JOURNAL of ANESTHESIA and PERIOPERATIVE MEDICINE

Review Article

Perioperative Use of Benzodiazepines: A Reconsideration of Risks and Benefits

Yanzi Zhang[1], Yidan Tang[1], Jing Yang[1], Chunyu Gong[2], and Zhuo Li[3]

From the [1]Department of Anesthesiology and Translational Neuroscience Center, West China Hospital, [2]Department of Surgery, NO. 4 West China Teaching Hospital, Sichuan University, Chengdu, China; [3]Department of Pharmacy, Shaanxi Provincial People's Hospital, Xi'an, China.

Correspondence to Dr. Jing Yang at hxyangjing@qq.com.

Citation: Yanzi Zhang, Yidan Tang, Jing Yang, Chunyu Gong, Zhuo Li. Perioperative Use of Benzodiazepines: A Reconsideration of Risks and Benefits. *J Anesth Perioper Med* 2018;5:34-40.

doi: 10.24015/JAPM.2018.0010

ABSTRACT

Aim of review: Reconsideration of Benzodiazepines (BZDs) after many years′ widespread use, for development of recent new similar drugs and consideration about increased delirium with BZDs.

Methods: A comprehensive search in OVID MEDLINE, EMBASE and PubMed were performed from inception to Jan 31, 2016, the studies which involved pharmacological characteristics of BZDs and comparison among BZDs, placebo and some similar new drugs used for sedation and antianxiety in the perioperative period were included.

Recent findings: Routine use of BZDs as a sedative and antianxiety premedication is lack of benefits. BZDs did not improve the self-reported patient experience the day after surgery, but was associated with a lower rate of early cognitive recovery. Large numbers of using of other sedation drugs such as Propofol or Dexmedetomidine are replacing the using of BZDs for postoperative sedation. BZDs are important anesthesia-related predictors of postoperative delirium. Compared with those new drugs in sedation and anti-anxiety, BZDs has gradually lost its market.

Conclusion: As the developing of anesthesia monitoring technique and more beneficial pharmaceutical, the perioperative application of BZDs should be used with caution. (Funded by the National Natural Science Foundation of China.)

Benzodiazepines (BZDs), the benzodiazepine receptor agonists, has been widely used in the perioperative period for many years for their hypnotic, sedative, amnesia and anxiolytic effects. Dr. Leo Sternbach discovered BZDs after many years' hard work (1- 3). Firstly, in 1960, chlordiazepoxide was approved for internal medical use as the debut of BZDs. In the following years, more than one thousand sorts of BZDs had been synthesized (4). Of which, diazepam was firstly described for use as an intravascular anesthetic induction in 1963 (5). It was followed by the introduction of midazolam in 1983, which was also an intravascular BZDs and have a more rapid onset than other BZDs (6). Up to now, BZDs has been broadly used in the perioperative period to achieve two aims: one is to reduce anxiety (anxiolytic) and sedative-hypnotics for sleep, another is adjuncts to anesthesia to induce relaxation and amnesia (procedural memory loss). And midazolam (>75%), diazepam (7%) and lorazepam (2%) are being to the three most commonly used BZDs in the perioperative setting in the USA (7, 8).

Recently, however, as developing of anesthesia monitor technique and anesthetic drugs such as α2-adrenergic receptor agonists (Dexmedetomidine, for example) and Propofol, more and more pharmaceutical are further beneficial or replacing the role of BZDs in perioperative use. In

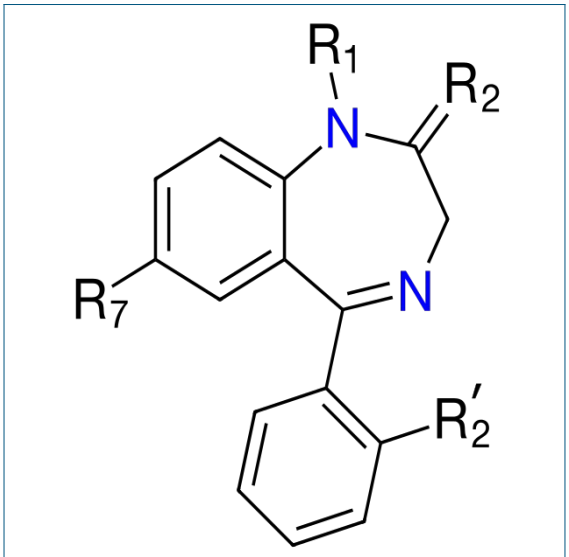

Figure 1. The Core Structure of BZDs.
"R" labels denote common locations of side chains, which give different BZDs their unique properties.

