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REFEREED PAPER

The use of intranasal midazolam in a special care dentistry department in a hospital setting; technique and cases.

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Abstract

Intranasally (IN) administered midazolam has allowed patients who require conscious sedation but struggle to tolerate cannulation to receive dental treatment under sedation. Studies have demonstrated a mean bioavailability of 82.4% can be achieved with IN midazolam due to the high vascularity within the nose. These studies have also demonstrated that peak plasma concentrations can be reached within 10 minutes, which signifies the fast onset of action. The standard bolus dose of IN midazolam is 10-12mg, which can be reduced or increased depending on the patient's age and susceptibility to benzodiazepines. The bolus can also be repeated if adequate sedation is not reached. Some 17 patients received a standard dose of 10mg of midazolam. There were two cases of desaturation below 92%, which responded with oxygen and encouraging the patient to breathe. A protocol for administering IN midazolam is outlined and two cases are discussed.

Introduction

For some people with disability, the continuing management of oral health including periodontal care, routine examinations and the provision of restorative treatment is very difficult.[1] The use of conscious sedation in dentistry is one of the most widely discussed and regulated areas in the profession. In the last twenty years, there have been many publications providing guidance and clinical standards for practice in this area.[2] The use of intravenous midazolam alone is defined as a standard technique.[3] Intravenous (IV) sedation using midazolam has had a greatly positive effect on the provision of dental care; it has improved access to dental care and reduced reliance on general anaesthesia. The patient must, however, be able to tolerate intravenous cannulation, and many patients with disability struggle with this aspect of conscious sedation. To overcome this problem, patients with disability were often premedicated with oral midazolam, but following oral administration it may take up to 60 minutes to achieve peak plasma concentrations.[4] The time taken to achieve an adequate degree of sedation is frequently protracted. Oral midazolam is broken down in the liver, and the first pass reduces its bioavailability to between 35-44%.[5] Veldhorst-Janssen et al. have found the mean bioavailability of intranasal midazolam is approximately 82.4%.[6] The main advantages of intranasal midazolam are, firstly, the high bioavailability, as the nasal route in not subject to first pass metabolism,[7] and secondly, peak plasma concentration of midazolam can be reached after 10 minutes.[8]

Intranasal sedation is not new, but has not been widely adopted and any method or technique which could help achieve better treatment outcomes for people with disability should be made widely available. The technique has been used in some areas of clinical practice for many years, and in the Special Care Department of Dorset County Hospital for six months prior to the preparation of this paper in 2015.

Clinical pharmacology of midazolam

Midazolam is an imidazobenzodiazepine and is the standard drug used in the practice of intravenous conscious sedation.[9] It has anxiolytic, sedative, hypnotic, anticonvulsant muscle-relaxant, and anterograde amnesic effects.[10] Midazolam enhances the effect of GABA, which is an inhibitory neurotransmitter. It also reduces the excitability of neurones in the brain by increasing the uptake of chloride ions.[11] Midazolam also impairs episodic memory.[12]

Rationale for the use of the intranasal route

The nasal route is a very attractive method of delivery due to the rich vascular plexus (Figure 1) that is present within the nasal cavity and the ease of accessibility to this vascular bed, allowing delivery of medications directly to the blood steam.[13] Other techniques of transmucosal sedation, including sublingual, are described in the literature, but often require a greater degree of patient cooperation.

The safest way to administer the agents in conscious sedation is by titrating them against the patient's response, and this is the recommended technique for intravenous sedation with midazolam. Intranasal administration of midazolam is, in effect, a bolus dose technique.

The potential for over-sedation is greater with bolus dose techniques. It is standard practice that, for all techniques where midazolam is used to produce conscious sedation, an intravenous cannula should be placed, as the patient may require reversal. For this reason, the technique should only be used by dentists and sedationists who are fully trained and competent in cannulation and should not be seen as a technique to provide sedation for patients with difficult IV access. The same standards of monitoring apply as for intravenous midazolam sedation.

