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ORIGINAL

Premedication with midazolam is equally effective via the sublingual and intravenous route of administration

TOMISLAV RUŽMAN • MARINA KREŠIĆ • DUBRAVKA IVIĆ • DANIJELA GULAM • NATAŠA RUŽMAN • JELENA BURAZIN

TOMISLAV RUŽMAN (✉)
Department of Anesthesiology
Resuscitation and Intensive care unit
University Hospital Osijek
Josipa Huttlera 4. 31000 Osijek, Croatia
Phone: +385 (0)31 511 502
Fax: +385(0)31 512 205
E-mail: tomislav1707@yahoo.com

TOMISLAV RUŽMAN • MARINA KREŠIĆ •
DUBRAVKA IVIĆ • DANIJELA GULAM
Department of Anesthesiology, Resuscitation and Intensive care unit
Clinical Hospital Centre Osijek
Medical Faculty, University Josip Juraj Strossmayer Osijek
Osijek, Croatia

NATAŠA RUŽMAN •
JELENA BURAZIN
Institute of Public Health for Osijek-Baranya County, Osijek, Croatia

ABSTRACT

Background. The aim of this study was to investigate the clinical efficacy and potential side effects of sublingual midazolam, used for premedication, in comparison with intravenous midazolam. The second aim was to explore cost-effectiveness of sublingual midazolam administration.

Methods. A prospective, randomized, controlled, single-blinded trial was conducted at the Clinical Hospital Centre Osijek, Croatia, during the period 1st of May till 31st of October, 2012. We enrolled 140 patients (American Society of Anesthesiologists (ASA) physical status I-II, age≥18 years) scheduled for some kind of elective surgical procedure. Exclusion criteria were ASA III or higher, psychiatric disorders, allergy to midazolam and use of psychotropic drugs. Patients were randomized into one of two groups. One group received 2.5 mg of midazolam intravenously and the other group received 1/4 of a midazolam tablet (approximately 3.75 mg) sublingually. Sedation was clinically evaluated using the Ramsey sedation scale at 0, 10, 20 and 30 minutes after drug administration. We also noted side effects and degree of amnesia.

Results. Ten minutes after administration of premedication, a significantly higher number of patients in the intravenous group had a Ramsey score of 2 (p=0.000). Ten and twenty minutes after drug administration, most of the patients in the sublingual group had a Ramsey score 1-2, and after 30 minutes most of them had a Ramsey score 2-3, which is comparable with the intravenous (p=0.642) group.

Conclusion. Sublingual application of midazolam has an equivalent sedative effect as intravenous midazolam 20 minutes after administration but is associated with a bitter taste and weaker amnestic effect.

Key words: premedication, midazolam, sublingual, intravenous

Introduction

Most patients are anxious, afraid or agitated while waiting for surgery. (1,2) This can lead to significant stress and adversely influence anesthetic induction, and often leads to a poorer recovery after surgery. (3-5) Anxiety can also decrease patient's satisfaction with the perioperative experience. (6) The most important drugs for premedication are benzodiazepines, opioids, alpha-2 adrenoreceptor agonists, melatonin, dexmedetomidine or other drugs which have an anxiolytic, analgesic or sedative effect. (7,8)

Sedative premedication can be administered orally, intramuscularly, intravenously, rectally, sublingually or nasally. Oral or sublingual application does not hurt, but it may have a slow onset or the medication may be spit out. Drug taste is the main determinant for the success of their administration. Intramuscular medications may hurt and may result in a sterile abscess. Intravenous medications may be painful during injection or at the start of the infusion. Rectal

Table 1. Ramsey sedation scale.

Score	Response to stimulation
0	Awake, oriented
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to command only
4	Brisk response to light glabellar tap or loud auditory stimulus
5	Sluggish response to light glabellar tap or loud auditory stimulus
6	No response to stimulus

medications, which are mostly used for children, may sometimes make the children feel uncomfortable and they may cause defecation, and occasionally burns. Nasal medications can be irritating, although their absorption is rapid. The choice of best premedication route and drug must be adapted to each patient. (9)

The ideal agent should have a rapid onset, a predictable duration of action and enable rapid recovery. Midazolam, a sedative from the benzodiazepines group, has most of the above attributes and is most frequently used for premedication before anesthesia. (7,10-13) Its advantage is good bioavailability regardless of route of application, such as intravenous, intramuscular or transmucosal (oral, intranasal, rectal or sublingual).

