 (SD 1.7) mg.

Cardiorespiratory monitoring

There were no statistically significant differences between group means for minimum heart rate, maximum heart rate or arterial blood pressure during treatment or at discharge ($p > 0.2$ for all comparisons). When we compared the change in heart rate for each patient, the mean change (increase) in heart rate was significantly greater in the midazolam group than in the propofol group (14 (SD 13) vs. 5 (SD 12) beats.min^{-1}, $p < 0.001$).

The minimum arterial oxygen saturation was significantly higher in the propofol group than in the midazolam group (mean 97.8 (SD 1.8) vs. 97.0 (SD 2.0)%, $p = 0.026$). Three patients in the midazolam group desaturated to < 94%, with one patient to 88%. In contrast, only three propofol patients had saturations of < 94%, and none were < 93% at any time.

Table 2 Propofol concentrations.

Event	Plasma level; μg.ml^{-1}		Effect-site level; μg.ml^{-1}	
	Mean (SD)	[Range]	Mean (SD)	[Range]
Ready for LA	1.4 (0.5)	[0.8–2.3]	1.3 (0.4)	[0.8–2.2]
Maximum	1.9 (0.5)	[1.0–3.0]	1.7 (0.5)	[0.9–3.0]
End of op.	1.8 (0.7)	[0.6–3.0]	1.8 (0.6)	[0.4–3.0]

LA, local anaesthetic.

Anxiolysis

The VAS recordings of anxiety taken after sedation and immediately prior to surgery were compared with baseline anxiety measurements. The propofol patients had a greater mean reduction in anxiety of 21 (SD 21) mm compared to the midazolam patients, who had a mean reduction in anxiety of 11 mm (SD 18) mm ($p = 0.010$).

Psychomotor function

Psychomotor function was significantly less impaired in the propofol group both intra-operatively and on discharge (Table 3). After sedation, prior to surgery the mean net DSST (total score – errors) was higher for propofol patients compared to midazolam patients ($p < 0.001$). When re-tested after they had been assessed fit for discharge by a blinded recovery nurse, the propofol patients again scored higher than midazolam patients in terms of the mean net DSST ($p = 0.001$).

Times for sedation, surgery and discharge

The mean time from start of sedation until the patient expressed readiness for local anaesthesia was significantly shorter in the midazolam group compared to the propofol group (9 (SD 2.6) min vs. 11 (SD 3.6) min; $p = 0.002$). There was no significant difference in the mean surgery times between the midazolam and propofol groups (14 (SD 5.9) vs. 14 (SD 5.7) min; $p = 1.000$). The mean time from the end of surgery until assessed ready for discharge by a blinded nurse was significantly shorter in the propofol group (18 (SD 5.5) vs. 25 (SD 9.0) min; $p = 0.001$). Accordingly, the mean time from start of

Table 3 Digital Symbol Substitution Task Results – Mean (SD).

	Total score		Total errors		Net score (total score – total errors)		
	PMS	OSM	PMS	OSM	PMS	OSM	PMS vs. OSM
Before sedation	70.6 (15.7)	73.6 (13.4)	0.5 (1.9)	2.1 (10.6)	70.1 (16.0)	71.6 (15.5)	p = 0.630
After sedation	55.4 (20.3)	30.1 (16.5)	2.7 (3.6)	5.3 (6.3)	52.7 (21.9)	24.9 (17.1)	p < 0.001
Discharge	75.8 (17.1)	66.8 (13.6)	0.9 (2.3)	2.4 (10.7)	74.9 (17.0)	64.4 (14.9)	p = 0.001

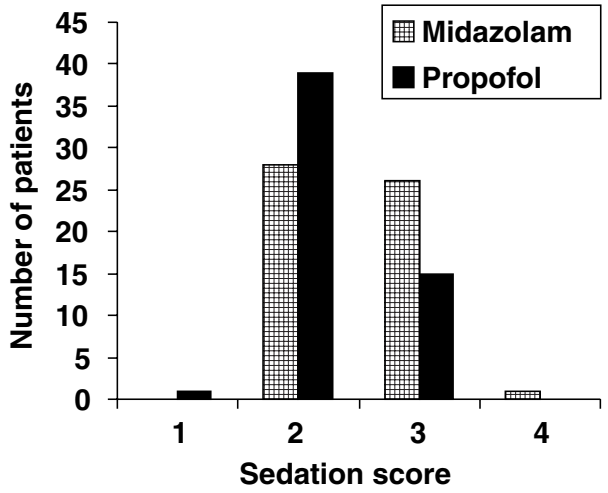

Figure 2 Sedation score (1 = fully awake, 2 = drowsy, 3 = eyes closed and responds to verbal command, 4 = eyes closed and responds to physical stimulation).

sedation until discharge was shorter in the propofol group than in the midazolam group (43 (SD 8.8) vs. 49 (SD 9.8) min; $p = 0.002$).

