Safety and efficacy of different administration order on paradoxical reactions following midazolam in children: a randomised, controlled trial

change zhu
Children's Hospital of Shanghai https://orcid.org/0000-0003-3569-624X
Saiji Zhang
Children's Hospital of Shanghai
Rong Wei (18521770157@126.com)
https://orcid.org/0000-0001-7891-9170

Research article

Keywords: fentanyl, paradoxical reactions, midazolam, induction, randomized controlled trials

Posted Date: October 15th, 2019

DOI: https://doi.org/10.21203/rs.2.15831/v1

Abstract

Study Objective Midazolam is commonly used for Anesthesia induction. However, the paradoxical reactions increase risk of self-injury and bring pressure on anesthesiologist. Although various drugs have been showed effective, but the potential adverse effects limit the application. We compared safety and efficacy of different administration order on the occurrence of paradoxical reactions in children.

Design Prospective, randomized, double-blinded study.

Setting Operating room of a university-affiliated hospital.Patients 1306 ASA physical status I pediatric patients, aged 6 months to 12 years, scheduled for general anesthesia.Interventions Patients were divided into three groups. In the fentanyl group, patients were given fentanyl followed by midazolam at induction; In the midazolam group patients received midazolam followed by fentanyl at induction; In the blank group, patients were given saline followed by fentanyl at induction. Propofol was administrated 2.5 mg/kg intravenously (IV).Measurements Onset of paradoxical reactions and BIS values were observed and recorded.

Main Results Preferentially and slowly injecting fentanyl could decrease the incidence of paradoxical reaction ($p<0.05$). Children displaying paradoxical reactions were mostly aged 8 months-2 years old ($p = 0.001$). Bispectralindex values increased significantly when paradoxical reactions burst out ($p< 0.05$). There were no significant differences in terms of side-effects.

Conclusion Changing the administration order was safe and effective to decrease the incidence of paradoxical reactions.

Backgrounds

Paradoxical reactions (PR) to midazolam are characterized by excitement, extremely panic, rage, violent behavior, and self-mutilating behavior,[1]which often appears after a brief period of calm state.[2] Several studies have demonstrated that the occurrence of paradoxical reactions following midazolam was associated with injection rate,[3] dose, age,[4] personality and mental factor,[5] genetic background[6] and alcoholism.[7] Therefore, various drugs have been showed effective for paradoxical reaction, such as physostigmine,[8] haloperidol,[9] flumazenil[10–14] and ketamine.[2] But the potential adverse effects limit the application and those agents are only recommended to rescue the most serious side effects of midazolam in children. [14] The mechanism of PR is still unclear. Several hypotheses have been proposed. It includes cortical de-suppression, diversity of GABA receptor, central cholinergic effect.[15, 16] Interestingly, recently studies observed excitatory effect of sevoflurane, which are epileptic spikes on the electroencephalographic (EEG) during anesthesia induction.[17] The possible mechanism is that overloaded GABAergic activity inhibits neuronal chloride channels and eventually leads to inhibition potentials being converted to excitatory potentials.[18] Furtherly, McCarthy et.al indicated interneuron anti-synchrony might provide an explanation for paradoxical reactions generated by propofol.[19]

With experience, changing administration order during anesthesia induction seemed to be effective for preventing paradoxical reaction. Therefore, the present study was designed to investigate whether the dosing sequence could affect the incidence of PR.

2 Methods

2.1 Study population

We undertook a double-blind, parallel-group, randomised controlled trial of single center. We included patients aged 6 months to 12 years who were scheduled general anesthesia, but we excluded individuals who had a history of psychological disorders, mental retardation, hypoxia and hypotension before surgery, or gave consent for another interventional study or declined to participate. Written informed consent was obtained from a parent or guardian for participants under 16 years old.

The study was approved by the research ethics boards of Shanghai Children's Hospital, Shanghai, China the protocol number that was attributed by this ethics committee was 2018R012-F01 on 15 March 2018 and the name of the Chairperson of the ethics committee was Guangjun Wu.

2.2 Randomisation and masking

Randomization was done by using computer generated random numbers. Patients were randomly assigned in a 1:1:1 ratio to one of three parallel arms to receive different administration order during induction of anesthesia. Patients were blinded to group assignment.

