Ketamine and Midazolam for Invasive Procedures in Children with Malignancy: A Comparison of Routes of Intravenous, Oral, and Rectal Administration

by Durgul Ozdemir,[a] Ertan Kayserili,[b] Sertac Arslanoglu,[c] Pamir Gulez,[b] *and* Canan Vergin[d]
[a]*Department of Paediatrics, School of Medicine, Dokuz Eylul University, Izmir, Turkey*
[b]*Department of Paediatrics and* [d]*Department of Paediatric Haematology, Dr. Behçet Uz Children's Hospital, Izmir, Turkey*
[c]*Department of Paediatrics, School of Medicine, Ege University, Izmir, Turkey*

Summary

We investigated the efficacy of a combination of ketamine and midazolam, comparing intravenous, oral, and rectal administrations for invasive procedures in children with malignancy. Seventy-three children under 5 years of age, who were scheduled for invasive procedure, were assigned to one of three groups: IV group (n = 25), ketamine 1 mg/kg and midazolam 0.05–0.1 mg/kg were given intravenously; PO group (n = 24), ketamine 3 mg/kg and midazolam 0.5 mg/kg were given orally; and PR group (n = 24), ketamine 3 mg/kg and midazolam 0.5 mg/kg given rectally. Vital signs including blood pressure, pulse rate, respiratory rate, and oxygen saturation were monitored, and patients were observed for side-effects. Optimal sedation (drowsy and asleep) was provided in 78 per cent of all patients and no statistical difference was observed among the three groups. No severe complications were observed in all groups. Recovery time from sedation was significantly longer in the intravenous group (>120 min in two patients). Hallucination was noted in three (12 per cent) patients given intravenous medication, but not in those given oral or rectal medications. It is concluded that intravenous, oral, and rectal midazolam/ketamine are equally effective for invasive procedures in children with malignancy. The use of intravenous ketamine/midazolam may produce prolonged sedation and psychedelic effects in children. These adverse effects may alter the child's comfort and parental satisfaction.

Introduction

Multiple invasive procedures, such as bone marrow aspirations and lumbar punctures, are performed on children with malignancy during the course of their illnesses. These procedures cause substantial pain and distress in children. Anxiety can be extreme and often affects the relatives of patients. During these procedures, the inadequate management of pain and distress may cause depression and other long-term psychological disorders in children.[1,2]

Sedatives such as chloral hydrates, narcotic analgesics, and phenothiazine cocktails are largely ineffective and have a prolonged recovery time. Intravenous agents, such as propofol, generally require anaesthesiology support because of the high risk of respiratory depression.[3–5]

Recently, the combination of ketamine and midazolam has been commonly used for painful procedures in children. Ketamine has sedative, anaesthetic, and analgesic properties. It also stimulates the cardiovascular system, and causes minimum respiratory depression.[6] Midazolam is an anxiolytic drug used in preanaesthetic medication for surgical procedures.[7,8] It has been reported that the combination of intravenous ketamine and midazolam is free of the adverse effects of ketamine alone and provides rapid onset of sedation with minimal haemodynamic or respiratory compromise.[9] These agents have the advantage over many other sedatives and analgesic drugs in that therapeutic plasma levels can be obtained with intravenous, intramuscular, oral, rectal, sublingual, and nasal administration.[10–17] However, the preferred route of administration remains in dispute.

The combination of intravenous ketamine and midazolam had also been used for paediatric oncology patients.[18–20] In the present study, we investigated the efficacy of a combination of ketamine and midazolam, comparing intravenous, oral, and rectal administrations for invasive procedures in children with malignancy.

Materials and Methods

Seventy-three children under 5 years of age attending Dr. Behçet Uz Children's Hospital for bone

Correspondence: Durgul Ozdemir, MD, Huzur M. Pir Sultan Abdal S. No: 42/C D: 7, Narlidere Izmir, Turkey. E-mail <durgulozdemir@yahoo.com>.

marrow or lumbar puncture tests in the course of their treatment for malignancy were included in this study. Fifty-eight children (79.4 per cent) were treated for blood malignancy and 15 children (20.5 per cent) for solid tumours. Children with increased intracranial pressure, severe neurological dysfunction, and cardiovascular and respiratory malformation, active respiratory infection, liver or renal failure, and drug allergies were excluded. Informed parental consent was obtained for all children.

