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Can adding Ephedrine to Admixture of Propofol & Lidocaine Overcome Propofol Associated Hemodynamic Changes and Injection Pain?

Research Article

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Abstract

Purpose: There are numerous studies researching ways to alleviate propofol injection pain. In this study, we evaluated and compared the use of propofol-lidocaine admixture vs propofol-lidocaine combined with ephedrine, on vascular pain and hemodynamic changes associated propofol.

Methods: This double-blinded, prospective, randomised study was performed on 100 patients with ASA I-II who were divided into two group. The first received admixture consisting of 20 mg of lidocaine and propofol 1% 20 ml (Group L), and the other received admixture consisting of 20 mcg ephedrine, 20 mg lidocaine and propofol 1% 20 ml (Group LE). Baseline and after induction heart rate, mean arterial pressure and rate pressure product (RPP) were recorded per minute. Vascular pain were evaluated with verbal rating scale.

Results: Data of 40 patients in group L and 39 patients in Group LE were evaluated in the study. The incidence of pain in group L was 90%, it was 38.4% for Group LE. Mild pain was observed significantly more in Group L when compared to Group LE ($p<0.05$). Average blood pressure and RPP immediately after induction and 1 min after intubation were significantly higher in group LE compared to group L ($p<0.05$). Heart rate was higher in Group LE immediately after induction and at initially 4 minutes after intubation.

Conclusion: Our study has demonstrated significant decrease in rate of vascular pain and increased hemodynamic stability in patients receiving 20 mg ephedrine added to 20 ml % 1 propofol and 20 mg lidocaine admixture when compared to those who only received the lidocaine-propofol admixture.

Keywords: Propofol; Injection Induced Pain; Ephedrine.

Introduction

Propofol is an anaesthetic agent widely used for anesthesia induction, total intravenous anesthesia and sedoanalgesia [1-3]. Injection pain, hypotension and bradycardia are common side effects of propofol although more serious and life threatening conditions such as propofol infusion syndrome observed especially in small children [1, 4] and sepsis secondary to contamination may also be seen [1, 5]. The cause of pain during injection of propofol is theorised to be due to endothelial damage, osmolality difference, non-physiological pH, stimulation of venous nociceptive receptors and free nerve ends although it is generally accepted to be multifactorial [6-8]. Bradycardia and hypotension is seen after administration of propofol especially in elder patients [7, 9, 10]. Hypotension is more pronounced in elderly patients due to inadequate autonomic system and decreased adrenergic response to myocardial depression and vasodilatation [9-12].

There are numerous studies researching ways to alleviate injection pain for propofol. The most frequently used agent for this purpose has been lidocaine that is used before or with propofol [13-15]. There are also studies on the use of hypnotic agents (thiopental sodium, ketamine etc), opiates (alfentanil, sufentanil, remifentanil), dexmedetomidine, magnesium, nonsteroidal analgesic medication, antiemetics and physical applications such as cold packs to alleviate injection pain [13, 14, 16-21].

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There are also studies evaluating the use of ephedrine [9, 10, 22-25]. Ephedrine is different from other agents used for decreasing injection pain as it is also the subject of studies evaluating its effect on bradycardia-hypotension response of propofol [9, 10, 23].

Although there are many studies, the problem of pain during administration of propofol remains a controversial topic. In this study, we evaluated and compared the use of propofol-lidocaine admixture vs propofol-lidocaine combined with ephedrine, on vascular pain and hemodynamic changes associated propofol administration.

Material & Method

This double-blinded, prospective, randomised study was performed after IRB approval and informed consent was obtained from all patients. The study included American Society of Anesthesiology (ASA) physiologic score 1-2 patients aged < 65 years undergoing elective orthopedic, abdominal, urological or gynecological surgery under general anesthesia. Patients with hypertension, cardiac failure, rhythm abnormalities, diabetes mellitus and similar pathologies leading to autonomic dysfunction, morbidly obese patients, pregnant patients, patients with history of undergoing general anesthesia or sedoanalgesia previously, those with psychiatric problems or severe anxiety on clinical observation, those taken nonsteroidal anti-inflammatory medicine within the last 24 hours or steroids within the last 3 months were excluded. Also, patients > 65 years of age were excluded due increase susceptibility to hemodynamic changes in these patients.