Table 1. Theα- subunit Subtypes and Relative Activity of Diazepam and Midazolam (6)

α- Subunit Subtypes	α1	α2	α3	α4	α5	α6
Diazepam	++	++	++	-	++	-
Midazolam	++		++	-	++	-

Activity: ++ high, - negligible or none; blank = no data.
Function: α1-Sleep, Anti-epilepsis; α2-Anxiolysis, Anti-epilepsis; α3-Anti-epilepsis; α4-Anti-epilepsis; α5-Amnesia; α6-no description.

Table 2. Physicochemical Characterization of Three BZDs (15)

	Diazepam	Lorazepam	Midazolam
Molecular weight (D)	284.7	321.2	362
pKa	3.3 (20°)	11.5 (20°)	6.2 (20°)
Water soluble	No	Almost insoluble	Yes*
Lipid soluble	Yes, highly lipophilic	Yes, relatively less lipophilic	Yes, highly lipophilic*

*pH dependent: pH >4, lipid soluble; pH <4, water soluble.

this paper, we aim to revisit the BZDs by introducing them from aspects of pharmacological characteristics, perioperative uses and side effect, especially relationship with postoperative delirium.

Pharmacological Characteristics

Physicochemical Structure

Figure 1 showed the core structure and side chains of BZDs. "R" labels denote the common locations of side chains, which give different BZDs their unique properties (Figure 2). For example, Midazolam is approximately 3 to 6 times and lorazepam 5 to 10 times, as potent as diazepam (9). Midazolam and diazepam have a more rapid onset (usually within 30 to 60 seconds) of action than lorazepam (60 to 120 seconds) (9).

Mechanism

All BZDs have hypnotic, sedative, anxiolytic, amnesic, anticonvulsant, and centrally produced muscle- relaxing properties. The mechanism of action of BZDs is reasonably well understood (10- 12). Gamma- aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the nervous system. The GABAA receptor is a chloride channel formed by 5 subunits. BZDs bind to sites distinct from GABA itself (allosteric modulation), increasing the receptor' s affinity for GABA, therefore enhance GABA action (13). The α-subunit of the GABAA receptor, of which there are six subtypes, is the predominant determinant of BZDS affinity and function (Table 1).

As the first BZDs antagonist antidote, Flumazenil (Anexate, Romazicon) can be given intravenously in the emergency setting to reverse the effects of a BZDs overdose (14). The structure of flumazenil is similar to midazolam and other classic BZDs except for the absence of the phenyl group, which is replaced by a carbonyl group (Figure 2). Therefore, Flumazenil can competitively bind on the BZDs site of GABAA receptor to blocks the central effect of BZDs.

Characterization of Physicochemical and Pharmacokinetics

Physicochemical characterization of BZDs (Table 2) is closely association with its pharmacokinetics (Table 3).

The more rapid redistribution of midazolam compared with diazepam and lorazepam (presumably because of the lower lipid solubility of