An application to the American Academy of Paediatrics (AAP) for guidelines on the use of sedative agents in children was granted.[21] Patients were instructed to intake nothing for 4 h before sedation. Children were admitted to the intervention room 1 h before the scheduled procedure. The intravenous line was established and intravenous fluid infused. Before administration of the sedative medication, the baseline vital signs were recorded and then the patient was monitored for heart rate, respiratory rate, and oxygen saturation. The measurement of blood pressure was performed every 5 min during the procedure and the recovery period. The children were assigned to one of three groups: group 1 (IV, $n = 25$), ketamine 1 mg/kg and midazolam 0.05 mg/kg given intravenously; group 2 (PO, $n = 24$), ketamine 3 mg/kg and midazolam 0.5 mg/kg in 5 ml cherry syrup given orally; group 3 (PR, $n = 24$), ketamine 3 mg/kg and midazolam 0.5 mg/kg in 5 ml 0.9 per cent normal saline given rectally.

Sedation state was assessed before drug administration and thereafter every 5 min by a second observer blinded to the route of medication. The quality of sedation was graded according to the scale used by Karl, *et al.*,[15] as follows: grade 1 being agitated, grade 2 anxious, grade 3 calm, grade 4 drowsy, and grade 5 asleep. Less than grade 3 was failed sedation, grade 3 was considered as acceptable sedation and grade 4 or 5 was considered as the optimal sedation. When sedation grade was 3 or more, the procedures were performed after local anaesthesia was administered using lidocaine 1 per cent by infiltration. After the procedure, patients were observed in the waiting room. Recovery from the sedation was assessed by level of awareness (fully awake) and age-appropriate orientated responses to verbal or motor stimuli. Recovery time was the time from the completion of the procedure until the child was entirely alert again. All patients were discharged according to the criteria recommended by AAP.[21] We contacted the children's parents 24 h after discharge, and asked them to assess their satisfaction with the consequences of the sedation regime used on their child.

Statistical analysis was performed using one-way analysis of variance, Mann–Whitney test and the chi-squared test or Fisher exact test. A p-value less than 0.05 was considered statistically significant.

TABLE 1
The demographic and procedure data

	IV group	PO group	PR group
n	25	24	24
Sex (M/F)	11/14	12/12	13/11
Age (years)	3.6 ± 1.2	3.9 ± 1.3	3.7 ± 1.1
Weight (kg)	16.2 ± 2.8	15.6 ± 3.1	15.8 ± 2.3
Type of procedure			
BMA (*n*)	7	8	4
BMA+ LP (*n*)	8	9	11
BMA + BMB (*n*)	10	7	9

Data are mean ± SD or number of patients**.** No significant differences among the three groups.
LP, lumbar puncture; BMA, bone marrow aspiration; BMB, bone marrow biopsy; IV, intravenous; PO, per oral; PR, per rectal.

Results

There were no significant differences among the three groups in terms of age, sex, weight, and type of procedure used. Demographic and procedure data are shown in Table 1.

As expected, the onset of sedation was quite rapid after intravenous administration, with clinical effects seen within 3–5 min. The onset of sedation following rectal administration was similar to that after oral administration (15–20 min). The time to statistically compare the sedation state after drug administration was the 5th min for the IV group, and the 20th min for the PO and PR groups. The optimal sedation (grades 4 or 5, drowsy and asleep) was provided in 78 per cent of all patients and no statistical difference was observed among the three groups (Table 2). The mean recovery time was longer (statistically significant) in the intravenous group (>90 min in two patients) compared with the other groups (Table 3).

No severe complications were observed in all groups. In each of the three groups, the baseline and after-procedure vital signs are shown in Table 4. There was cardiovascular stability during and after the procedure. No patient was documented to have significant tachycardia, hypo/hypertension, or respiratory depression. The pulse rate remained within 5 per cent of baseline values in most patients. In only five patients was transient tachycardia noted. The oxygen saturation was over 90 per cent in all patients. There was no apnoea or need to assist ventilation.

The observed adverse effects were increased salivation, agitation, hallucination, and vomiting. The former was seen in most of the patients but did not interfere with respiratory effort. Vomiting was noted in nine (12 per cent) of the patients during recovery from sedation and associated with neither route of administration nor procedure type. Aspiration was neither observed nor suspected. Four (5.4 per cent)

TABLE 2
The quality of sedation

Groups	Sedation state		
	Failed (grade 1–2)	Acceptable (grade 3)	Optimal (grade 4–5)
IV group, *n* (%)	0/25 (0)	5/25 (20)	20/25 (80)
PO group, *n* (%)	0/24 (0)	6/24 (25)	18/24 (75)
PR group, *n* (%)	0/24 (0)	5/24 (21)	19/24 (79)
Total, *n* (%)	0/73 (0)	16/73 (22)	57/73 (78)

Data are number of patients. No significant differences among the three groups ($p > 0.05$).
IV, intravenous; PO, per oral; PR, per rectal.