Intranasal Midazolam Dosing

It is widely accepted that the standard dose for IN midazolam is 0.25-0.3mg/kg body weight up to a maximum of 10-12mg given as a single bolus dose. This bolus can be repeated if the patient is not adequately sedated. The bolus can also be increased or

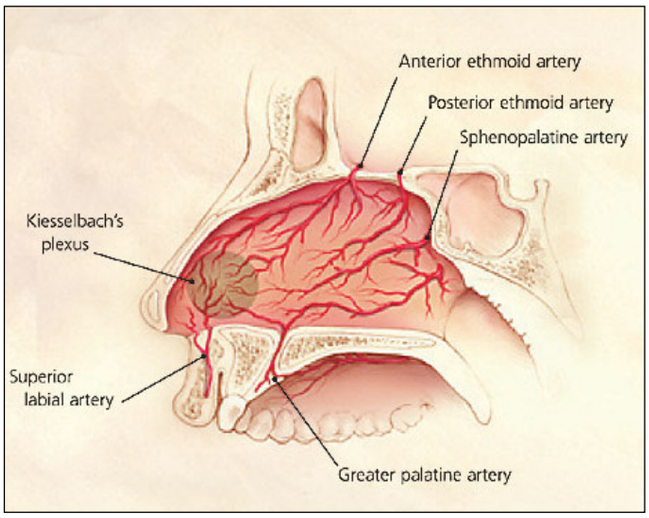

Figure 1: Figure 1 illustrates the vascular anatomy of the nasal septal blood supply. A large number of arteries supply the area and converge to form Kiesselbach's plexus.

decreased. This bolus dose initially seems very high. Veldhorst-Janssen found a mean bioavailability of 82.4% for IN administered midazolam,[6] this would equate to a dose of around 8.24mg of midazolam. This technique has a high record of safety, and Manley[14] conducted an audit of 222 episodes using this technique. Only one episode of significant desaturation was recorded, which responded with the administration of oxygen.

Some patients are tolerant to midazolam. In these patients, the standard dose may not be sufficient to produce an adequate degree of sedation to allow dental treatment to be completed. In some cases, it may be possible to place an intravenous cannula and titrate midazolam to the endpoint. In others, there may be insufficient anxiolysis to allow the patient to accept cannulation. If the patient cannot accept either cannulation or treatment, it is often recommended that they are allowed to recover and reappointed either to have an increased dose of sedative or treatment under general anaesthesia.

To allow treatment to proceed as planned, an appropriately experienced sedationist might consider giving a supplemental intranasal dose of midazolam. The decision as to whether to give the additional dose and, if so, how much to give and when, must be judged by careful patient assessment, including their response to the initial dose. The potential for over-sedation should not be underestimated. This procedure should not be a matter of routine, but a considered judgement taken case-by-case. The second dose would normally be no greater than 50% of the initial dose. The authors would only consider using this approach when the 40mg/ml presentation of midazolam is used.

The technique involves the administration of two bolus doses of midazolam. The advantages of titration vs bolus doses have already been discussed. The administration of a second bolus dose will increase rather than decrease the unpredictability. This technique, whilst practised in a number of centres has not been the subject of any clinical trials, and so must be viewed as the personal opinion of the authors. A third dose should not be administered

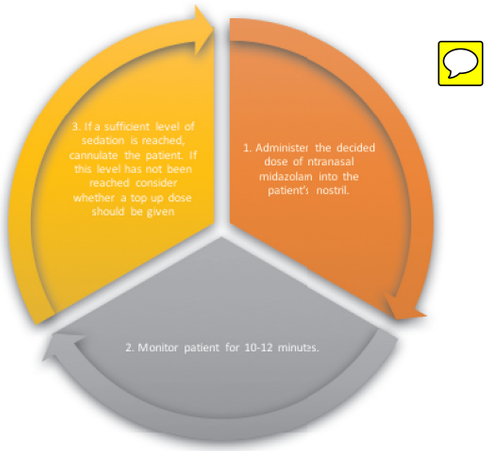

Figure 2: IN Midazolam is given as a non-titratable bolus, and the patient's response cannot a predicted.

Protocol for Intranasal sedation

The patient must go through a pathway of selection, assessment, history, examination, contraindications and consent. These processes should follow the IACSD standards[15] and are described in the relevant texts[16,17] Table 1, outlines a practical protocol which can be followed. IN 40mg/ml midazolam + 2mg/ml Lidocaine is prepared in boxes of five ampoules. Each ampoule has a volume of 0.5ml, thus 10mg of Midazolam would equate to 0.25ml of solution. A Luer lock syringe must be used to attach the MAD device, as this prevents the mucosal atomisation device (MAD) from detaching during application.