The sublingual route of administration for some medications is a good choice because of good pharmacokinetic properties and simple application without pain. One advantage of this route of application is avoidance of the first pass effect and an increase in bioavailability of the drug and thus more predictable pharmacological effects. (14,15) Sublingual administration of the parenteral soluble form of midazolam was investigated in many previous studies, especially in children and just a few studies have described sublingual application of oral midazolam tablets. (16)

The aim of this study was to investigate clinical efficacy and potential side effects of sublingual application in comparison with intravenous application of midazolam used for premedication.

Methods

Ethical approval for this study (Ethical Committee N° 25-1:3160-6/2012) was provided by the Ethical Committee of Clinical Hospital Centre Osijek, Osijek, Croatia (Chairperson Anto Rašić) on 18th April, 2012.

It was a prospective, randomized, controlled, single-blinded investigation. The studied population included 140 patients undergoing elective orthopedics, abdominal, urologic, maxillofacial or thoracic surgery, who were due to receive midazolam as a premedication. The main inclusion criteria included ASA (American Society of Anesthesiologists) physical status class I or II and older than 18 years of age. Exclusion criteria were an ASA physical status of class III or higher, patients with psychiatric disorders, and those taking antipsychotics, chronic use of benzodiazepines, and allergy to midazolam.

The patients were randomized into one of two groups. One group (intra venous group) received 2.5 mg of Midazolam intravenously (Roche Dormicum, 15 mg/3mL ampulla) and the other group (sublingual group) of patients received 1/4 of a midazolam oral tablet (approximately 3.75 mg; Roche Dormicum, 15 mg tablets) sublingually (s.l.). The dose of ¼ midazolam tablet was clinically estimated as the amount needed for adequate premedication, and was relatively comparable with 2.5 mg of midazolam administered intravenously (i.v.), which is the mostly frequently used dose for premedication for the average patient.

In the sublingual group, the tablet was placed under the tongue and patients were instructed not to swallow the tablet. Assessments were carried out before and after midazolam administration by an anesthesiologist who did not know about the administration route. Anxiety and sedation were evaluated using the Ramsey sedation scale (table 1). A baseline sedation score was noted by a researcher prior to drug administration. Then the patients were observed at an interval of 10, 20 and 30 minutes after drug administration in the surgical holding areas. At the end of the study, the patients in both groups were asked about side effects and amnesia. Also, the investigator noted demographic data and data about surgery and type of anesthesia.

All data were entered in a database, and analyses were done with SPSS 17.0 statistical programme. Most of the data are reported as mean ± SD or percentage (%). Differences between groups were analyzed using Chi-square or unpaired Student's t-tests. P was considered statistically significant if $p < 0.05$.

Results

This analysis identified epidemiological and clinical characteristics of two different applications of midazolam premedication at the Department of Anesthesiology, Resuscitation and Intensive Care Unit (ICU), University Hospital Osijek in Croatia. The study included 140 patients who underwent some kind of surgery, with six patients excluded due to chronic use of antipsychotics, benzodiazepines or other psychotropic drugs. Epidemiological data for each group were described in table 2. There were no statistically significant differences between the groups for most of the tested demographic variables except height ($p=0.034$). The studied population consisted of 83.57 % (117/140) orthopedics patients and 14.28 % (20/140) abdominal surgery patients. The rest included one urological, one thoracic and one maxillofacial patient. Also, 60 % (84/140) of operations were conducted under spinal anesthesia, 20.7 % (29/140) under general anesthesia and 19.3 % (27/140) using ultrasound guided regional nerve blocks, and there was no statistical difference

Table 2. Epidemiological characteristics of study groups.