TABLE 3
Recovery time from sedation

Recovery time (min)	IV group	PO group	PR group
Mean time	38 ± 23	19 ± 13	24 ± 10
Range	28–130	14–46	18–55

Data are mean ± SD.
$p < 0.01$ for IV vs. PO groups; $p < 0.05$ for IV vs. PR groups.
IV, intravenous; PO, per oral; PR, per rectal.

of all patients experienced agitation during recovery but no significant difference was observed among the groups. Hallucination was noted in three (12 per cent) patients given intravenous medication, but not in those given oral or rectal medications.

Most of the parents reported that they were satisfied with the consequences of the sedation: 68 per cent, 71 per cent and 75 per cent for the intravenous, oral, and rectal groups, respectively. However, three (12 per cent) parents in the intravenous group stated that they were very worried because their child had hallucinations.

Discussion

A combination of ketamine and midazolam has been commonly used for invasive procedures in children. This combination has both sedative and analgesic properties. When these agents are used as single agents, midazolam and ketamine may produce respiratory depression and dysphoric reaction, respectively. The use of lower doses of midazolam with ketamine has been shown to result in more rapid onset of analgesia, more amnesia of the procedure, and less adverse effects. Previous studies reported that the combination of ketamine and midazolam is effective and safe in patients with malignancy.[18–20] In all of these studies, intravenous administration of these agents was used and found to be safe and effective. Our study provides evidence that a combination of midazolam and ketamine is effective and safe with both intravenous and transmucosal (oral and rectal) administrations.

Oral ketamine alone (10 mg/kg) was used for painful procedures in children with cancer and analgesia was achieved in 85 per cent of the children.[22] Auden, *et al.*[17] reported that oral ketamine/midazolam can be superior to intramuscular meperidine, promethazine, and chlorpromazine for sedating children with congenital heart disease. In this study, ketamine 10 mg/kg and midazolam 1 mg/kg were used in children ≤3 years old. Roelofse, *et al.*[23] compared midazolam (1 mg/kg) alone and midazolam (0.35 mg/kg) combined with ketamine (5 mg/kg) for sedation of paediatric dental patients. They reported that both drug groups had reliably good anxiolysis and sedation without loss of respiratory drive or protective airway reflexes. Funk, *et al.*[24] reported that significantly better anxiolysis and separation were observed with a combination of oral midazolam (0.5 mg/kg) and ketamine (3 mg/kg) than with midazolam (0.5 mg/kg) or ketamine (6 mg/kg) alone for preanaesthetic medication. In our study also, the combination of ketamine (3 mg/kg) and midazolam (0.5 mg/kg) was used orally in children

TABLE 4
Vital signs at baseline and end of sedation

	IV group		PO group		PR group	
	Baseline	End of sedation	Baseline	End of sedation	Baseline	End of sedation
HR (beats/min)	118 ± 28	122 ± 12	116 ± 19	128 ± 17	121 ± 8	118 ± 10
RR (beats/min)	30 ± 13	34 ± 17	32 ± 12	34 ± 14	32 ± 11	31 ± 22
SBP (mmHg)	108 ± 11	104 ± 14	102 ± 10	108 ± 12	105 ± 12	106 ± 15
DBP (mmHg)	68 ± 18	61 ± 12	64 ± 15	58 ± 11	67 ± 13	68 ± 12
SaO_2 (%)	98 ± 2.2	97 ± 2.1	97 ± 2.4	98 ± 2.1	97 ± 3.8	98 ± 2.3

Data are mean ± SD. No significant changes were between baseline and end of sedation in all three groups.
HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SaO_2, oxygen saturation; IV, intravenous; PO, per oral; PR, per rectal.

aged 1–5 years. All patients can accept oral medication. The optimal sedation was achieved in 80 per cent of patients and there was no significant difference compared with intravenous and rectal administrations.

Ketamine alone or combined with midazolam has been commonly used rectally for premedication and dental procedures. However, early studies with rectal ketamine in children yielded controversial results. Significant adverse effects have been reported after rectal administration of 8–10 mg/kg ketamine.[25–27] Beebe, *et al*.[12] found that the efficacy of rectal ketamine was unacceptable or inferior to midazolam. Recently, Tanaka, *et al*.[28] reported that rectal ketamine, 10 mg/kg, had a delayed onset but was as effective as 1 mg/kg midazolam for premedication. Thus, 10 mg/kg rectal ketamine is not recommended for brief surgeries because of prolonged sedation. In our study, the satisfactory sedation was achieved with rectal midazolam (0.5 mg/kg) and ketamine (3 mg/kg) for invasive procedures in children with malignancy.