Patients did not undergo premedication. The study planned to recruit 100 ASA 1-2 patients. Patients were all evaluated and given information on the study preoperatively. On the day of their procedures, patients were asked to randomly choose closed envelopes that included them in either Group L (Propofol with lidocaine) or Group LE (Propofol with lidocaine plus ephedrine). The draw was performed by the patient under the supervision of an anesthesiology technician who were both blinded to the study.

Preparation of admixtures

Group L: 200 mg/20 mL 1% propofol, 1 mL 2% lidocaine (20 mg) and 1 ml saline solution was prepared to a 50ml injector.

Group LE: 200 mg/20 mL 1% propofol, 1 mL 2% lidocaine (20 mg), 0.4 mL (20 mg) Ephedrine and 0.6 mL saline was prepared to a 50ml injector.

All mixtures were prepared by persons who were not involved in either patient selection or subsequent follow-up.

Standard monitorization included electrocardiogram, pulse oximetry and non-invasive blood pressure monitorization. Intravenous access was made via the dorsum of the non-dominant hand with a 20 G cannula. A facemask was used to administer 6 lt/m fresh O_2 for 3 minutes before induction.

Basal heart rate, blood pressure measurements and rate pressure product (RPP) were recorded, followed by infusion of propofol at 18.3 mL/min was commenced and continued until dose of 2.5mg/kg was reached. The patient was informed that they would be asked if they had pain while induction occurred, and were instructed to answer using a scale of 0 to 3:0 no pain, 1 mild pain, 2 moderate pain, 3 severe pain. This question was asked to the patient at 5 second intervals until consciousness was lost. The anesthesiologist also used McCrirrick and Hunter's verbal rating scale (VRS) to evaluate patients' pain [21, 26] (Table 1).

Following propofol infusion, 1 mcg/kg fentanyl and 0.1 mg/kg vecuronium was administered and patients were intubated. Patients' pulse and blood pressures were noted per minute for 7 minutes after induction.

Sample Size

Previously published data [26-29] has reported the frequency of pain during injection of propofol as approximately 90%. A reduction from 90% to 50% with the use of our admixtures were considered to be of significance, with $\alpha = 0.05$ and $1 - \beta = 0.8$. To provide 80% power to detect such a difference using a 2-sided test at a level of 0.05, a sample size of 30 patients per group was calculated.

Statistical Analysis

Statistical analysis were carried out using SPSS for Windows software program version 13.0 (*SPSS, IBM Corp. Chicago, IL*). Values are expressed as means ± SD. Demographic data were compared by use of the Student's *t*-test. Nonparametric data, that is, patients' subjective assessment of the intensity of pain and the hemodynamic data were analyzed with the Kruskal–Wallis test analyzes of variance and U-test, respectively. The incidence of pain was analyzed using the 2-test. Also, χ^2 test and Fisher's exact test assessed differences among groups in frequency and severity of pain on injection.

Table 1. Verbal Rating Scale for propofol Injection Pain.

Pain Score	Severity of Pain
None (0)	no pain, negative response to questioning.
Mild (1)	pain reported only in response to questioning without any behavioral signs (i.e., no spontaneous expression of pain).
Moderate (2)	pain reported only in response to questioning and accompanied by a behavioral sign or symptom (i.e., expression of pain) reported spontaneously without questioning.
Severe (3)	Strong verbal response or response accompanied by facial grimacing, arm withdrawal, or tears.

Results

Preliminary interview was performed with 100 patients. Sixteen patients were excluded according to the criteria previously mentioned. Four patients refused to be included in the study. One patient was later excluded due to the requirement of additional drugs and prolongation of intubation time due to difficult intubation.

Patients' demographic information and pain distribution is presented in Tables 2 and 3 respectfully. While the incidence of pain in group L was 90%, it was 38.4% for Group LE. Mild pain was observed significantly more in Group L when compared to Group LE ($p < 0.05$). There were seven patients in Group L with moderate pain, yet none in group LE ($p < 0.001$). Severe pain was not observed in any group. Average blood pressure immediately after induction and 1 min after intubation was significantly higher in group LE when compared to group L ($p < 0.05$) (Table 4). Pulse was higher in Group LE immediately after induction and at 1st, 2nd, 3rd and 4th minutes after intubation (Table 5). Average

Table 2. Patients' demographic information.

	Group L (n:40)	Group LE (n:39)	p
Age (Year)	41.73 ± 10.9	44.10 ± 14.6	0.86
Sex (F/M)	19/21	18/21	
ASA I/II	23/17	24/15	
Weight (kg)	64.9 ± 10.5	62.2 ± 11.3	0.64
Baseline Heart rate	81 ± 24	89 ± 19	0.15
Mean arterial pressure (mmHg)	76 ± 15	88 ± 11	0.058

Table 3. Distribution of patients according to pain scale.