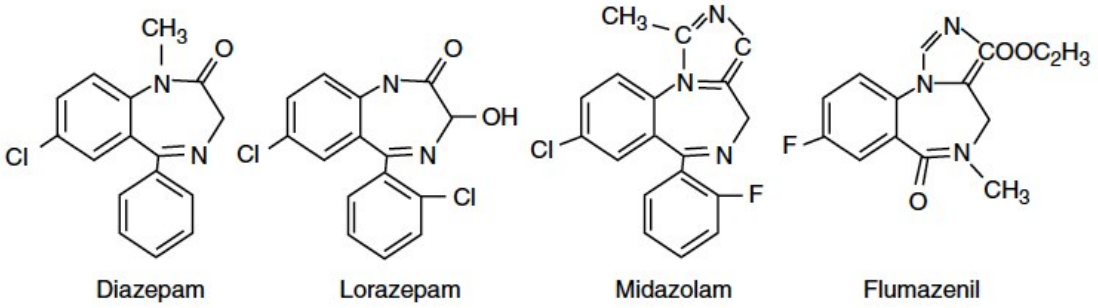

Figure 2. The structures of three BZDs and BZDs antagonist used in clinical anesthesia practice.

Table 3. Pharmacokinetic Variables for The Three BZDs Used in Perioperative Period

Elimination	Elimination Half-Life (hr.)	Clearance (mL/kg/min)	Vd_{ss} (L/kg)
Diazepam	20-50	0.2-0.5	0.7-1.7
Lorazepam	11-22	0.8-1.8	0.8-1.3
Midazolam	1.7-2.6	6.4-11	1.1-1.7

Vd_{ss}, apparent volume of distribution at steady state

diazepam and lorazepam) accounts for the more rapid onset and the shorter duration of its actions (16). The three BZDs are classified as short-lasting (midazolam), intermediate-lasting (lorazepam), and long-lasting (diazepam), according to their metabolism and plasma clearance (Table 3). And after long-term repeated administration, or after prolonged continuous infusion, blood concentration of midazolam decrease more rapidly than those of the other drugs because of greater hepatic clearance.

Biotransformation of the BZDs occurs in the liver. All of the three BZDs forms active metabolites, which add to and prolong the drug's effects (17). It is excreted largely by the kidneys and can cause profound sedation in patients with renal impairment (18). In addition, because pH-dependent solubility of midazolam, it is water soluble as formulated in a buffered acidic medium (pH 3.5), which have its advantage over diazepam and lorazepam in clinical use.

Perioperative Use

The BZDs are usually used as premedication, intraoperation and postoperative adjuvant to reduce anxiety (anxiolytic) and sedative-hypnotics for sleep. However, as developing of some new anesthetic drugs and anesthesia monitor technique in sedation and antianxiety, BZDs has gradually lost its market.

Premedication

Oral or intravenous BZDs were given for preoperative sedation for many years, but more and more evidence suggests a lack of benefit with routine use of BZDs as sedative and antianxiety premedication (Table 4).

BZDs VS. Placebo

Lorazepam is particularly unpredictable with regard to duration of amnesia. A randomized placebo-controlled clinical trial compared lorazepam (1 to 1.5 mg) intravenously vs. NaCl 0.9% as a premedication prior to day-case surgery. Lorazepam did not improve quality of recovery. Postoperative mean Quality of Recovery-40 scores were similar in both groups at first postoperative working day (174.5 vs. 176.4, P = 0.34) and 7th day after surgery (172.8 vs.176.3, P = 0.38). Furthermore, lorazepam may delay the decrease in postoperative anxiety and aggression (19).