We observed a few adverse effects with both intravenous and transmucosal administrations of this sedation regime; hallucination was noted in three (12 per cent) patients given intravenous medication. This condition caused their parents to worry. Hallucination is one of the side-effects of ketamine, occasionally with manic or hysterical episodes. The psychedelic effects are related to intravenous or intramuscular administrations.[6,19,29–31] This side-effect has not been reported in children given oral and rectal administrations.[10,12–14,17,24,28–31] There is a high first pass metabolism following oral administration. The metabolite norketamine also causes sedation and analgesia.[30,31]

One of the limiting factors in the use of most benzodiazepines for sedation is the length of action.[32] Parker, *et al*.[18] used i.v. midazolam (0.05–0.1 mg/kg) and ketamine (1–6 mg/kg) for therapeutic and diagnostic procedures in children and they found that recovery time ranged from <15 min to 120 min with >70 per cent of patients recovering within 30 min. In our study, the mean recovery time was significantly longer in the intravenous group compared with the other groups. Recovery time was longer than 120 min in two patients who received intravenous midazolam and ketamine. However, both patients had no respiratory depression and flumazenil therapy was not given. Flumazenil has proven to reverse the effect of sedative and respiratory depressant actions of midazolam.[33] However, flumazenil has been reported to precipitate seizures in the overdose situation.[34,35] Another concern about the use of flumazenil is its short half-life. Consequently, rebound sedation and respiratory depression may occur in patients to whom high doses of midazolam have been administered.[36,37]

In conclusion, we report that intravenous, oral, and rectal ketamine/midazolam is equally effective for invasive procedures in children with malignancy. The use of intravenous midazolam/ketamine may produce prolonged sedation and psychedelic effects in children. These adverse effects may alter the child's comfort and also the parent's satisfaction.

References

1. Jay S, Elliott CH, Fitzgibbons I, Woody P, Siegel S. A comparative study of cognitive behaviour therapy versus general anaesthesia for painful medical procedures in children. Pain 1995; 62: 3–9.
2. Weisman S, Bernstein B, Schecter N. Consequences of inadequate analgesia during painful procedures in children. Arch Pediatr Adolesc Med 1998; 152: 147–49.
3. American Academy of Pediatrics, Committee on Drugs. Reappraisal of lytic cocktail/Demerol, Phenerpan, and Thorazine (dpt) for sedation of children. Pediatrics 1995; 95: 598–602.
4. Terndrup TE, Dire DJ, Madden CM, Davis H, Cantor RM, Gavula DP. A prospective analysis of intramuscular meperidine, promethazine and chlorpromazine in pediatric emergency department patients. Ann Emerg Med. 1991; 20: 31–5.
5. Nahata ML, Clotz MA, Kropg EA. Adverse effects of meperidine, promethazine and cholorpromazine for sedation in pediatric patients. Clin Pediatr 1985; 24: 558–60.
6. White PF, Way WL, Trevor AJ. Ketamine: Its pharmacology and therapeutic uses. Anesthesiology 1994; 80: 1414–15.
7. Kain ZN, Mayes LC, Bell C, Weisman S, Hofstadter MB, Rimar S. Premedication in the United States: a status report. Anesth Analg 1997; 84: 427–32.
8. Haas U, Motsch J, Schreckenberger R, Bardenheuer HJ, Martin E. Premedication and preoperative fasting in pediatric anesthesia. Results of a survey. Anaesthesist 1998; 47: 838–43.
9. Audenaert SM, Wagner Y, Montgomery CL, *et al*. Cardiorespiratory effects of premedication for children. Anesth Analg 1995; 90: 506–10.
10. Lokken P, Bakstad OJ, Fonnelop E, *et al*. Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. Scand J Dent Res 1994; 102: 274–80.
11. Pruilt SW, Goldwasser MS, Sabol SR, Prstojevich SJ. Intramuscular ketamine, midazolam, and glycopyrrolate for pediatric sedation in the emergency department. J Oral Maxillofac Surg 1995; 53: 13–7.
12. Beebe DS, Belani KG, Chang PN, *et al*. Effectiveness of preoperative sedation with rectal midazolam, ketamine, or their combination in young children. Anesth Analg 1992; 75: 880–84.
13. Lovon A, Reddy VG. Nasal midazolam and ketamine in pediatric sedation during computerized tomography. Acta Anaesthesiol Scand 1994; 38: 259–61.
14. Malinovsky JM, Populaire C, Cozian A, Lepage JY, Lejus C, Pinaud M. Premedication with midazolam in children. Effect of intranasal, rectal and oral routes on plasma midazolam concentration. Anaesthesia 1994; 49: 782–85.
15. Karl HW, Rosenberger JL, Larach MG, Rufftle JM. Comparison of the safety and efficacy of nasal midazolam or sulfentanil for preinduction of anesthesia in pediatric patients. Anesthesiology 1992; 76: 209–15.
16. Walberg EJ, Willis RJ, Eckhert J. Plasma concentrations of midazolam in children following intranasal administration. Anesthesiology 1991; 74: 233–35.
17. Auden SM, Sobczyk WL, Solinger RE, Goldsmith LJ. Oral