A research nurse placed the random numbers in sealed envelopes and one anesthetist who did not follow the patient, opened the closed envelop to know the random allocation scheme, prepared the drugs, and performed intravenous drug administration.

Judgment of paradoxical reaction was performed by two anesthesiologists, who were engaged in pediatric anesthesia for more than 10 years. Additionally, they remained unaware of the random scheme. The random allocation was also concealed from patients, research staff, and the independent statistician.

2.3 Outcomes

The primary outcome was the incidence of the paradoxical reactions. Secondary endpoints included bispectral index values, extubation duration, recovery duration and safety endpoint, which included hemodynamics, fentanyl-induced cough and respiratory depression during the recovery period.

2.4 Procedures

All the patients were placed an intravenous line before they were brought into the operation room. electrocardiogram (ECG), noninvasive blood pressure, heart rate, temperature, oxygen saturation, exhaled

CO^2 (end tidal CO^2) and BIS were monitored. Two investigators performed intravenous induction according the random allocation. The administration order for the three study groups were as following:

The fentanyl group: fentanyl 2μg.kg−1, midazolam 0.1mg.kg−1, atropine 0.01 mg.kg−1, propofol 3 mg.kg−1.

The midazolam group: Midazolam 0.1mg.kg−1, fentanyl 2μg.kg−1, atropine 0.01 mg.kg−1, propofol 3mg.kg−1.

The blank group: 0.9% saline 0.1ml.kg−1, fentanyl 2μg.kg−1, atropine 0.01 mg.kg−1 propofol 3 mg.kg−1.

Two anesthesiologists, who were engaged in pediatric anesthesia for more than 10 years judged the presence of a paradoxical reaction. Additionally, they remained unaware of the random scheme and did not participant in other parts of the study. Sudden burst of abnormal symptoms were defined as paradoxical reactions, which include extremely panic, rage, violent and self-mutilating behavior. These symptoms are different from separation anxiety and the frightened reaction caused by encountering unfamiliar situation[1]. Additionally, patients showed temporary calmness before paradoxical reactions burst[1].

Paradoxical reaction occurred at about 3 minutes after administration of midazolam,[2, 3] so investigators observed the patients for 5 min after administration of midazolam and then given other drug according to the plan. Additionally, the injection rate significantly influences the incidence of paradoxical reactions, so we dosed midazolam at a constant rate of 0. 1mg.s−1 by an intravenous pump.[3] Furthermore, it takes 15 second for plasma concentration of fentanyl reaching the threshold inducing cough[20], so the duration of administrating fentanyl was more than 30 seconds[21]. Finally, propofol is pumped at a rate of 20 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$. When paradoxical reaction happened, an anesthesia nurse dosed flumazenil 0.01 mg.kg−1 intravenously.

2.5 Statistical analysis

The incidence in the midazolam group was reported ranged from 1.4% to 11.1% and it was estimated as 5.4% in our pre-test and 1.5% in the fentanyl group.[1, 2, 22–27] The sample size was adequate (302 patients for each group) with a = 0.05 and a power of 0.8. Assuming the drop rate was 10%, 1200 patients were enough. Continuous data were expressed as mean, and frequencies and percentages (%) for categorical data. ANOVA test was used for continuous data (including age, weight, extubation and recovery period,BIS value) and fisher's exact test was used for categorical data (including incidence of PR, sex, patients with Chest wall rigidity, cough and SpO_2 < 95%). All comparisons were two-tailed. A *P* value < 0.05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS) Windows version 25.0 (IBM Corp., Armonk, New York, USA) was used in the statistical analysis.

3 Results

The study was reported in accordance with CONSORT statement. From March, 2018, to January, 2019, 1320 patients were randomly assigned, received intended treatment, and fourteen patients were excluded due to missing data.

So 1306 were analysed for the primary outcome including 436 individuals in the fentanyl group, 432 participants in the midazolam group and 438 patients in the saline group.

3.1 Comparison of the incidence of PR in the three groups

There were no detectable differences between the three groups in terms of demographic data, table1. Paradoxical reactions were recorded in 5 (1.15%) of 436 patients in the fentanyl group versus 26 (5.98%) of 432 individuals in the midazolam group (odds ratio (OR) 0.18; 95% confidence interval (CI): 0.015–0.22); p < 0.00001, table 2). Once the paradoxical reaction happened, it could not be eliminated by fentanyl but responded rapidly to flumazenil.