Another randomized double-blind study com-

Table 4. Studies of Anesthetics Are Prior to BZDs as Sedative and Antianxiety

Trial	Type of surgery	Time of use	Intervention	Sampe size	Outcomes
Mijderwijk H, 2013 (19)	Day-case surgery	30 min before induction	lorazepam 1 - 1.5mg, iv NaCl 0.9%	198 200	Quality of Recovery- 40 (QoR-40) score
Weitz G, 2007 (20)	ERCP	-	lorazepam 1mg, oral Placebo	47 48	Total amount of administered propofol
Beydon L, 2015 (22)	Non- ambulatory general surgery	Zopiclone, the night before surgery	Zopiclone 7.5m, oral Alprazolam 0.5mg Placebo	204 206 68	Anxiety
Maurice- Szamburski A, 2015 (21)	-	Alprazolam, the morning of surgery	Lorazepam,2.5mg No premedication Placebo	330 319 322	Anxiety Questionnaire (Evaluation du Vécu de l'Anesthésie Generale; EVAN-G) Early cognitive recovery
Almenrader N, 2007 (24)	-	Day before surgery	Midazolam 0.5 mg/kg, oral Clonidine 4 microg/kg, oral		Drug acceptance Preoperative sedation and anxiolysis Quality of mask acceptance Recovery profile and parental satisfaction
Vargo JJ, 2002 (29)	ERCP and EUS	Prior to mask induction	Propofol Meperidine/midazolam	38 37	Recovery times Cost-effectiveness analysis
Cox CE, 2008 (30)	ICU	Gastroenterologist-administered	Propofol 2,773 (290) mg/day, continuous Lorazepam 12 (2), intermittent Midazolam 54 (6), continuous		Cost-effectiveness analysis
Aydogan MS, 2013 (31)	Underwent scoliosis surgery in ICU	During mechanical ventilation	Dexmedetomidine 0.4 µg/kg/h, continuous infusion Midazolam 0.1 mg/kg/h, continuous infusion	22 20	Fentanyl consumption Incidence of delirium Numeric Visual Analog Scale (NVAS)

pared 1 mg of lorazepam vs. placebo given orally before ERCP (20). Patients pretreated with lorazepam even needed more Propofol in the early phase of sedation (275 +/- 39 vs 159 +/- 37 microg/kg in minutes 5-10, $P < 0.05$) and the total amount of ketamine administered was higher in the lorazepam group (15.8 +/- 1.4 vs 11.3 +/- 1.2 microg/kg/min, $P < 0.05$).

There was also a randomized clinical trial that randomized patients into three groups each to receive 2.5 mg of lorazepam, no premedication, or placebo (21). The results were, premedication with lorazepam did not improve the Evaluation du Vécu de l'Anesthésie Generale (EVAN- G) mean global index for overall level of patient satisfaction compared with no premedication or placebo ($P = 0.38$). There were no significant differences found in the EVAN- G mean global index with the three groups ($P = 0.18$). And the rate of early cognitive recovery was 51%, 71% and 64%, respectively ($P < 0.001$). Among patients undergoing elective surgery under general anesthesia, sedative premedication with lorazepam compared with placebo or no premedication did not improve the self-reported patient experience the day after surgery, but was associat-

ed with a lower rate of early cognitive recovery.

BZDs VS. Other Anesthetics

Zopiclone is a nonbenzodiazepine hypnotic agent used in the treatment of insomnia, which increases the normal transmission of the neurotransmitter GABA in the central nervous system, as benzodiazepines do, but in a different way. A multi-center RCT compared zopiclone 7.5 mg, alprazolam 0.5 mg and controls received placebo as premedication for non-ambulatory consecutive surgical patients undergoing general surgery (22). Finally, in the operating room, anxiety and comfort were moderate and did not differ significantly among groups on a 1-10 scale: zopiclone: 2 [1-4] and 2.5 [1-5]; alprazolam: 2 [1,4] and 2 [1-5]; placebo: 3 [1-5] and 3 [1-5]. The patients who were more anxious preoperatively remained so in the operating room. Premedication of alprazolam and zopiclone in non-ambulatory surgery is no more effective than a placebo.

α2 - adrenergic receptor agonists

Otherwise, as anesthetic premedication, both α2-adrenergic receptor agonists have been compared with BZDs in many clinical trials (23). One of which, compared oral midazolam 0.5 mg/kg with oral clonidine 4 mg/kg in terms of drug acceptance, preoperative sedation, quality of mask acceptance, and recovery profile. They found the taste of clonidine is better and the onset of sedation is faster with midazolam, and the level of sedation is better with clonidine. The quality of mask acceptance was equally satisfactory, and they noted a trend toward an increased incidence of postoperative agitation after midazolam premedication (24). Moreover, a meta-analysis summarized 10 similar trials and found that clonidine, in comparison with midazolam, produced a more satisfactory level of sedation at induction (odds ratio, OR = 0.49), decreased emergence agitation (OR = 0.25), and produced more effective early postoperative analgesia (OR = 0.33) (25).

