Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Evaluating different sedative drugs applied in procedural sedation

Azadeh Tafakori (MD)[1*], Mohammad Gharavifard (MD)[2], Hamid Zamani (MD)[1]

[1] *Department of Emergency Medicine, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[2] *Department of Anesthesia, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

ARTICLE INFO

Article type
Review article

Article history
Received: 1 Apr 2014
Revised: 20 Apr 2014
Accepted: 24 Apr 2014

Keywords
Analgesia
Emergency
Etomidate
Ketamine
Procedural Sedation
Propofol

ABSTRACT

There are various criteria that affect the efficacy of the procedural sedation strategies required for performing different processes in emergency departments. Selecting the most effective and the safest sedative with or without analgesic effect for every individual patients and intervention is one of the main parts of the each emergency department practices. Based on previous studies, various sedative agents have been proposed, which have different benefits and adverse effects including propofol, ketamine, etomidate etc. Different side effects of administrating each drug, alone or in combination with each other, have been proposed such as vomiting, respiratory depression, hypoxia, hypotension and cardiac arrest. In this study we aimed to briefly review the properties of applied sedatives in different studies and also mention few related clinical trials with proper blinding, which were conducted to evaluate the efficacy of the sedative in procedural sedation.

Please cite this paper as:

Tafakori A, Gharavifard M, Zamani H. Evaluating different sedative drugs applied in procedural sedation. Rev Clin Med. 2015;2 (1):28-31.

Introduction

Due to perfectly performing various medical procedures in emergency department, the presence of expert physicians with different skills including successful airway management, cardiovascular and ventilator revival methods, procedural sedation and analgesia and etc is necessary. Procedural sedation and analgesia refers to the strategies of applying sedatives, which is commonly used in emergency departments for alleviating the patients' pain and consciousness and elevating the patients' tolerance while performing medical interventions (1). Continued application of the procedural sedative techniques, selecting the most effective sedative medications with or without analgesia effect and evaluating the most optimum dosage for every intervention, have become controversial issues in emergency medicine.

According to the literature, different levels of sedation including mild, moderate and deep had been used for patients. In minimal depth of the sedation, which is used during minor medical interventions, a near-baseline change in cognitive function has been induced pharmacologically in which the patient could respond to the verbal stimulates. Properties of the moderate level of sedation are reported as spontaneous ventilation, response to the verbal commands with tactile stimulation or purposefully, amnesia and etc. Benzodiazepine and fentanyl are among medications that have been applied for obtaining moderate sedation. During the deep level of the sedation, ventilation function is needed to be assisted and

***Corresponding author:** Azadeh Tafakori .*
Department of Emergency Medicine, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
***E-mail:** dr.azadeh.tafakori@hotmail.com*
***Tel:** 09173147528*

the verbal responses would be obtained by intensive stimulations. Controlling the heart rate, pulse rhythm and blood pressure should be considered in this level of the sedation, which is used mostly while performing painful processes. Propofol, etomidate, benzodiazepine, fentanyl or morphine sulfate are such medications, which can be used for decreasing the pain and achieving to the deep level of the sedation (2,3). Due to the different effects of the drugs used in procedural sedation, the exact awareness of the physicians about the administrated drugs and controlling the patients' responses to these medications are needed for reducing the possible cardiovascular and ventilator complications such as airway obstruction, apnea, hypotension, hypoventilation, hypoxia and dysrhythmias (4,5).

Based on literature, due to the appearance of the complications during the sedation procedure, performing various interventions might be necessary including severe tactile stimulation, airway management and patient repositioning, suctioning, supplemental or increased oxygen delivery, insertion of the oropharyngeal or a nasopharyngeal airway, chest compressions, providing positive-pressure ventilation using face masks, intubation, using reversal agents and antidysrhythmic medications and etc (6).

According to the literature, variety of sedative medications can be administrated for obtaining different levels of the sedation, which facilitate performing several painful emergency procedures. In this study, we aimed to briefly review the different articles regarding the efficacy of the sedative drugs in providing safe sedation in patients.

Agents used in procedural sedation

Different kind of sedative agents have been proposed in literature, which can be applied while performing the emergency processes. Different properties of each medication have been studied including dose-dependent effects, contraindications, individual patients' response, the onset and duration of the sedation, the recovery time and etc. Administrating short acting sedative drugs (etomidate and propofol) were considered in various studies. Based on these studies, applying this group of drugs lead to lower duration of consciousness dysfunction, patients monitoring time and decreasing the possibility of the side effects occurrence such as respiratory impairments (7).

