ORIGINAL ARTICLE

The influence of clonidine on oral ketamine-midazolam premedication in intellectually disabled patients indicated for dental procedures: Double-blind comparison of two sedation regimes

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Abstract

BACKGROUND: Dental procedures on intellectually disabled patients represent a clinical challenge. The oral administration of sedating drugs can remediate the problems with cooperation and enable the medical procedures to take place. Standard guidelines are lacking for oral sedation of the intellectually disabled.
OBJECTIVE: To compare two oral combinations of sedating drugs in terms of time to the onset and achievement of full sedation, vital signs, behavioral measures and safety.
METHODS: In a group of 29 intellectually disabled patients we compared two oral combinations for analgosedation: ketamine (5 mg/kg) – clonidine 2 μg/kg – midazolam 0.3 mg/kg (N=17) or ketamine 5 mg/kg – midazolam 0.3 mg/kg (N= 12 patients). Drugs were dissolved in a sweet drink.
RESULTS: Full sedation was achieved within 25 min. in 27 patients and serious side effects were not detected. Clonidine in combination with ketamine and midazolam did not exert any significant effect by means of the onset of sedation, time to the achievement of full sedation, vital signs and behavioral measures of sedation (Vancouver Interaction and Calmness Scale) and agitation (Pittsburgh Agitation Scale).
CONCLUSIONS: Our study is the first to document that oral administration of ketamine and midazolam in low doses represents a safe and effective method of premedication in intellectually disabled patients indicated for dental procedures. Clonidine co-administration did not exert any substantial benefit and should be left out in this clinical setting.

INTRODUCTION

Medical and surgical procedures on intellectually disabled patients represent a challenge and a highly relevant problem. Uncooperativeness, anxiety and aggressiveness complicate both diagnostic and therapeutic procedures in these patients (Gordon *et al.* 1998; Haavio 1995). General anesthesia is the standard clinical approach but the risk-benefit ratio is questionable especially in routine procedures such as dental examinations and treatments (Balogh *et al.* 2012). Intravenous access is also not usually feasible in intellectually disabled patients. The lack of access to dental care in uncooperative intellectually disabled patients results in poor oral health and lower quality of life (Maeda *et al.* 2005; Martin *et al.* 1997).

Analgesic sedation can remediate the problem with cooperation during dental procedures and represents an approach alternative to general anesthesia (Mistry & Nahata 2005). In addition, oral administration of sedative drugs resolves the problem of cooperation essential for venous or muscular injections in these patients. Oral premedication is usually effective and safe (Funk *et al.* 2000). The drugs used most commonly for premedication are benzodiazepines (typically midazolam soluble in water) and ketamine. Midazolam induces anxiolysis, amnesia and sedation in a dose-dependent manner (Amrein *et al.* 1990). Bioavailability of oral midazolam is 36% with high interindividual differences in pharmacokinetics (Cote *et al.* 2002). Ketamine is a dissociative anaesthetic drug inducing sedation, analgesia, catalepsy and anaesthesia via N-methyl-D-aspartate receptors antagonism (Bubenikova-Valesova 2008). Ketamine has a sympathomimetic effect but its effect on respiration is minimal. Ketamine is typically administerd via muscular or intravenous injections, or nasally in children. The oral application of ketamine has been less common due to the high first pass effect. However, recent data indicate that the bioavailability of ketamine and its first (and fully active) metabolite norketamine is 59% (Mistry & Nahata M. C. 2005).

The co-administration of ketamine and midazolam enables achievement of the sedating effect with lower doses of both drugs and eliminates the psychotomimetic effect of ketamine (Horacek *et al.* 2010; Mistry & Nahata 2005). The oral co-administration of ketamine (3 mg/kg) and midazolam (0.5 mg/kg) was successfully tested in uncooperative children. The combination was more effective and had less side effects (negative memories, nightmares) than oral ketamine and midazolam alone (Funk *et al.* 2000).