Dexmedetomidine is a more selective a2-adrenergic receptor agonist than clonidine with a faster onset of action, quicker time to reach the peak plasma concentration, and a shorter elimination half-life. Recently, two meta-analyses (26, 27) found that dexmedetomidine was associated with more satisfactory sedation upon separation from parents and upon mask acceptance than midazolam as premedication. Furthermore, dexmedetomidine also decreased the severity of acute postoperative pain and reduce the number of requests for rescue analgesics after surgery, incidence of emergence delirium, and the incidence of postoperative shivering (26, 28).

Sedation in ICU

Sedation for longer periods, such as in the ICU, also is accomplished with BZDs. However, prolonged infusion results in accumulation of drug (midazolam) and significant concentration of the active metabolite. Recently, large numbers of using of other sedation drugs are replacing the using of BZDs in long care situation (Table 4).

BZDs VS. Propofol or Dexmedetomidine

For sedation, Propofol or Dexmedetomidine is generally similar with the amnesia and hemodynamic stability but with more rapid emergence or wake-up than midazolam (29). When lorazepam is compared with propofol for critically ill patients undergoing mechanical ventilation, propofol also has superior economic value (30). When midazolam is compared with dexmedetomidine for sedation during the early postoperative period in adolescents who underwent scoliosis surgery, dexmedetomidine was associated with the decreased postoperative fentanyl consumption, Numeric Visual Analog Scale (NVAS) pain scores, and a decreased incidence of delirium (31).

A systematic review and meta-analysis of six randomized trials enrolling 1235 patients suggest that use of a dexmedetomidine or propofol based sedation regimen rather than a benzodiazepine (midazolam or lorazepam) based sedation regimen in critically ill adults may reduce ICU length of stay and duration of mechanical ventilation (32).

Side effect of BZDs: Postoperative delirium

Delirium has recently been shown as a predictor of death, increased cost, and longer duration of stay especially in ventilated patients. Current evidence most strongly associates use of benzodiazepines with increased postoperative delirium, longer delirium duration, and possible transition to

delirium in patients.

Long-term use of BZDs is closely related to postoperative delirium (POD). Recent research reported that premedication with BZDs is important anesthesia-related predictors for POD (OR, 1.8) (33-36), and the use of BZDs in the first 24 h after admission is also a risk factor related to delirium (OR, 2.28) (37).

Voepel-Lewis T, et al. (38) present a case of a 5-year-old boy who had severe agitation after PACU discharge after midazolam premedication for minor otologic surgery. Furthermore, a meta-analysis of seven RCTs with 466 children (24) demonstrated that dexmedetomidine premedication can decrease the incidence of emergence delirium, and the incidence of postoperative shivering (RR:0.59; 95% CI:0.40, 0.88). For elderly people, Marcantonio ER (39) presented a 76-year-old woman who developed delirium first after colectomy with complications and again after routine surgery. He concluded limiting use of sedating medications (especially BZDs) is the key strategy for successful prevention and treatment of delirium for elderly people.

In ICU patients, lorazepam has been an independent risk factor for transitioning to delirium (OR, 1.2; P = 0.003), whereas fentanyl, morphine, and propofol were associated with higher but not statistically significant odds ratios (40). Recent study also found that midazolam produces more delirium compared with dexmedetomidine in complicated post-surgical patients with sepsis and mechanical ventilation (41). Hence, it is important to underline that to avoid BZDs in ICU patients is associated with a reduced risk for POD.

For pharmacologic interventions used to treat postoperative delirium in older surgical patients, American Geriatrics Society strongly recommended that the prescribing practitioner should not use benzodiazepines as a first-line treatment of the agitated postoperative delirious patient who is threatening substantial harm to self and/or others to treat postoperative delirium. And healthcare providers should also not prescribe antipsychotic or benzodiazepine medications for the treatment of older adults with postoperative delirium who are not agitated and threatening substantial harm to self or others (42).