Etomidate is a kind of imidazole, nonbarbiturate hypnotic agent, which is used as a sedative agent since 1983 (8). No analgesic effect has been reported for this drug. Recent articles have shown its safety and efficacy as an excellent medication to be used in adults. Its effect starts after one minute and with short-duration effect (10-15 min). Oxygen desaturation, vomiting, myoclonus, pain and adrenocortical impairment are known as some of the reported side effects of the etomidate (9).

Propofol, (2,6-diisopropylphenol) is a nonopiod, nonbarbiturate sedative hypnotic medication, which is recently used for the procedural sedation techniques in emergency departments. The sedative function of the propofol was firstly proposed in 1996 by Swanson et al. (10). Propofol has dose depending effect on patient consciousness, which can be used for emergency processes required deep level of sedation such as fracture and dislocation reduction, incision and drainage of abscesses and cardioversion (11). For reducing the risk of adverse effects, administrating propofol should be done with cautious in some conditions including patient allergy to the eggs or soy product, aged patients, cases with dehydration or blood loss and fasting. Some potential side effects have been observed by using propofol within appropriate dosage such as insufficient or oversedation, hypoxemia, respiratory event of airway obstruction, hypotention, apnea and emesis, which have resulted in conducting various clinical trials regarding the efficacy of propofol in procedural sedation (7,12,13). Due to propofol rapid onset, short half life, metabolic clearance and distribution, it is an attractive anesthetic drug for the procedural sedation.

Ketamine is among the short-half life and rapid acting medications with sedative and analgesic effects in procedural sedation (14). The safety (beneficial effects on the cardiovascular and respiratory functions), efficacy and low cost of the ketamine have increased the prevalence of the ketamine application as anesthetic agent especially for pediatrics and in emergency strategies (15).

Midazolam is one of the benzodiazepines, mostly applied for the procedural sedation due to its anxiolysis, sedation and amnesia properties. It is mostly suggested to be administrated in a lower doses and in combination with other drugs especially opioids (16).

Alfentanil is another medication with sedative effect, which can be used for procedural sedation. It is proposed as an ultrashort-acting analogue of the fentanil (17).

Remifentanil is a kind of short-acting opioid analgesic medication, which is usually administrated intravenously in different doses based on the patient age, severity of the disease and the emergency procedure (0.1 to 0.5 mg/kg) (18).

Dexmedetomidine is a α2-adrenergic agonist agent. Its efficacy in the procedural sedation is under consideration. Various adverse effects including hypotension, hypertension and bradycardia complications might be associated with dexmedetomidine. It represents its effects (sedative, analgesic and anxiolysis) through activating the α2-adrenergic recep-

tors of the central nervous system (19).

Literature review

Among the articles studied in this review, some trials were performed to evaluate the safety and efficacy of propofol alone or in combination with other drugs to be administrated in the procedural sedation with analgesia in the emergency departments. According to the literature, end-tidal CO2 (ETCO2)>5 mm Hg, respiratory rate<8 breaths/min, O2 saturation<90%, apnea (15 seconds) and airway manipulation rate are considered as the respiratory depression parameters. Based on one double blind control trial in 2011, administrating the combination of propofol/ketamine (ketofol) has led to the lesser propofol requirement dose for maintaining the sedation process. Decreased risk of the patient respiratory depression and hypotension as the main results observed in the mentioned study, were not statistically significant. It is also concluded that more consistent sedation would be obtained by administrating propofol/ketamine instead of propofol alone (20).

In another blinded randomized control trial on pediatric procedural sedation, the combination of the ketamine/propofol was proposed as the favorable sedative agent compared with ketamine alone. In his study, although the sedation and recovery time appeared to be statistically significant in the combination group compared with the placebo group, the clinical significance of this difference (almost 3 minutes) was still under debate. The occurrence rate of the adverse effects was similar in the combination group compared with ketamine alone. Only the rate of vomiting decreased statistically in the combination group (21).

The effect of the ketamine in increment of the circulatory norepinephrine was proposed to result in decreasing the risk factors associated with using propofol alone. It was also proposed that the decreased rate of nausea by administrating the combined drug might be due to the antiemetic and anxiolytic characteristics of the propofol. The efficacy of the strategy of applying this combined medications (ketofol) in reducing the side effects, which have been identified while using ketamine or propofol alone, was confirmed in other articles (2,22-24).

Other studies, which applied other medications as adjuvant for the ketamine including ondansetron and atropine, concluded a significant lower rate of postoperation vomiting and hypersalivation (25,26).