Clonidine is a partial agonist of α2 adrenergic receptors with anxiolytic, sedating and analgetic effect in a dose-dependent manner. In addition, the α2 adrenergic effect also induces a decrease in blood pressure, heart rate and improves circulatory stability in general (Hess *et al.* 2010, Sezer et al., 2011). Clonidine can potentiate the sedative effect of benzodiazepines (Salonen *et al.* 1992) and reduces the sympathomimetic and psychomimetic effects of ketamine (Levanen *et al.* 1995). Clonidine co-administration enabled the dose of oral ketamine to be reduced from 6–10 mg/kg to 3 mg/kg (Bozkurt 2007).

Standard guidelines for sedation of intellectually disabled patients who do not cooperate during dental procedures are lacking. The aim of our study was to compare two oral combinations of sedating drugs (ketamine and midazolam or ketamine, midazolam and clonidine) in terms of time to the onset and achievement of full sedation, vital signs, behavioral measures of sedation and agitation, cardiac effect and safety in general. We expected that clonidine in this combination would have a beneficial effect on haemodynamic stability and quality of analgosedation.

METHODS

Subjects

Subjects were residents of a large social care facility for people with intellectual disabilities. Twenty-five (15 males/14 females, mean age 36.7±1.7) intellectually disabled polymorbid patients with severe and profound mental retardation according to ICD 10 were involved in the study. The most frequent other diagnoses were cerebral palsy (13 subjects), Down's syndrome (6 subjects) and epilepsy (8 subjects); microcephaly (2 subjects), Sotos syndrome (1 subject), Rubinstein–Taybi syndrome (1 subject), narcolepsy (1 subject), birth trauma (1), hypothyreosis (1 subject), mucopolysacharidosis type V (1 subject) and status post meningitis (2 subjects) were the other important diagnoses. Patients were scheduled for dental treatment with the following inclusion criteria: (a) previous dental examinations and treatments required general anesthesia due to a lack of cooperation and/or aggressiveness, and (b) poor state of oral health. Exclusion criteria were (a) known allergies to the experimental drugs or honey and (b) severe medical illness (ASA 4 according American classification of Anesthesiologists). All women of fertility age were treated with contraceptives as a part of their standard medication; therefore pregnancy tests were not needed. Dental care was performed at the Department of Stomatology for High Risk Patients, Charles University, which is equipped for monitoring and administering of general anesthesia, if necessary. The study was approved by a local ethics committee and the State Institute for Drug Control and complied with the Declaration of Helsinki. The caregivers signed informed consent on behalf of the patients.

Treatment

Patients, dentist, anesthesiologists, nurses, caregivers and raters were blinded to the treatment. Subjects were orally administered with one of the two drug combinations: ketamine 5 mg/kg (Calypsol, Gedeon Richter) + clonidine 2 μg/kg (Catapresan, Boehringer Ingelheim) + midazolam (Midazolam Torrex, 5 mg/ml, Torrex

Chiesi) 0.3 mg/kg (KCM group, 17 patients – 9M/8F) or ketamin 5 mg/kg + midazolam 0.3 mg/kg (KM group, 12 patients – 6F/6M). The oral premedication was flavored with 5 ml of certified honey and drinking water was added to a total volume of 20 ml. If the sedation was not satisfactory to perform dental treatment within one hour after the administration of the oral premedication, patients were administered with a short-acting anesthetics propofol or etomidate in standard doses to induce sufficient sedation. At the end of the procedures the patients with persisting profound sedation were treated with flumazenil to shorten the recovery.

Experimental procedure

Before patients were introduced to the oral premedication they were asked whether they know what their name and where they are at the moment, they were also asked to walk back and forth and were asked to perform a simple task on demand (pick up a newspaper, touch their nose with one finger). Four categories were then scaled as follows: able to perform the task, able to perform the task with the help of a caregiver, unable to perform the task and not evaluated (e.g. walking in quadruparetic patients). Subsequently, the patients drunk the oral premedication and were seated in the dental chair when the first signs of sedation were present or when they started to be more cooperative or less aggressive. After full sedation developed, a peripheral vein catheter was inserted and blood pressure, heart rate and oxygenation were measured. Subsequently, the dental care was performed including extraction. All procedures before, during and after the oral care were recorded on videotape and were stored for further offline processing by independent raters (TP, JH).