In conclusion, more and more pharmaceutical are further beneficial or replacing the role of BZDs in perioperative use. In addition, as the developing of anesthesia monitoring technique, amnesia effect of BZDs may not be that important. Therefore, the perioperative application of BZDs should be used with caution.

This work was supported by a grant (81271201) from the National Natural Science Foundation of China.

The author declares no conflicts of interest.

References

1. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *Eur Psychiatry* 2013;28:7-20.
2. Ban TA. In memory of three pioneers. *Int J Neuropsychopharmacol* 2006;9(4):475-7.
3. Froestl W. An historical perspective on GABAergic drugs. *Future Med Chem* 2011;3(2):163-75.
4. Mandrioli R, Mercolini L, Raggi MA. Metabolism of benzodiazepine and non-benzodiazepine anxiolytic – hypnotic drugs: an analytical point of view. *Curr Drug Metab* 2010;11(9):815-29.
5. Stovner J, Endresen R. Diazepam in intravenous anesthesia. *Lancet* 1965;2(7425):1298-9.
6. Howard P, Twycross R, Shuster J, Mihalyo M, Wilcock A. Benzodiazepines. *J Pain Symptom Manage* 2014;47(5):955-64.
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(2):427-32.
8. Kain ZN, Caldwell-Andrews AA, Krivutza DM, Weinberg ME, Wang SM, Gaal D. Trends in the practice of parental presence during induction of anesthesia and the use of preoperative sedative premedication in the United States, 1995-2002: results of a follow-up national survey. *Anesth Analg* 2004;98(5):1252-59.
9. Mould DR, DeFeo TM, Reele S, Milla G, Limjuco R, Crews T, et al. Simultaneous modeling of the pharmacokinetics and pharmacodynamics of midazolam and diazepam. *Clin Pharmacol Ther* 1995;58(1):35-43.
10. Möhler H, Richards JG. The benzodiazepine receptor: A pharmacological control element of brain function. *Eur J Anaesthesiol Suppl* 1988;2:15-24.
11. Amrein R, Hetzel W. Pharmacology of Dormicum (midazolam) and Anexate (flumazenil). *Acta Anaesthesiol Scand Suppl* 1990;92:6-15.
12. Möhler H, Fritschy JM, Rudolph U. A new benzodiazepine pharmacology. *J Pharmacol Exp Ther* 2002;300(1):2-8.
13. Rudolph U, Mohler H. GABA-based therapeutic approaches: GABAA receptor subtype functions. *Curr Opin Pharmacol* 2006;6:18-23.
14. Brogden RN, Goa KL. Flumazenil: A reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. *Drugs* 1991;42:1061-89.
15. Swarbrick J. Clarke's Isolation and Identification of Drugs. *J Pharm Sci* 1987;76:420-1.
16. Greenblatt DJ, Shader RI, Abernethy DR. Drug therapy: Current status of benzodiazepines. *N Engl J Med* 1983;309:354-8.
17. Barr J, Donner A. Optimal intravenous dosing strategies for sedatives and analgesics in the intensive care unit. *Crit Care Clin* 1995;11:827-47.
18. Bauer TM, Ritz R, Haberthür C, Ha HR, Hunkeler W, Sleight AJ, et al. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet* 1995;346(8968):145-7.
19. Mijderwijk H, van Beek S, Klimek M, Duivenvoorden HJ, Grüne F, Stolker RJ. Lorazepam does not improve the quality of recovery in day-case surgery patients: a randomized placebo-controlled clinical trial. *Eur J Anaesthesiol* 2013;30(12):743-51.
20. Weitz G, Homann N, von Jagow DC, Wellhöner P, Sauer A, Ludwig D. Premedication with orally administered lorazepam in adults undergoing ERCP: a randomized double-blind study. *Gastrointest Endosc* 2007;66(3):450-6.
21. Maurice-Szamburski A, Auquier P, Viarre-Oreal V, Cuvillon P, Carles M, Ripart J, et al. Effect of sedative premedication on patient experience after general anesthesia: a randomized clinical trial. *JAMA* 2015;313(9):916-25.
22. Beydon L, Rouxel A, Camut N, Schinkel N, Ma-