Pain score	0 (%)	1 (%)	2 (%)	3 (%)
Group L (n:40)	4 (10)**	29 (72.5)*	7 (17.5)**	0
Group LE (n:39)	24 (61.5)**	15 (38.4)*	0	0

**$p < 0.001$, *$p < 0.05$

Table 4. Patients' mean arterial pressures (MAP).

MAP	Group L	Group LE	P
Baseline	77.83 ± 10.35	82.38 ± 10.42	0.96
After induction	72.55 ± 10.07	79.04 ± 8.46	0.03
1 min after intubation	71.87 ± 14.74	78.71 ± 10.06	0.02
2 min after intubation	77.24 ± 11.03	80.16 ± 12.41	0.46
3 min after intubation	75.10 ± 14.41	79.28 ± 15.57	0.63
4 min after intubation	80.09 ± 17.26	77.46 ± 13.65	0.15
5 min after intubation	81.19 ± 16.72	82.45 ± 13.39	0.17
6 min after intubation	79.47 ± 15.30	83.26 ± 14.21	0.65
7 min after intubation	82.09 ± 12.82	84.73 ± 13.27	0.83

Table 5. Patients' heart rate (beats per minute).

BPM	Group L	Group LE	P
Baseline	80.77 ± 10.86	83.44 ± 12.16	0.48
After induction	70.00 ± 13.50	79.02 ± 8.92	0.01
1 min after intubation	83.75 ± 13.42	90.01 ± 9.44	0.03
2 min after intubation	81.92 ± 14.90	88.24 ± 10.46	0.03
3 min after intubation	82.52 ± 11.21	87.65 ± 9.44	0.04
4 min after intubation	86.6±14.02	91.55 ± 10.90	0.04
5 min after intubation	81.57 ±15.05	82.46 ± 13.70	0.56
6 min after intubation	78.97 ±17.45	83.54 ± 15.82	0.54
7 min after intubation	80.10 ±16.08	86.80 ± 13.26	0.23

rate pressure product immediately after induction and 1 min after intubation was significantly higher in group LE when compared to group L ($p < 0.05$) (Table 6). No pain, erythema or edema was reported on or around the vessel trace at which drug mixtures were administered.

Discussion

Propofol is one of the most commonly used hypnotic agent used in sedoanalgesia and anesthesia induction [7, 14, 17]. A very common unwanted effect of propofol, seen in 80-90% of patients, is pain observed especially when it is injected into small veins such as those on the dorsum of the hand. Bradycardia and hypotension are less commonly observed side effects [30].

The incidence of pain when 200 mg propofol and 20 mg lidocaine was administered and the decrease rate of pain when lidocaine was added in our study was similar to those reported in the literature. This study also found that the addition of 20 mg ephedrine significantly decreased the rate of pain (38.5%) and lead to more stable hemodynamics.

Many agents such as lidocaine [9, 13, 14, 18, 27, 31], thiopental sodium [28], dexmedetomidine [2, 19, 20], ketamine [9], magnesium [16, 17, 26], opiates [3, 18] have been used to decrease the pain caused by propofol administration. Although many of these agents were found to decrease pain, lidocaine with or immediately before propofol is most commonly used [9, 18].