ketamine/midazolam is superior to intramuscular meperidine, promethazine, and chlorpromazine for pediatric cardiac catheterization. Anesth Analg 2000; 90: 299–305.
18. Parker RI, Manhan RA, Giuglliano D, Parker MM. Efficacy and safety of intravenous midazolam and ketamine as sedation for therapeutic and diagnostic procedures in children. Pediatrics 1997; 99: 427–31.
19. Pellier I, Monrigal JP, Le Moine P, Rod B, Rialland X, Granry JC. Use of intravenous ketamine-midazolam association for pain procedures in cancer. A prospective study. Paediatr Anaesth 1999; 9: 61–8.
20. Marx CM, Stein J, Tyler MK, Nieder ML, Shurin SB, Blumer JL. Ketamine-midazolam versus meperidine-midazolam for painful procedures in pediatric oncology patients. J Clin Oncol 1997; 1: 94–102.
21. American Academy of Pediatrics Committe on Drugs. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics 1992; 89: 1110–15.
22. Tobias JD, Phipps S, Smith B, Mulhern RK. Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. Pediatrics 1992; 90: 537–41.
23. Roelofse JA, Louw LR, Roelofse PG. A double blind randomized comparison of oral trimeprazine-methadone and ketamine-midazolam for sedation of pediatric dental patients for oral surgical procedures. Anesth Prog 1998; 45: 3–11.
24. Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. Br J Anaesth 2000; 84: 335–40.
25. Saint-Maurice C, Languenie G, Couturier C, Goutail-Flaud F. Rectal ketamine in paediatric anaesthesia. Br J Anaesth 1979; 51: 573–74.
26. Idvall J, Holasek J. Rectal ketamine for induction of anaesthesia in children. Anaesthesia 1983; 38: 60–4.
27. Holm-Knudsen R, Nygard E, Laub M. Rectal induction of anaesthesia in children. A comparison between ketamine-midazolam and halothane for induction and maintenance of anaesthesia. Acta Anaesthesiol Scand 1989; 33: 518–21.
28. Tanaka M, Sato M, Saito A, Nishikawa T. Reevaluation of rectal ketamine premedication in children: comparison with rectal midazolam. Anesthesiology 2000; 93: 1217–24.
29. Bowdle TA, Radant AD, Cowley DS, Kharash ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology 1998; 88: 82–8.
30. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effect of i.m. and oral ketamine. Br J Anaesth 1981; 53: 805–9.
31. Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanasthetic medication in children. Anesthesiology 1992; 76: 28–33.
32. Sievers TD, Yee JD, Foley ME, Blanding PJ, Berde CB. Midazolam for conscious sedation during pediatric oncology procedures: safety and recovery parameters. Pediatrics 1991; 88: 1172–79.
33. Glass PS, Jhaveri RM, Ginsberg B, Ossey K. Evaluation of flumazenil for reversing the effects of midazolam-induced conscious sedation or general anesthesis. South Med J 1993; 12: 17–20.
34. Mordel A, Winkler E, Almog S, Tirosh M, Ezra KA, Stanley TH. Seizures after flumazenil administration in a case of combined benzodiazepine and tricyclic antidepressant overdose. Crit Care Med 1992; 20: 1733–34.
35. Lheureux P, Vranckx M, Leduc D, Askenasi R. Flumazenil in mixed benzodiazepine/tricyclic antidepressant overdose: a placebo controlled study in the dog. Am J Emerg Med 1992; 10: 184–88.
36. Breheny FX. Reversal of midazolam sedation with flumazenil. Crit Care Med 1992; 20: 736–39.
37. Salentin M, Malchow H, Muhlhofer H, Fischer M, Pilot J, Rohde H. A randomised controlled trial to evaluate the effects of flumazenil after midazolam premedication in outpatients undergoing colonoscopy. Endoscopy 1991; 23: 331–33.