3.2 *Paradoxical reaction and age*

A total of 31 individuals experienced paradoxical reactions, among them, 26 patients were aged 8 months to 2 years old (83.9%), two were younger than 8 months (6.5%) and three were older than two years old (9.7%). So, children with paradoxical reactions were most aged 8 months to 2 years old; p< 0.05.

3.3 Changes in BIS values

BIS electrodes could not be placed before induction owing to agitation in 106 children in the midazolam group, 114 in the fentanyl group and 157 in the blank group. There was no difference in BIS before and after saline injection (92.1±4.9 vs.91.4±5.7; p = 0.24). However, BIS increased significantly when paradoxical responses burst out in the fentanyl group (90.6±1.9 vs. 79.4±1.5; p < 0.00001; median difference (MD) 11.2; 95% CI: 9.08–13.32).) and in the midazolam group (90.9±2.5 vs. 83.2±2.7; p < 0.00001; MD 7.7; 95%CI: 6.29–9.11).) (Fig.2). Even more interesting is the fact that paradoxical reactions occurred after an initial sedative period following midazolam administration.

3.4 Safety and side-effects

Hemodynamics was stable and there were no fentanyl induced cough and respiratory depression seen in each of the groups. Additionally, there was no significant difference in terms of time to extubation, recovery duration in the three groups (Table 2).

4 Discussion

In this randomized blind controlled study, we found decreased incidence of PR by changing the order of midazolam and fentanyl administration. However, administration of fentanyl seems invalid to relieve when these reactions have already burst out. Additionally, we found that BIS was significantly higher when children displayed PR.

Paradoxical reactions following midazolam were reported as an incidence varies from 1.4% to 11.1% in different studies.[1, 2, 22–27] This may be related to heterogeneity in terms of study design, dose and route of administration, purpose of medication, judgment criteria for PR, age, and selectivity bias.[2, 14, 28] In our study, 5.98% patients occurred PR in the midazolam group and the incidence was significant reduced by preferentially and slowly injecting fentanyl. The mean time of onset of the reaction occurred at 1.8 minutes (standard deviation ±1.4 minutes) after administration of midazolam in our study. The mechanism of paradoxical reactions has not yet been elucidated. Various mechanisms proposed to explain paradoxical reactions. Our study found that BIS was significantly higher when children developed PR and it is in fact with that paradoxical

reactions occurred after an initial sedative period of following midazolam administration. As a GABA receptor agonist, midazolam has sedative and anti-epileptic effects.[29] Activation of the GABAA receptor induces inward chloride currents, hyperpolarizing post-synaptic neurons, ultimately leading to pyramidal neuronal suppression and GABAA receptor-mediated inhibition is essential for inhibition of brain excitability.[30] However, the midazolam-induced excitatory response seems to contradict the GABAA receptor-mediated inhibition of midazolam. Interestingly, sevoflurane and propofol can also induce excitatory response, which are epileptic spikes on the electroencephalogram during anesthesia induction.[17] Similarly, excitability in the cerebral cortex appears to be conflict with the strong GABAergic effect of sevoflurane and propofol. Recently studies showed that all anesthetics that enhance GABAergic neurotransmission have both inhibitory and convulsive effects because overloaded GABAergic activity inhibits neuronal chloride channels and eventually leads to inhibition potentials being converted to excitatory potentials, which we named the double-sided effect of GABAergic neurotransmission.[18] This double-sided effect may explain why midazolam causes contradictory reactions. Even more interesting is that epileptiform discharges during anesthesia induction are similarly to the PR of midazolam. On one hand, we found that PR usually occurs after a period of sedation in our study. BIS usually drops first and then rises sharply when PR occurs. This is very similar to the appearance of suppression with spike in EEG, which is outbreak of brain waves after a period of brain wave suppression.[19] On the other hand, suppression with spikes is only seen during anesthesia induction, which varies from other types of epileptic discharges, such as interictal spike events, also seen in other functional brain disorder. (E.g. ADHD, migraine, Epilepsy).[27, 31, 32] Finally, PR and epileptiform discharges both belong to hyperexcitability.[28] Hence the mechanism of PR might be further clarified by EEG.