	Sublingual group n(%), mean ± SD	Intravenous group n(%), mean ± SD	p value
AGE (years)	44,16 ±15,69	48,37±16,88	0,128
SEX male female	39 (55,7) 31 (44,3)	38 (54,3) 32 (45,7)	0,865
WEIGHT (kg)	82,37±17,31	83,84±21,00	0,652
HEIGHT (cm)	173,58±8,99	166,24±27,18	0,034*
BMI (kg/m^2)	27,23±4,96	27,17±5,79	0,948
ASA physical status I II	22 (31,4) 48 (68,6)	16 (22,9) 54 (77,1)	0,254

ASA physical status, American Society of Anesthesiologist physical status; BMI, body mass index.
Independent Student t-test was used for obtaining statistical difference between groups
*p< 0.05

Table 3. Clinically assessed Ramsey scores at 0, 10, 20, 30 minutes after midazolam premedication.

	Sublingual group	Intravenous group	p value
RS0 0 1 2 3 4	 19 (13,6) 50 (35,7) 1 (0,7)	 15 (10,7) 53 (37,9) 2 (1,4)	0,640
RS10 0 1 2 3 4	 7 (5) 61 (43,6) 2 (1,4)	 2 (1,4) 51 (36,4) 17 (12,1)	0,000*
RS20 0 1 2 3 4	 0 (0) 44 (31,4) 26 (18,6) 0 (0)	 1 (0,7) 38 (27,1) 27 (19,3) 4 (2,9)	0,141
RS30 0 1 2 3 4	 (0) (0) (26,4) 28 (20) 5 (3,6)	 1 (0,7) 1 (0,7) 32 (22,9) 31 (22,1) 5 (3,6)	0,642

RS0, Baseline Ramsey score; RS10, Ramsey score after 10 minutes; RS20, Ramsey score after 20 minutes; RS30, Ramsey score after 30 minutes.
Chi-square test was used for obtaining a statistical difference between groups
*p< 0.05

between these groups. One half of the patients (70/140) received midazolam sublingually and the other half received premedication intravenously. The sublingual tablets dissolved within 3-5 minutes. The characteristics of sedation are described in table 3. None of the patients in the intravenous group had side effects after premedication, and 24 (34.3%) patients in the sublingual group complained about the bitter taste of the tablet (p=0.000). Partial or complete anterograde amnesia after surgery was experienced by 17.9 % (25/140) of the patients, most of them (19/140) in the intravenous group (p=0.016).

Discussion

Most patients are anxious or afraid before anesthesia and surgery and they require some kind of premedication. We conducted this study to show the benefits of sublingual administration of midazolam tablets for premedication.
Like most studies, we found that only 25 % of patients seemed relatively calm, and more than 72 % of surgical patients had fear or anxiety before interventions. Therefore, premedication before anesthesia is necessary to alleviate anxiety, to facilitate smooth induction of anesthesia and to inhibit autonomic

reflexes without prolonging the recovery period. There are numerous drugs for this, but in our daily practice midazolam is used most often because it has been found to fulfill many of the above criteria. (7) The anesthesiologist must choose the best route for premedication which must be simple, painless, and pleasant for the patient. This can be achieved by transmucosal application across oral, nasal or rectal mucosa. (17-21) The sublingual route has an advantage because of mucosal absorption directly into the systemic circulation, with no first pass through the liver, due to the rich blood supply of oral mucosa, it is easy to administer, has rapid onset of action, a reliable, predictable effect and the drug is not destroyed by gastrointestinal enzymes. There are many studies which compare effects of different routes for midazolam application. (9,15-17,20,22,23) Studies which compared sublingual with orogastric route showed that midazolam plasma levels are greater after sublingual application in comparison with orogastric route. A study by Fujii et al. had proven better bioavailability by sublingual route in comparison with oral route for midazolam tablets. (22) There is one study which compared intravenous and sublingual midazolam application. In this study Odou's et al. in France showed no significant differences between pharmacokinetic parameter values after intravenous (0.5 mg solution) and sublingual administration (0.5 mg tablet) in six rabbits. (24)