Scales used

Two different scales for the measurement of patient behavior, sedation and cooperation were used. The VICS (Vancouver Interaction and Calmness Scale) consists of two separate scores, the interaction score and the calmness score. Each score is composed of five categories, with each category graded on a scale from 1 to 6 giving a continuum from 5 to 30 points (de Lemos *et al.* 2000). The Pittsburgh Agitation Scale (PAS) is an easy-to-use instrument, based on direct observations of the patient originally designed to monitor severity of agitation in demented patients. It consists of four subscales: aberrant vocalization, motor agitation, aggressiveness and resisting care. Each subscale has 5 categories scaled from 0 (not present) to 4 (most pronounced) (Rosen *et al.* 1994).

Statistics

All statistical analyses were performed using the Statistica 9 program. The analyses were performed by Mann Whitney tests and for comparisons of categorical measures by Chi-square tests (showed in the text). The p-values <0.05 were considered as significant.

RESULTS

Demographic characteristics of subjects

There were no differences between the two treatment groups in terms of age (in the KM group 35.88±2.06, KCM group 38.1±2.9; p=0.51). Six patients from the KM group and five from the KCM group suffered from stereotypy or dyskinesia, four patients from the KM group and three from the KCM group were not able to walk voluntarily and one patient from each group only walked when aided. Ten patients from the KM group and eight from the KCM group were not able to speak coherently. Seven patients from the KM group and one from the KCM group were not able to perform simple tasks on demand at all and three patients from the KM group and six from the KCM group performed simple tasks on demand with the help of a caregiver. In none of the above parameters were significant differences between the treatment groups (Chi-square tests with p=0.68 for stereotypy and dyskinesia, p=0.27 for walking, p=0.89 for talking and p=0.11 for performing a simple task).

The onset and effectiveness of the oral premedication

The onset of sedation in the KM group was in 12.3±3.6 min and in the KCM group 10.6±1.1 min, full sedation was achieved in the KM group in 23.8±3.5 min and in the KCM group in 20.9±1.9 min with no difference being present between the two groups (p=0.36 and p=0.6, respectively).

Blood pressure during full sedation in the KM group was 123.6±5.3 / 74.6±3.2 mmHg and in the KCM group 117.4±6.1 / 84.8±3.3 mmHg, there were no significant differences between systolic blood pressure (p=0.69), however for diastolic blood pressure we found a slight increase in the KCM group compared to the KM group revealing a borderline significance (p=0.06). Heart rate in the KM group was 94.2±5.4, in the KCM group 88.6±9.3, oxygenation in the KM group was 95.4±0.7%, in the KCM group 94.5±0.7%. There were no differences between the two treatments (p=0.51 and p=0.47, respectively).

In each group, full sedation did not develop in one patient within one hour from the administration of the treatment therefore they had to be administered with a short-acting anesthetic as stated above. Finally,

Tab. 1. Mean values (±SEM) of scores on PAS subscales. The last line shows p-values of Mann-Whitney comparisons between the treatment groups.

	Aberant vocalization	Motor agitation	Aggressive behavior	Resisting care
KM group	0.06±0.06	0.06±0.06	0	0.12±0.12
KCM group	0.5±0.19	0.08±0.08	0	0.5±0.19
KM vs KCM	p=0.11	p=0.71	NA	p=0.39

flumazenil was introduced to eight patients from the KM group and seven from the KCM group, again the Chi-square test did not reveal any significant difference between the two groups (p=0.56).

Measurements of sedation and cooperativeness

In general, both scales showed that the patients were deeply sedated and able to undergo the dental treatment. In the VICS interaction scale patients in the KM group scored 6.9±0.9 and in the KCM group 5.4±0.3 with no significant difference between the groups (p=0.23). Most patients were completely sedated as was shown by the calmness score: 28.1±1.1 for the KM group and 29.4±0.7 for the KCM group. Again, there were no differences between the groups (p=0.24).