The MAD is locked onto the syringe and then placed into the right or left nostril and the bolus is given (Figure 3). It may helpful to stand behind the patient's head and use safe holding to gently brace the head when working with patients who might not be able to stay still. If given successfully, the effects should occur within 10-12 minutes, at which point the patient should be cannulated. If the sedation is not sufficiently effective after 12-15 minutes, a decision needs to be taken as to the next course of action, as described above.

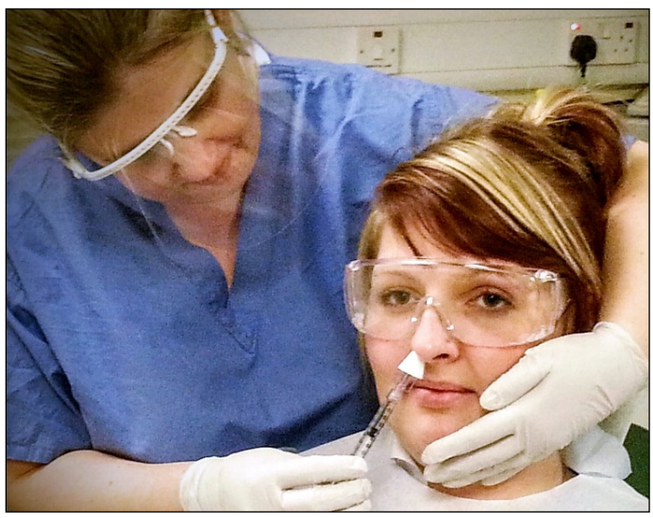

Figure 3: An example of IN device being used.

Table 1 - Suggested protocol for administering IN conscious sedation.

Suggested Sequence	Action
1.	Carry out pre-sedation checks.
2.	Check the ampoule of Midazolam paying attention to the name Midazolam HCl 40mg/ml + Lidocaine 20mg/ml, Batch number and expire date.
3.	Insert a 1ml Luer locking syringe into the ampule and draw up the decided volume + additional dead space volume. Carefully label the syringe Midazolam 40mg/ml + Lidocaine 20mg/ml and dispose of the sharps.
4.	Inspect the nostrils for blockages, attach a monitor to the patient to monitor SpO_2 and Pulse.
5.	Lock the MAD device onto the Luer lock syringe, place into the patient's nostril and advise the patient to sniff as the plunger is pushed.
6. 7.	Continue monitoring the patient's vital signs for and look for changes in consciousness. After 10-12 minutes assess the patient for acceptability of intravenous cannulation and dental treatment.
8.	Cannulate patient if sufficiently sedated. If compliant, carry out dental treatment.
9.	If the patient tolerates intravenous cannulation, but cannot tolerate the dental treatment consider adding a titrated dose of intravenous midazolam.
10.	If the patient is unable to tolerate intravenous cannulation or dental treatment, consider a second dose of intranasal midazolam.

Cases

Patient 1

An eighteen-year-old male attended with his parents. He complained of pain in the lower left quadrant. He presented with a mobile tender LL4. He also had an UL1 with an incisal edge fracture. Medically, the patient had adult learning difficulties, was partially deaf and was undergoing testing for Marfan's syndrome. He communicated with sign language and picture cards on his ipad. All previous treatment had been conducted under general anaesthetic.

The options for treatment were discussed, and a treatment plan was formulated which involved the extraction of the LL4 tooth and the restoration of the UL1 tooth under conscious sedation using IN Midazolam. The patient was consented with best interests.

A 10mg dose of IN midazolam was administered in the right nostril, and after approximately 12 minutes the patient was sufficiently sedated to allow cannulation. We were able to extract the LL4 and restore the UL1 without providing the patient with supplemental intranasal midazolam or intravenous midazolam. Pulse, SpO_2 and blood pressure remained normal throughout the treatment.

Patient 2

A seventy-year-old woman attended the clinic in pain with her husband, who is her carer. Medically, the patient suffers from dementia and can only manage to sit down briefly for dental examinations before getting up and walking around the surgery. On examination, UR6 was symptomatic.

Options were discussed. The plan agreed involved extracting the tooth with IN Midazolam conscious sedation, and if that failed, to extract the tooth under general anaesthetic. The patient was consented with best interests.