In our study with 140 patients, clinical comparison was made between the sublingual and intravenous application of midazolam used as premedication before some surgical interventions. Each group was studied for sedation scores after midazolam application and for possible unwanted effects and amnesia after surgery. There was no significant difference in most demographic variables except in height between these two groups. After clinically assessing sedation levels, we found that sublingual application of midazolam had a sedative effect which is comparable with intravenous. We did not find a significant difference in baseline sedation scores before premedication between the groups. Although ten minutes after midazolam application both groups had satisfactory Ramsey scores (RS 1-2), significantly more patients from the intravenous group had RS score 2 ($p=0.000$) due to direct application of the drug into blood. However, twenty minutes after premedication, most of the patients in the sublingual group had satisfactory sedation levels which ensured calm and quality induction of anesthesia. Only a few patients in the intravenous group had RS score 4 at the same time. Because of a slower increase in blood concentration in the sublingual group, RS score 4 was noted only 30 minutes after premedication. Thirty minutes after midazolam application the patients had reasonably deeper scores (RS 2-4), but without statistical differences between the groups ($p=0.642$). Also, none of the patients had an unacceptably deep level of sedation, higher then Ramsey score 4. Likewise, recent studies showed a rapid and good sedation effect after sublingual midazolam application due to very fast absorption across oral mucosa. (9,15,17,20,23) Gupta et al. found, in a population of 60 children, that the desirable level of sedation and separation before surgery was achieved earlier in the case of sublingual midazolam than the oral route. (23)

Just a small percentage of the patients in both groups (17.9 %) had complete or partial anterograde amnesia after surgery. We can explain this with the small doses of midazolam used for premedication. These doses provide satisfactory anxiolysis and good sedation but are most probably insufficient for amnesia development. About one third of the patients in the sublingual group complained about a bitter taste after tablet dissolving, and none of the patients in the intravenous group had unwanted side effects. We observed that female patients complained more often about tablet taste.

After using midazolam tablets sublingually, we think that the only disadvantages are the taste and a large tablet dose which requires dividing the tablet into small parts. In the future, the pharmaceutical industry should consider developing special midazolam tablets for sublingual premedication with the appropriate dose and good taste.

In our study, we did not investigate consumption of anesthetics and analgesics during anesthesia, nor postanesthesia recovery variables, but we clinically observed that there was no difference between these groups regarding recovery time after surgery. Also, we did not measure plasma levels of midazolam because of technical limitations and large costs.

Finally, our intention in this study was also to show the cost-effectiveness of sublingual application of midazolam tablets. One tablet of 15 mg of midazolam costs about 0.30 Euro, and one ampoule of 15 mg of midazolam costs about 1.6 Euros. There is also the cost of needles and syringes for intravenous application. Therefore, sublingual application is cheaper than intravenous. This may not seem significant, but in hospitals that have a large number of surgical patients savings might be significant.

In conclusion, sublingual application of an oral midazolam tablet reaches equivalent sedative effects compared with intravenous midazolam 20 minutes after administration but is associated with a bitter taste and less amnesic effect. Given the slower onset, difficulty for tablet dissolving (unreliable absorption), the unpleasant bitter taste, the possibility of administrative process induced anxiety and less amnesic effect, we cannot say sublingual administration is better than iv administration in adults.