The analysis of PAS subscales did not reveal any significant difference between the two groups; patients were sedated with no aggressiveness and did not resist care (Table 1).

DISCUSSION

The main finding of our study is the excellent clinical effect of oral sedation in intellectually disabled patients indicated for dental procedures. Both treatment regimes were well accepted and enabled dental intervention to take place in its entirety. Patients could be moved to the dental chair and cannulated without restraint within 25 min. after the oral administration. We did not observe any serious side effects like hypotension, agitation or respiratory complications.

Full sedation was not achieved and propofol or etomidate had to be applied in only one patient in each group. Due to the sweet taste of the medication none of mentally handicapped patients refused the drink. The use of honey for flavoring the drink could also improve absorption through the buccal mucosa due to its viscosity. The buccal utilization bypassing the liver metabolization could be responsible for the fast onset of sedation in some cases. Early onset within 5 min. after administration of the anlagosedation mixture occurred in 3 patients form the KCM and 2 from the KM group.

The dosing of analgosedating agents in intellectually handicapped patients represents another substantial problem. Population of these patients is highly heterogeneous with different physical and metabolic comorbidities (Forster *et al.* 2011) which can affect the pharmacokinetics of psychotropic agents. Controlled studies on different doses of midazolam and ketamine in this population are completely lacking. However, the required doses for sedative agents in intellectually disabled patients were described significantly higher than that required for other subjects (Miyawaki *et al.* 2004). The doses proposed in our protocol were derived from studies in children but they were lower than recommended in pediatric patients (Funk *et al.* 2000; Manley *et al.* 2000; Neckel *et al.* 1992). This approach was inspired by the expected synergistic effect of two or three compounds with different mechanisms of action. Our results demonstrate that the combination of lower doses of midazolam and ketamine compared to previous studies is effective and induces sedation fully relevant for dental procedures.

We did not detect any substantial clinical benefit of clonidine co-administration. Clonidine in combination with ketamine and midazolam did not exert any significant effect in terms of the onset and quality of the sedation and circulatory parameters. The treatment regimes showed no difference either in interaction or calmness scores (VICS), or even in agitation quantified by PAS. The lack of the expected beneficial effect of clonidine would be attributed to the pharmacokinetics of clonidine. The plasma concentration of clonidine rises to a peak at about 2 h after a single oral dose and the absorption half-life is more than 30 min. (Keranen *et al.* 1978). Patients in our study were fully sedated within 25 min. of drinking the sedating mixture. During this period of time clonidine could not exert its psychotropic effect. This interpretation is also supported by the absence of the hypotensive effect of clonidine during the period of observation. Future study should test the effect of oral clonidine if its administration precedes the ketamine plus midazolam for 1.5 hrs.

In conclusion, our study is the first to document that oral administration of ketamine and midazolam in low doses represents a safe and effective method of premedication in intellectually disabled patients indicated for dental procedures including intravenous cannulation. Full sedation was achieved within 25 min. Clonidine co-administration with ketamine and midazolam did not exert to any substantial benefit and should be left out in this setting.

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Statement of Interest

All authors confirmed their agreement to submission and declared that they have no competing financial interests.

REFERENCES

1 Amrein R, Hetzel W (1990). Pharmacology of Dormicum (midazolam) and Anexate (flumazenil). Acta Anaesthesiol. Scand. Suppl **92**: 6–15.

2 Balogh RS, Ouellette-Kuntz H, Brownell M, Colantonio A (2012). Factors associated with hospitalisations for ambulatory care-sensitive conditions among persons with an intellectual disability – a publicly insured population perspective. J Intellect. Disabil. Res., doi: 10.1111/j.1365-2788.2011.01528.x.

3 Bozkurt P (2007). Premedication of the pediatric patient – anesthesia for the uncooperative child. Curr. Opin. Anaesthesiol. **20**: 211–215.