Our study has several limitations. First, the judgment of PR is objective and might lead to measurement bias. Fortunately, judgment of paradoxical reaction was performed by two anesthesiologists, who were engaged in pediatric anesthesia for more than 10 years. Secondly, most anesthesiologists do not induce with midazolam, however, many sites still premedication midazolam, which might also cause paradoxical reactions. In the present study, preferentially and slowly administrated fentanyl was helpful to prevent occurrence of PR, which was beneficial to patients with malignant hyperthermia or susceptibility, patients allergic to fluoride, and hospitals in developing countries.

Conclusion

In summary, we observed that preferentially and slowly injecting fentanyl during anesthesia induction resulted in lower incidence of paradoxical reactions following midazolam. BIS was significantly higher when children displayed PR. There were no significant differences in terms of extubation duration, recovery duration and safety endpoint between fentanyl group and midazolam group.

Declarations

PR: paradoxical reactions

EEG: electroencephalographic

CI: confidence interval

ECG: electrocardiogram

SPSS: Statistical Package for Social Sciences

MD: median difference

Acknowledgements

The study was carried out at Department of Anesthesiology, Shanghai Children's Hospital (Shanghai, China). The authors acknowledge the support of Shanghai Children's Hospital for providing infrastructure and funding to ensure that all patients at this center are treated free of costs with no commercial or financial gains to any member of the team.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This trial was approved by IRB (2018R012-F01) from Shanghai Children's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, and registered at http://www.chictr.org.cn (ChiCTR1800018912). Written informed consent was obtained from a parent or guardian for participants under 16 years old. Detailed registration information is provided on http://www.chictr.org.cn/showproj.aspx?proj = 31862

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Mancuso CE, Tanzi MG, Gabay M. Paradoxical reactions to benzodiazepines: literature review and treatment options. Pharmacotherapy 2004; 24: 1177-85. 2. Golparvar M, Saghaei M, Sajedi P, Razavi SS. Paradoxical reaction following intravenous midazolam premedication in pediatric patients - a randomized placebo controlled trial of ketamine for rapid tranquilization. Paediatric Anesthesia 2004; 14: 924-30. 3. Moallemy A, Teshnizi SH, Mohseni M. The injection rate of intravenous midazolam significantly influences the occurrence of paradoxical reaction in pediatric patients. Journal of Research in Medical Sciences 2014; 19: 965-9. 4. Shin YH, Kim MH, Lee JJ, et al. The effect of midazolam dose and age on the paradoxical midazolam reaction in Korean pediatric patients. Korean Journal of Anesthesiology 2013; 65: 9-13. 5. Weinbroum AA, Szold O, Ogorek D, Flaishon R. The midazolam-induced paradox phenomenon is reversible by flumazenil. Epidemiology, patient characteristics and review of the literature. European Journal of Anaesthesiology 2001; 18: 789-97. 6. Heller M, Hayes CM, Krejci NC. Paradoxical reaction to midazolam reversed with flumazenil in a patient undergoing tumescent liposuction. Dermatologic Surgery 2009; 35: 1144-6. 7. Tae CH, Kang KJ, Min BH, et al. Paradoxical reaction to midazolam in patients undergoing endoscopy under sedation: Incidence, risk factors and the effect of flumazenil. Digestive and Liver Disease 2014; 46: 710-5. 8. Knaack-Steinegger R, Schou J. Therapy of paradoxical reactions to midazolam in regional anesthesia. Anaesthesist 1987; 36: 143-6. 9. Khan LC, Lustik SJ. Treatment of a paradoxical reaction to midazolam with haloperidol. Anesthesia and Analgesia 1997; 85: 213-5. 10. Jackson BF, Beck LA, Losek JD. Successful flumazenil reversal of paradoxical reaction to midazolam in a child. The Journal of Emergency Medicine 2015; 48:e67-72. 11. Sanders JC. Paradoxical reaction to midazolam reversed with flumazenil. Paediatric Anaesth 2003; 13: 369-70. 12. Thurston TA, Williams CG, Foshee SL. Reversal of a paradoxical reaction to midazolam with flumazenil. Anesthesia and Analgesia 1996; 83: 192. 13. Kamijo Y, Masuda T, Nishikawa T, Tsuruta H, Ohwada T. Cardiovascular response and stress reaction to flumazenil injection in patients under infusion with midazolam. Critical Care Medcine 2000; 28: 318-23. 14. Saltik IN, Ozen H. Role of flumazenil for paradoxical reaction to midazolam during endoscopic procedures in children. American Journal of Gastroenterology 2000; 95: 3011-2. 15. Short TG, Forrest P, Galletly DC. Paradoxical reactions to benzodiazepines–a genetically determined phenomenon? Anesthesia Intensive Care 1987; 15: 330-1. 16. McKenzie WS, Rosenberg M. Paradoxical reaction following administration of a benzodiazepine. Journal of Maxillofacial and Oral Surgery 2010; 68: 3034-6. 17. Koch S, Rupp L, Prager C, et al. Incidence of epileptiform discharges in children during induction of Anesthesia using Propofol versus Sevoflurane. Clinical Neurophysiology 2018; 129: 1642-8. 18. Farrant M, Kaila K. The cellular, molecular and ionic