Patient sedation and co-operation

There was no difference in the difficulty of the procedure between groups as assessed by the surgeon ($p = 0.578$). When assessed with a simple four-point sedation scale by the surgeon, propofol patients were less sedated than midazolam patients ($p = 0.038$) (Fig. 2). There was no significant difference between the propofol or midazolam group with respect to the median co-operation scores at time of local anaesthestic ($p = 0.241$); or at the time of tooth extraction ($p = 0.069$).

Patient recall and satisfaction

When comparing recall of the words and pictures they had been given to remember before sedation, 100% of both groups (all 110 patients) recalled the picture shown; 93% (51/55) of propofol and 91% (50/55) of midazolam patients recalled the word ($p = 0.728$). When recall was tested for words and pictures given after sedation but before surgery, a greater proportion of the propofol than the midazolam patients recalled the picture (75% (41/55) vs. 4% (2/55), $p < 0.001$) and similarly the word (66% (36/55) vs. 4% (2/55), $p < 0.001$). When recall was compared for actual events, this difference in recall was less pronounced: 93% (51/55) of patients in the propofol group recalled the local anaestetic injection compared to 45% (25/55) of the midazolam group ($p < 0.001$). However, at the time of extraction there was no difference in recall; 76% (42/55) of the propofol group, and 71% (39/55) of the midazolam group having recall ($p = 0.516$). Patient satisfaction was high in both groups, with only two patients in each group stating they would not like the same technique again. When the patients rated their satisfaction with the overall experience there was no significant difference between the propofol and midazolam group ($p = 0.077$). On closer inspection, 22% (10/45) of the midazolam group compared to 8% (4/53) in the propofol group described the experience as 'unpleasant'.

Discussion

Although midazolam has been compared with propofol given by different techniques for sedation previously, this is the first randomised controlled trial of patient-maintained propofol vs. bolus doses of midazolam.

In this study, both midazolam administered by the operator and propofol administered by PMS were effective and provided a level of sedation consistent with the definition of conscious sedation. Importantly, patients were satisfied with both techniques. Propofol offered superior reduction in VAS-rated anxiety measured before surgery compared to the more traditional use of a benzodiazepine. This was despite the two groups having similar trait anxiety (or baseline tendency to anxiety). In addition, the patients in the propofol group were less sedated as assessed by the surgeon. The superior anxiolysis with propofol offers the tantalising prospect of better anxiolysis with less sedation, and consequently less risk of over-sedation. The surgeon found the co-operation of the patients satisfactory in both groups. Whilst the median co-operation score was higher in the propofol group, the difference from midazolam failed to reach statistical significance.

The 'lighter' sedation level in the propofol group was associated with less amnesia for pictures and words given prior to surgery, and for the local anaesthetic injection. There was, however, no difference between the groups for the recall of the actual event of tooth extraction. This suggests that although midazolam provides superior amnesia for tests or trivial events, midazolam amnesia can be overcome by a greater stimulus. It has been shown that propofol and midazolam produce the same degree of memory impairment at equi-sedative concentrations [21]. The relative lack of amnesia in the propofol group in this study could be explained by these patients achieving the level of anxiolysis they desired at lower levels of clinical sedation.

The surgery in this study was day surgery, and in general, the vast majority of sedation is performed on an out-patient basis. For instance, in 2000–2001 there were over 500 000 completed episodes of upper

gastrointestinal endoscopy, 72% of these being day surgery [22]. The time taken from the end of surgery until our patients were ready for discharge was significantly lower in the propofol group, reducing the overall duration of their hospital visit. This is not a new or surprising observation. Propofol is redistributed and metabolised more rapidly than midazolam; indeed, recovery from propofol sedation has previously been shown to be quicker than that from midazolam [23, 24]. Although the time saved with the propofol technique was on average only 6 min per patient, this translates to approximately an extra patient slot being available for every eight patients treated (assuming an average sedation to discharge time of 49 min in the midazolam group). This has obvious waiting list and financial implications.