REFERENCES

1. Wetsch WA, Pircher I, Lederer W, Kinzl JF, Traweger C, Heinz-Erian P, et al. Preoperative stress and anxiety in day-care patients and in patients undergoing fast-track surgery. BJA 2009;103:199–205.
2. Kain ZN. Premedication and parental presence revisited. Curr Opin Anaesthesiol 2001;14:331-7.
3. Narita K, Murata T, Hamada T, Takahashi T, Omori M, Suganuma M, et al. Interactions among higher trait anxiety, sympathetic activity, and endothelial function in the elderly. J Psychiatr Res 2007;41:418-27.
4. Jamison RN, Parris WC, Maxson WS. Psychological factors influencing recovery from outpatient surgery. Behav Res Ther 1987;25:31-7.
5. Kain ZN, Sevarino F, Alexander GM, Pincus S, Mayes LC. Preoperative anxiety and postoperative pain in women undergoing hysterectomy: a repeated-measure design. J Psychosom Res 2000;49:417-22.
6. Bauer KP, Dom PM, Ramirez AM, O'Flahertv JE. Preoperative intravenous midazolam: benefits beyond anxiolysis. J Clin Anesth 2004;16:177-83.
7. Jukić M, Marinov V. Examination, preparation and premedication of patient before anaesthesia. In: Jukić M, Hudedžinović I, Kvolik S, Majerić Kogler V, Perić M, Žunić J, editors. Clinical Anaesthesiology. Zagreb: Medical Edition; 2013. P. 549-78.
8. Zalunardo MP, Ivleva-Sauerborn A, Seifert B, Spahn DR. Quality of premedication and patient satisfaction after premedication with midazolam, clonidine or placebo: Randomized double-blind study with age-adjusted dosage. Anesthetist 2010;59:410-8.
9. Kumar N, Sharma R, Sharma M, Verma I, Sharma M. Midazolam Pre-medication in Paediatrics: Comparison of the Intranasal and Sublingual Routes by Using an Atomizer Spray. JCDR 2012;6:65-8.
10. Bergendahl H, Lonnqvist PA, Eksborg S. Clonidine in paediatric anaesthesia: A review of the literature and comparison with benzodiazepines for premedication. Acta Anaesthesiol Scand 2000;50:135-43.
11. Ghai B, Grandhe RP, Kumar A, Chari P. Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication. Paediatr Anaesth 2005;15:554-9.
12. Schmidt AP, Valinetti EA, Banderira D, Bertacchi MF, Simoes CM, Auler JR. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. Paediatr Anaesth 2007;17:667-74.
13. Dundee JW, Wilson DB. Amnesic action of midazolam. Anaesthesia 1980;35:459-61.
14. Marshall J, Rodarte A, Blumer J, Khoo KC, Akbari B, Kearns G. Pediatric pharmacodynamics of midazolam oral syrup. Pediatric Pharmacology Research Unit Network. J Clin Pharmacol 2000;40:578-89.
15. Karl HW, Rosenberger JL, Larach MG, Ruffle JM. Transmucosal administration of midazolam for premedication of pediatric patients. Comparison of the nasal and sublingual routes. Anaesthesiology 1993;78:885-91.
16. Lim TW, Thomas E, Choo SM. Premedication with midazolam is more effective by the sublingual than oral route. CJA July 1997;44:723-6.
17. Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: A comparison of four routes of administration. Paediatr Anaesth 2002;12:685-92.
18. Wilton NC, Leigh J, Rosen DR, Pandit UA. Preanaesthetic sedation of pre schoolchildren using intranasal midazolam. Anesthesiology 1988;69:972-5.
19. Coté CJ, Cohen IT, Suresh S, Rabb M, Rose JB, Weldon BC et al. A comparison of three doses of commercially prepared oral midazolam syrup in children. Anaesth Analg 2002;94:37-43.
20. Naqash I, Waqar-ul N, Zargar J. Midazolam premedication in children: Comparision of nasal and sublingual routes. Anaesth Clin Pharmacol 2004;20:141-5.
21. Saint-Maurice C, Meistleman C, Rey E. Pharmacokinetics of rectal midazolam for Pre-medication. Anesthesiology 1986;65:536-8.
22. Fujii J, Intosume N, Nakano M. Relative bioavailabiliy of midazolam following sublingual versus oral administration in healthy volunteers. J Pharmacobio Dyn 1988;11:206-9.
23. Gupta S, Gadani H, Kedia S. Is premedication with midazolam more effective by the sublingual than the oral route? Anesth Essays Res 2011;5:43-7.
24. Odou P, Barthélémy C, Chatelier D, Luyckx M, Brunet C, Dine T et al. Pharmacokinetics of midazolam: comparison of sublingual and intravenous routes in rabbit: Eur J Drug Metab Pharmacokinet 1999;24:1-7.