The majority of the articles about the midazolam have investigated its efficacy in combination with other drugs such as ketamine or fentanyl. In the study of Cevik E. et al. administrating the combination of ketamine and low dose midazolam resulted in slightly higher effectiveness in procedural sedation and analgesia compared with the combination of the midazolam and fentanyl. According to the study, both of the combinations of the drugs could be used for the procedural sedation and analgesia (27). Based on other studies, the administration of adjunctive midazolam with ketamine might result in increased recovery time and the respiratory side effects. The decreased emesis rate is also proposed as the effect of the adjuvant midazolam with the ketamine. In one study, the effectiveness of the midazolam was compared with etomidate in children and resulted in longer recovery time for the midazolam and greater efficacy of the etomidate in procedural sedation (28). Detailed data of these trials are summarized in Table 1.

Based on our search strategy, there was no randomized clinical trial with proper blinding on the efficacy of alfentanil with or without other drugs for procedural sedation in the emergency departments. The only trials, which studied the efficacy, presence of side effects and recovery time of the propofol alone or in combination with alfentanil, concluded no beneficial changes in the occurrence of postprocedural pain and an increased rate of cases needed stimulation to induce the respiration. In this regard, the addition of alfentanil to the propofol for procedural sedation is not recommended (17).

Conclusion

Despite wide variety of the drugs used for procedural sedation, there are still controversies about their adverse effects in each patient. Selecting the most appropriate and the safest sedative with the optimum dosage for every individual and for every emergency procedure is a core part of the emergency medicine. There are no specific sedative or a combination of drugs, which can be recommended for all patients or all emergency procedures. The awareness of the emergency department physicians and nurses about adverse effects or benefits associated with each sedative medication for the sedation and analgesia and the exact diagnosis of the cases injury are the most important factors, which increase the chance of successful performance. Further studies are recommended to investigate the efficacy of the newly discovered sedatives according to their classification.

Acknowledgement

We would like to thank Clinical Research Development Center of Ghaem Hospital for their assistant in this manuscript. This study was supported by a grant from the Vice Chancellor for Research of the Mashhad University of Medical Sciences for the research project as a medical student thesis with approval number of 910361.

Table 1. Randomized control trials blinded properly about the different sedative agents alone or in combination

Author Year Reference	Intervention	Outcome measure	Results
David 2011 (20)	Adults+children Placebo: N: 96, propofol(1+0.5 mg/kg) Treatment: N:97, propofol (1+0.5 mg/kg)+ketamine(0.5 mg/kg)	Rate of respiratory depression markers, Dose of propofol, Sedation quality	- Respiratory depression groups differences: 6%, (95% confidence interval: -6% to 18%) - Lower dose of propofol was applied for the treatment group - The sedation quality increased in treatment group
Shah 2011 (21)	Children Placebo: N:69, ketamine (1+0.25 mg/kg) Treatment:N:67, propofol (0.5mg/kg)+ketamine(0.5+0.25mg/kg)	Total sedation and recover time, sedation quality	- Total shorter sedation and recovery time in treatment group - Group adverse events difference:- 24% , (95% confidence interval:-39% to-8%) - The sedation quality increased in treatment group
Cervik 2013 (27)	Children and adults Goup1:Midazolam+fentany (MF), N:30 Group2: ketamine + low dose Midazolam (KM), N:31	Hypoxia, duration of hypoxia, sedation time, recovery time, sedation depth, quality of the sedation	- KM group: significantly lower hypoxia, duration of hypoxia. Slightly quicker onset of the sedation - Similar sedation depth and recovery time
Di Liddo 2006 (28)	Children Group1: Etomidate (0.2 mg/kg) Group2:Midazolam (0.1 mg/kg)	Recovery time, adverse events rate, quality of the sedation	- Lower recovery time for etomidate group - Similar adverse effects rate - The presence of myoclonus was higher in etomidate group

Conflict of Interest

The authors declare no conflict of interest.