A 10mg dose of IN midazolam was administered, and after approximately 12 minutes the patient was sufficiently sedated to allow cannulation. The patient was adequately sedated to allow the extraction of the tooth without the need for additional intravenous midazolam. Pulse, SpO_2 and blood pressure remained normal throughout the treatment.

Lessons from these cases histories

These two patients had very different needs. Intranasal midazolam (40mg/ml midazolam and 20mg/ml lidocaine) is an off-license medication, and that must be explained and documented as part of the consent process. The first patient with good support managed to have dental treatment using intranasal sedation. This case shows the benefits to both patient and carers. The fact that the patient was not required to starve made his parents' lives much easier. His parents commented that, as treatment was conducted in familiar surroundings, the episode was less distressing for their son.

The second patient, with the help and support of her husband, managed to have an extraction using intranasal sedation. The

patient's husband was keen to avoid general anaesthetic for his wife when we realised that the treatment plan would involve the extraction of a tooth. The patient was not required to starve prior to treatment, and the total time in which the patient remained in the clinic from admission to discharge was significantly shorter than if she had undergone general anaesthesia. After treatment, the patient's husband wrote a thank you card and admitted he had been sceptical of the technique, but that it had made things so much easier for both him and his wife.

There are some patients who will never accept dental treatment under local anaesthesia without additional pharmacological intervention. Conscious sedation with intravenous midazolam has bridged the gap between dental treatment with local anaesthesia and general anaesthetic, but only if the patient can tolerate cannulation. A significant number of patients with cognitive impairment find accepting any form of injection impossible to tolerate. Both the patients would most likely have been offered extractions under general anaesthetic as the only option for treatment. The use of IN sedation in the special care dentistry department allowed these patients to receive a full spectrum of dental care. There are also a large number of needle-phobic individuals for whom IN sedation offers the chance to access dental care.

Adverse effects, risks and contraindications

The risk from IN administered conscious sedation is the same as for IV midazolam. Some patients have complained of a blocked or runny nose for 24 hours, and teary eyes. The method is contraindicated in patients who suffer from nasal polyps, in patients with cold- and flu-like symptoms, and for patients who suffer from regular nose bleeds. An absolute contraindication is that this technique must not be carried out by practitioners who are not experienced in cannulation, as there would be no way to reverse the patient if required. It is, however, sometimes difficult to administer the solution to patients with challenging behaviour. Training in safe handling is required if considering using this technique in people with special needs and challenging behaviour.

Initial Results

The Special Care Dentistry Department at Dorset County Hospital has seen great early success with this technique. 17 patients received a standard dose of 10mg of Midazolam. This was administered either as a single dose, repeated or used with or without additional IV midazolam or IV propofol. All the patients were men and women over the age of twelve and were ASA 1 or ASA 2. There were two cases of desaturation below 92%, which responded to oxygen and encouraging the patient to breathe. Two patients experienced epistaxis: one patient with learning difficulties placed his fingers in his nose which caused a resultant bleed, and the other had a spontaneous bleed a few minutes after the IN bolus was given.

Flumazenil use

Flumazenil was administered to three patients who had moderate to severe behavioural difficulties. The patients all had normal vital signs. Flumazenil was administered to these patients to improve disorientation rather than reverse any ill effects from over sedation. As discussed, this technique of conscious sedation is new to the department and the cohort of patients is very small.

Discussion

The technique involving the titration of intravenous midazolam has allowed many patients to access dental care, including those with special needs and needle phobias who have previously been unable to receive dental treatment with the IV technique. The intranasal technique could be beneficial to these patients. IN midazolam application is a basic technique provided that the practitioner can demonstrate competence in intravenous sedation.[3] The technique of IN sedation is not as widely used as IV sedation, however, research has found it effective and safe; Manley et al.[14] found that in 222 episodes of sedation, 128 (57.65%) accepted treatment.

Conclusion

The purpose of this paper was to demystify the use of IN midazolam as a technique in conscious sedation. This paper also outlines a practical protocol which other clinicians could follow in their own practices for administering IN midazolam. The Special Care Dentistry Unit at Dorset County Hospital is within a teaching hospital, and our sedation service is consultant anaesthetist led. At the time of writing in 2015, the technique had been in use within the department for a period of six months. The initial results have been very positive.

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Conflict of interest

No conflict.

Sources of Funding

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