Another aspect of sedation and recovery from sedation is psychomotor function. Propofol patients had significantly less deterioration of their DSST score, and quicker recovery postoperatively than did midazolam patients. This may add to the evidence pointing to equally acceptable sedation at lower levels of impairment in the propofol group. The present study provides tentative evidence of relatively less cognitive impairment due to propofol during sedation, and at the time of discharge. Although DSST is a sensitive and validated test of attention and psychomotor ability, this must be viewed in the context of its necessarily brief and simple nature.

If adequate sedation with propofol were achieved at a lower sedative level than midazolam, then it might be postulated that propofol sedation would be less likely to cause over-sedation and in particular loss of verbal contact. No patient in this study lost verbal contact, suggesting that this is a rare event when sedation is carried out in a correct and safe manner. Our study was not powered to detect a difference in this rare event. Rather, it was powered to detect arterial desaturation, a more frequent event in sedation.

The mean lowest arterial oxygen saturation was significantly lower in the midazolam group than in the propofol group. Admittedly, the size of the difference was small in clinical terms (around 1%); however, the only significant arterial desaturation (to 88%) in this study was in the midazolam group. A larger study to determine the true incidence of arterial desaturation of both techniques would be required to state categorically that propofol sedation was safer in this respect.

Although patient-maintained sedation with propofol offered some advantages in this study, concern has been raised regarding the safety of propofol sedation, particularly when administered by non-anaesthetists [25, 26]. In the UK, propofol is only licensed for administration by 'those trained in anaesthesia'. Obviously, the availability and cost of anaesthetic manpower would be a major drawback if patient-maintained sedation were to be introduced into clinical practice. However, there is extensive experience in Australia of non-anaesthetic trained physicians administering propofol for endoscopy, whose critical incident incidence rates seemingly were no different from those of anaesthetists [27]. Furthermore, there is increasing evidence from the USA of safe nurse-administered sedation with propofol [28]. It should be remembered that the patient is controlling their sedation with the PMS system, and if they become over-sedated they do not request more propofol. In fact, after a time the system automatically reduces the rate of administration.

In summary, we have compared midazolam sedation with propofol patient-maintained sedation in patients during third molar surgery. This was a randomised controlled, partially blinded trial using a reproducible surgical stimulus. Propofol patient-maintained sedation was easily operated by the subjects, and proved well tolerated, and at least as safe as the standard sedation with midazolam. In addition, propofol sedation offered superior anxiolysis and quicker recovery than standard midazolam sedation. Propofol patients were objectively more awake during surgery, exhibited less amnesia and less depression of simple psychomotor function. Overall, satisfaction with both techniques was similarly high.

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Appendix: Target-controlled infusions and patient-maintained sedation

Target-controlled infusions (TCI)

Propofol was delivered by a Graseby 3400 infusion pump controlled by a microprocessor system that was programmed with the pharmacokinetic data set previously published by Marsh *et al.* [7, 21]. The patient's age, and weight, and the concentration of propofol in the syringe are entered into the microprocessor. When a requested 'target' plasma concentration of propofol is entered into the microprocessor, it calculates the required infusion rates required to achieve that, and in turn controls the infusion pump delivering propofol. This system is commercially available as the 'Diprifusor', and it has been shown to provide actual plasma concentrations that are remarkably equivalent to those requested. In addition, the system calculates the current 'actual' predicted plasma concentration and the theoretical brain concentration 'effect-site' concentration. These are both displayed.

Patient-maintained sedation

Using TCI technology, a requested target plasma concentration of propofol is delivered. If the patient wants additional sedation, they can request an increase in the target plasma concentration of propofol via a patient control handset. To do this they must successfully press the button twice within a 1-s interval; this requires some degree of motor control and the ability to achieve this is inhibited by excessive sedation. After a successful handset press there is a 'lockout time' to allow the plasma concentration to equilibrate with the brain and achieve the maximum clinical effect. If they fail to request further increases in plasma concentration, by successful button presses for a certain time period ('decrement time'), the plasma concentration is automatically decreased by the microprocessor. The amount by which the plasma concentration is increased by the patient or reduced by inactivity, the 'incremental step', can be varied. and a maximum allowable plasma concentration 'maximum concentration' can be set.

Consort flowchart