linovsky JM, Aveline C, et al. Sedative premedication before surgery--A multicentre randomized study versus placebo. *Anaesth Crit Care Pain Med* 2015;34(3):165-71.
23. Sheen MJ, Chang FL, Ho ST. Anesthetic premedication: new horizons of an old practice. *Acta Anaesthesiol Taiwan* 2014;52(3):134-42.
24. Almenrader N, Passariello M, Coccetti B, Haiberger R, Pietropaoli P. Premedication in children: a comparison of oral midazolam and oral clonidine. *Pediatr Anesth* 2007;17:1143-9.
25. Dahmani S, Brasher C, Stany I, Golmard J, Skhiri A, Bruneau B, et al. Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies. *Acta Anaesthesiol Scand* 2010;54:397-402.
26. Sun Y, Lu Y, Huang Y, Jiang H. Is dexmedetomidine superior to midazolam as a premedication in children? A meta-analysis of randomized controlled trials. *Pediatr Anesth* 2014;24:863-74.
27. Pickard A, Davies P, Birnie K, Beringer R. Systematic review and meta-analysis of the effect of intraoperative a2-adrenergic agonists on postoperative behaviour in children. *Br J Anaesth* 2014;112:982-90.
28. Schnabel A, Reichl SU, Poepping DM, Kranke P, Pogatzki-Zahn EM, Zahn PK. Efficacy and safety of intraoperative dexmedetomidine for acute postoperative pain in children: a meta-analysis of randomized controlled trials. *Pediatr Anesth* 2013;23:170-9.
29. Vargo JJ, Zuccaro G Jr, Dumot JA, Shermock KM, Morrow JB, Conwell DL, et al. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: A prospective, randomized trial. *Gastroenterology* 2002;123:8-16.
30. Cox CE, Reed SD, Govert JA, Rodgers JE, Campbell-Bright S, Kress JP. Economic evaluation of propofol and lorazepam for critically ill patients undergoing mechanical ventilation. *Crit Care Med* 2008;36(3):706-14.
31. Aydogan MS, Korkmaz MF, Ozgül U, Erdogan MA, Yucel A, Karaman A, et al. Pain, fentanyl consumption, and delirium in adolescents after scoliosis surgery: dexmedetomidine vs midazolam. *Pediatr Anaesth* 2013;23(5):446-52.
32. Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013;41(9 Suppl 1):S30-8.
33. Gusmao-Flores D, Salluh JI, Chalhub RÁ, Quarantini LC. The confusion assessment method for the intensive care unit and intensive care delirium screening checklist for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Crit Care* 2012;16;R115.
34. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304:443-51.
35. Schneider F, Böhner H, Habel U, Salloum JB, Stierstorfer A, Hummel TC, et al. Risk factors for postoperative delirium in vascular surgery. *Gen Hosp Psychiatry* 2002;24:28-34.
36. Taipale PG, Ratner PA, Galdas PM, Jillings C, Manning D, Fernandes C, et al. The association between nurse-administered midazolam following cardiac surgery and incident delirium: An observational study. *Int J Nurs Stud* 2012;49(9):1064-73.
37. Serafim RB, Dutra MF, Saddy F, Tura B, de Castro JE, Villarinho LC, et al. Delirium in postoperative nonventilated intensive care patients: risk factors and outcomes. *Ann Intensive Care* 2012;2(1):51.
38. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;104(1):21-6.
39. Voepel-Lewis T, Mitchell A, Malviya S. Delayed postoperative agitation in a child after preoperative midazolam. *J Perianesth Nurs* 2007;22(5):303-8.
40. Marcantonio ER. Postoperative delirium: a 76-year-old woman with delirium following surgery. *JAMA* 2012;308(1):73-81.
41. Pérez-Rada Fde J, Macías-García MT, Cataneo-Cerna AC. Postsurgical delirium complicated with sepsis. Dexmedetomidine versus midazolam. *Rev Med Inst Mex Seguro Soc* 2012;50(4):419-26.
42. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. *J Am Geriatr Soc* 2015;63(1):142-50.