References

1. Perina DG, Beeson MS, Char DM, et al. The 2007 Model of the Clinical Practice of Emergency Medicine: the 2009 update 2009 EM Model Review Task Force. Ann Emerg Med. 2011;57:e1-15.
2. Andolfatto G, Willman E. A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (ketofol). Acad Emerg Med. 2010;17:194-201.
3. Sacchetti A, Senula G, Strickland J, Dubin R. Procedural sedation in the community emergency department: initial results of the ProSCED registry. Acad Emerg Med. 2007;14:41-46.
4. Terndrup TE, Cantor RM, Madden CM. Intramuscular meperidine, promethazine, and chlorpromazine: analysis of use and complications in 487 pediatric emergency department patients. Ann Emerg Med. 1989;18:528-533.
5. Hogan K, Sacchetti A, Aman L, Opiela D. The safety of single-physician procedural sedation in the emergency department. Emerg Med J. 2006;23:922-923.
6. Campbell SG, Froese PC. Sedation-assisted Orthopedic Reduction in Emergency Medicine: The Safety and Success of a One Physician/One Nurse Model. West J Emerg Med. 2013;14:204.
7. Bassett KE, Anderson JL, Pribble CG, Guenther E. Propofol for procedural sedation in children in the emergency department. Ann Emerg Med. 2003;42:773-82.
8. Giese JL, Stanley TH. Etomidate: a new intravenous anesthetic induction agent. Pharmacotherapy. 1983;3:251-258.
9. Rothermel LK. Newer pharmacologic agents for procedural sedation of children in the emergency department-etomidate and propofol. Curr Opin Pediatr. 2003;15:200-203.
10. Lazar RH, Younis RT, Long TE. Functional endonasal sinus surgery in adults and children. Laryngoscope. 1993;103:1-5.
11. Taylor DM, O'Brien D, Ritchie P, et al. Propofol versus midazolam/fentanyl for reduction of anterior shoulder dislocation. Acad Emerg Med. 2005;12:13-19.
12. Burton JH, Miner JR, Shipley ER, et al. Propofol for emergency department procedural sedation and analgesia: a tale of three centers. Acad Emerg Med. 2006;13:24-30.
13. Coll-Vinent B, Sala X, Fernandez C, et al. Sedation for cardioversion in the emergency department: analysis of effectiveness in four protocols. Ann Emerg Med. 2003;42:767-772.
14. Albanese J, Arnaud S, Rey M, et al. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. Anesthesiology. 1997;87:1328-1334.
15. Miller AC, Jamin CT, Elamin EM. Continuous intravenous infusion of ketamine for maintenance sedation. Minerva Anestesiol. 2011;77:812-820.
16. Litman RS. Conscious sedation with remifentanil and midazolam during brief painful procedures in children. Arch Pediatr Adolesc Med. 1999;153:1085-1088.
17. Miner JR, Gray RO, Stephens D, et al. Randomized Clinical Trial of Propofol With and Without Alfentanil for Deep Procedural Sedation in the Emergency Department. Acad Emerg Med. 2009;16:825-834.
18. Sacchetti A, Jachowski J, Heisler J, et al. Remifentanil use in emergency department patients: initial experience. Emerg Med J. 2012;29:928-929.
19. Berkenbosch JW, Tobias JD. Development of bradycardia during sedation with dexmedetomidine in an infant concurrently receiving digoxin. Pediatr Crit Care Med. 2003;4:203-205.
20. David H, Shipp J. A randomized controlled trial of ketamine/propofol versus propofol alone for emergency department procedural sedation. Ann Emerg Med. 2011;57:435-441.
21. Shah A, Mosdossy G, McLeod S, et al. A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. Ann Emerg Med. 2011;57:425-433.
22. Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. Ann Emerg Med. 2007;49:23-30.
23. Erden IA, Pamuk AG, Akinci SB, et al. Comparison of propofol-fentanyl with propofol-fentanyl-ketamine combination in pediatric patients undergoing interventional radiology procedures. Paediatr Anaesth. 2009;19:500-506.
24. Messenger DW, Murray HE, Dungey PE, et al. Subdissociative-dose ketamine versus fentanyl for analgesia during propofol procedural sedation: a randomized clinical trial. Acad Emerg Med. 2008;15:877-886.
25. Langston WT, Wathen JE, Roback MG, et al. Effect of ondansetron on the incidence of vomiting associated with ketamine sedation in children: a double-blind, randomized, placebo-controlled trial. Ann Emerg Med. 2008;52:30-34.
26. Heinz P, Geelhoed G, Wee C, Pascoe E. Is atropine needed with ketamine sedation? A prospective, randomised, double blind study. Emerg Med J. 2006;23:206-209.
27. Cevik E, Bilgic S, Kilic E, et al. Comparison of ketamine-low-dose midozolam with midazolam-fentanyl for orthopedic emergencies: a double-blind randomized trial. Am J Emerg Med. 2013;31:108-113.
28. Di Liddo L, D'Angelo A, Nguyen B, et al. Etomidate versus midazolam for procedural sedation in pediatric outpatients: a randomized controlled trial. Ann Emerg Med. 2006;48:433-40.