4 Bubenikova-Valesova V, Horacek J, Vrajova M, Höschl C (2008). Models of schizophrenia in humans and animals based on inhibition of NMDA receptors. Neurosci Biobehav. Rev. **32**: 1014–1023.
5 Cote CJ, Cohen IT, Suresh S, Rabb M, Rose JB, Weldon BC *et al.* (2002) A comparison of three doses of a commercially prepared oral midazolam syrup in children. Anesth. Analg. **94**: 37–43.
6 de Lemos J, Tweeddale M, Chittock D (2000). Measuring quality of sedation in adult mechanically ventilated critically ill patients. the Vancouver Interaction and Calmness Scale. Sedation Focus Group. J. Clin. Epidemiol. **53**: 908–919.
7 Forster S, Gray KM, Taffe J, Einfeld SL, Tonge BJ (2011). Behavioural and emotional problems in people with severe and profound intellectual disability. J Intellect. Disabil. Res. **55**: 190–198.
8 Funk W, Jakob W, Riedel T, Taeger K (2000). Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. Br J Anaesth. **84**: 335–340.
9 Gordon SM, Dionne RA, and Snyder J (1998) Dental fear and anxiety as a barrier to accessing oral health care among patients with special health care needs. Spec. Care Dentist. **18**: 88–92.
10 Haavio M L (1995) Oral health care of the mentally retarded and other persons with disabilities in the Nordic countries: present situation and plans for the future. Spec. Care Dentist. **15**: 65–69.
11 Hess L, Votava M, Schreiberová J, Málek J, Horácek M (2010). Experience with a naphthylmedetomidine-ketamine-hyaluronidase combination in inducing immobilization in anthropoid apes. J Med Primatol. **39**: 151–159.
12 Horacek J, Brunovsky M, Novak T, Tislerova B, Palenicek T, Bubenikova-Valesova V et al (2010).Subanesthetic dose of ketamine decreases prefrontal theta cordance in healthy volunteers: implications for antidepressant effect. Psychol. Med **40**: 1443–1451.
13 Keranen A, Nykanen S, Taskinen J (1978). Pharmacokinetics and side-effects of clonidine. Eur. J Clin. Pharmacol. **13**: 97–101.
14 Levanen J, Makela ML, Scheinin H (1995) Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. Anesthesiology **82**: 1117–1125.
15 Maeda S, Kita F, Miyawaki T, Takeuchi K, Ishida R, Egusa M, Shimada M, et al (2005). Assessment of patients with intellectual disability using the International Classification of Functioning, Disability and Health to evaluate dental treatment tolerability. J Intellect. Disabil. Res. **49**: 253–259.
16 Manley MC, Skelly AM, Hamilton AG (2000). Dental treatment for people with challenging behaviour: general anaesthesia or sedation? Br Dent. J **188**: 358–360.
17 Martin DM, Roy A, Wells MB (1997). Health gain through health checks: improving access to primary health care for people with intellectual disability. J Intellect. Disabil. Res. **41**(Pt 5): 401–408.
18 Mistry RB and Nahata MC (2005). Ketamine for conscious sedation in pediatric emergency care. Pharmacotherapy **25**: 1104–1111.
19 Miyawaki T, Kohjitani A, Maeda S, Egusa M, Mori T, Higuchi H, et al (2004). Intravenous sedation for dental patients with intellectual disability. J Intellect. Disabil. Res. **48**: 764–768.
20 Neckel W, Jacobs FE, Tolksdorf W (1992). [Oral ketamine as preferred preanesthetic medication of uncooperative patients]. Anasthesiol. Intensivmed. Notfallmed. Schmerzther. **27**: 381–384.
21 Rosen J, Burgio L, Kollar M, Cain M, Allison M, et al (1994). A user-friendly instrument for rating agitation in dementia patients. Am. J. Geriatr. Psychiatry **2**: 52–59.
22 Salonen M, Reid K, Maze M (1992). Synergistic interaction between alpha 2-adrenergic agonists and benzodiazepines in rats. Anesthesiology **76**: 1004–1011.
23 Sezer Z, Sezer G, Tekol Y (2011). Ephedrine enhances the antinociceptive effect of dexmedetomidine in mice. Neuroendocrinol Lett. **32**: 552–6.