basis of GABA(A) receptor signalling. Progress in brain research 2007; 160: 59-87. 19. McCarthy MM, Brown EN, Kopell N. Potential network mechanisms mediating electroencephalographic beta rhythm changes during propofol-induced paradoxical excitation. Journal of Neuroscience 2008; 28: 13488-504. 20. Yeh CC, Wu CT, Huh BK, et al. Premedication with intravenous low-dose ketamine suppresses fentanyl-induced cough. J Clin Anesth,2007,19:53-56. 21. Kim JE, Min SK, Chae YJ, et al. Pharmacological and nonpharmacological prevention of fentanyl-induced cough: a meta-analysis. J Anesth, 2014, 28:257-266. 22 Massanari M, Novitsky J, Reinstein LJ. Paradoxical reactions in children associated with midazolam use during endoscopy. Clinical pediatrics 1997, 36:681-684. 23. Litchfield NB. Complications of Intravenous Diazepam - Adverse Psychological Reactions. (An assessment of 16,000 cases). Anesthesia Progress 1980, 27: 175-183. 24. Roelofse JA, Stegmann DH, Hartshorne J, et al. Paradoxical reactions to rectal midazolam as premedication in children. International journal of oral and maxillofacial surgery 1990, 19: 2-6. 25. Bahal-O'Mara N, Nahata MC, Murray RD, et al. Sedation with meperidine and midazolam in pediatric patients undergoing endoscopy. European Journal of Pharmacology 1994, 47: 319-323. 26. Elder JS, Longenecker R. Premedication with oral midazolam for voiding cystourethrography in children: safety and efficacy. American Journal of Roentgenology 1995, 164: 1229-1232. 27. Honan VJ. Paradoxical reaction to midazolam and control with flumazenil. Gastrointestinal Endoscopy 1994, 40: 86-88. 28. Papetti L, Nicita F, Parisi P, Spalice A, Villa MP, Kasteleijn-Nolst Trenite DG. "Headache and epilepsy"--how are they connected? Epilepsy Behavior 2013; 26: 386-93. 29. Feng HJ, Forman SA. Comparison of alphabetadelta and alphabetagamma GABAA receptors: Allosteric modulation and identification of subunit arrangement by site-selective general anesthetics. Pharmacological Research 2018; 133: 289-300. 30. Pieri L. Preclinical pharmacology of midazolam. British Journal of Clinical Pharmacology 1983; 16 Suppl 1: 17S-27S. 31. Hesdorffer DC, Ludvigsson P, Olafsson E, Gudmundsson G, Kjartansson O, Hauser WA. ADHD as a risk factor for incident unprovoked seizures and epilepsy in children. Archives of General Psychiatry 2004; 61: 731-6. 32. Chez MG, Chang M, Krasne V, Coughlan C, Kominsky M, Schwartz A. Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. Epilepsy Behavior 2006; 8: 267-71.

Tables

Table 1 Baseline characteristics of patients received different anesthesia induction order.

Group	Fentanyl group (N=436)	Midazolam group (N=432)	Blank group (N=438)
Age	72.85±46.75	71.10±40.85	71.74±38.18
Gender (Male/Female)	227/208	219/216	225/210
Rate of midazolam administration	0.1mg.s-1	0.1 mg.s-1	Saline 0.1 ml.s-1
Rate of fentanyl administration	more than 30s	more than 30s	Saline more than 30s

Age data is expressed as means ± SD. There were no statistically significant differences in the demographic data between the three groups. Fentanyl group received fentanyl followed by midazolam; Midazolam group received midazolam followed by fentanyl; Blank group received saline followed by fentanyl.

Table 2 Incidence of paradoxical reactions and side-effects.

Group	Fentanyl group (N=436)	Midazolam group (N=432)	Blank group (N=438)
Incidence (no. /%)	5/1.15	26/5.98	0/0
Respiratory depression	0	0	0
Cough	0	0	0
Time to extubation (min)	15.56±6.3	14.94±5.1	14.54±5.3
Recovery period (min)	47.0±8.8	46.83±8.1	46.39±7.4

min = minute Time to extubating: duration from the end of the sugery to tracheal extubation Values are expressed as means ± SD including time to extubation and recovery period. Fentanyl group received fentanyl followed by midazolam; Midazolam group received midazolam followed by fentanyl; Blank group received saline followed by fentanyl.

Figures

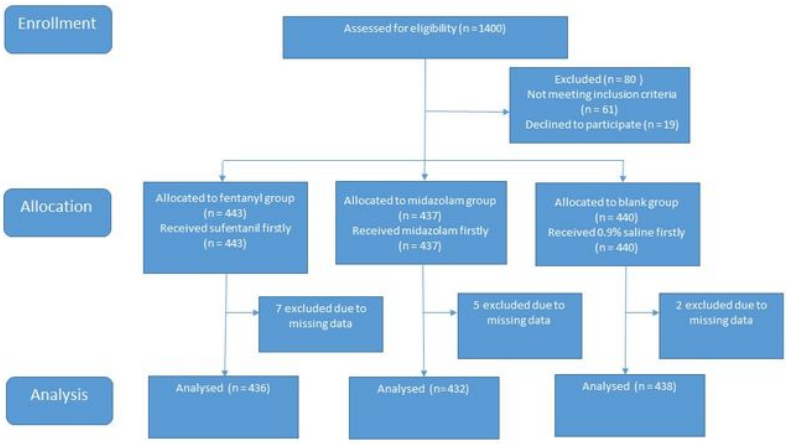

Figure 1

CONSORT flow diagram for patients included in the study

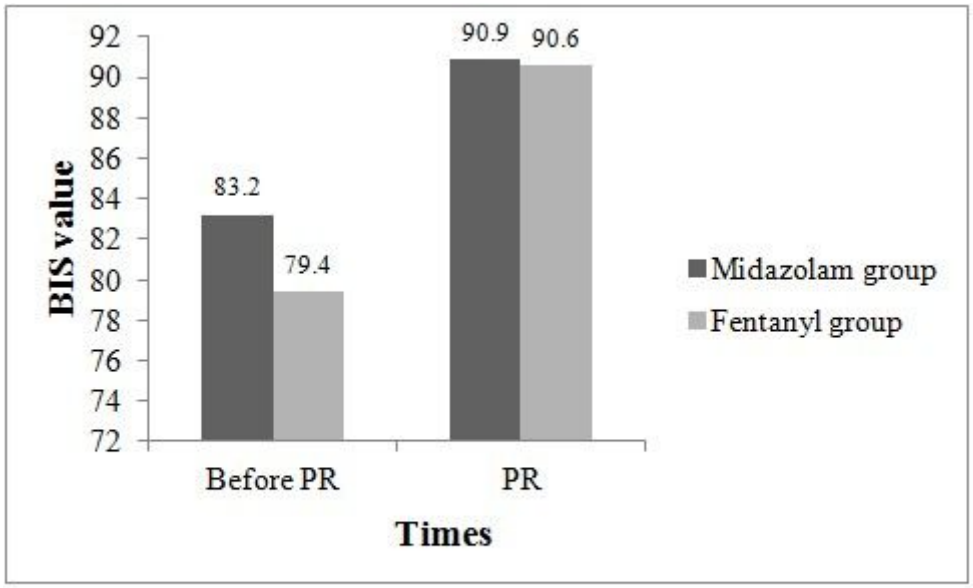

Figure 2

Changes in BIS values before and after the occurrence of PR in the midazolam group and fentanyl group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- consort2010checklist.doc