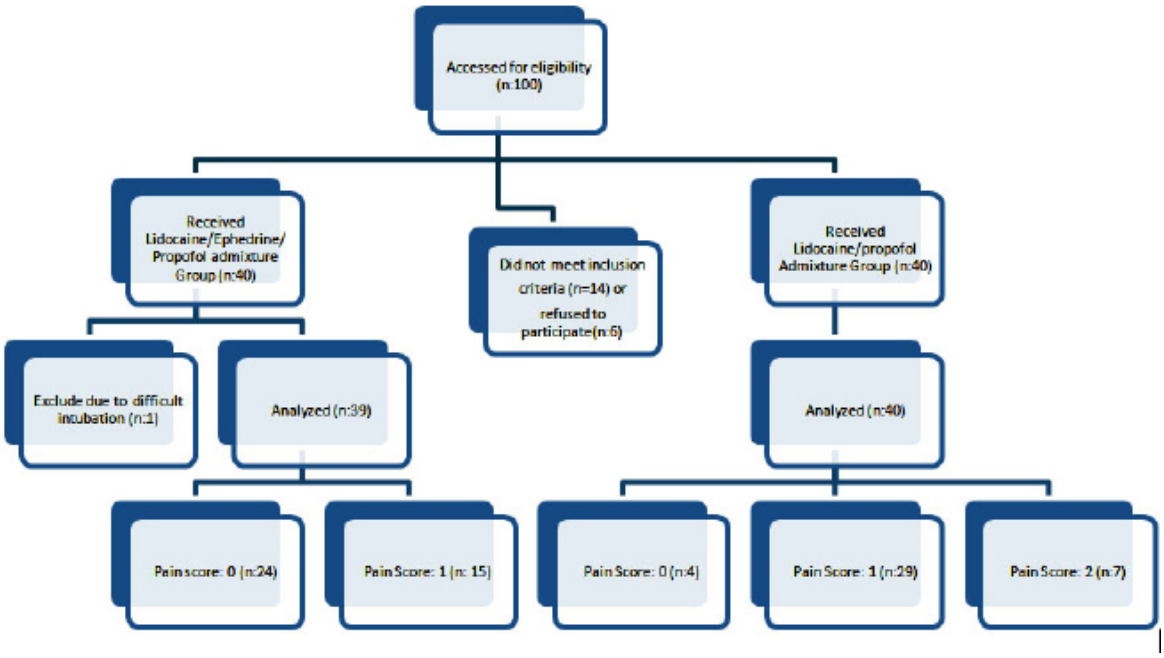
The aim of our study was to evaluate the effect of ephedrine used alone or with lidocaine in combined with propofol for prevention of pain and to maintain hemodynamic stability. There are similar studies. In their study, Cheong et al [24] compared groups of patients administered either 40 mg 2% lidocaine, 30-70-110-150 mcg/kg ephedrine and a control group that received saline thirty seconds before propofol injection. Pain was found to decrease in all groups other than control group, and hemodynamics were found to be more stable in patients receiving 30 or 70 mcg/kg dose of ephedrine.

Gilani et al [22] compared slow propofol administration after 20 mg lidocaine, fast propofol injection after 20 mg lidocaine and fast propofol injection after 10 mg ephedrine and found the highest frequency of vascular pain in the slow injection after lidocaine

Table 6. Patients' Rate Pressure Product (RPP).

RPP	Group L	Group LE	P
Baseline	8790 ± 1340	8840 ± 1450	0.62
After induction	7450 ± 1480	8760 ± 1020	0.02
1 min after intubation	8160 ± 1650	9010 ± 1190	0.04
2 min after intubation	8420 ± 1540	9120 ± 1290	0.49
3 min after intubation	10090 ± 1430	9745 ± 1370	0.79
4 min after intubation	9260 ± 1390	9520 ± 1350	0.85
5 min after intubation	9430 ± 1520	9040 ± 1280	0.29
6 min after intubation	8770 ± 1680	8850 ± 1540	0.59
7 min after intubation	8460 ± 1510	8950 ± 1330	0.43

Figure 1. Study Design.



group (52.5%) and the least frequency in the fast injection after ephedrine group (27.5%). Significant hypotension was reported to be observed after induction in all groups, but there was no difference between groups.

Ayatollahi et al [9] compared vascular pain and hemodynamic stability in four groups: 0.1mg/kg ephedrine, 2 ml 2% lidocaine and 0.1mg/kg ketamine 30 seconds before propofol injection and control group. While the decrease in vascular pain was similar in all groups receiving medication, the hypotensive effect of propofol was not as pronounced in the ephedrine group. These three studies [9, 22, 24] evaluated the use of ephedrine alone and generally administered 30 seconds before propofol injection. While pain was found to decrease in all studies with ephedrine, its effect on hemodynamics is controversial as different doses were used.

In our study we prepared admixtures where both lidocaine and lidocaine plus ephedrine were administered with propofol. We also found that with this administration, vascular pain was decreased and bradycardia and hypotension were prevented. Our study used a high dose of ephedrine compared to other studies.

Another practice, is the combination of lidocaine and ephedrine. Khezri et al [10] reported higher vascular pain when 70 mcg/kg ephedrine was injected before propofol when compared to a control group, but found similar vascular pain when 30 mcg/kg ephedrine was administered. They noted a significant decrease in vascular pain in patients given 0.5 mg/kg lidocaine (39.4%) and those given 30 mcg/kg ephedrine+0.5 mg/kg lidocaine (45.4%). They reported that there was no difference in hemodynamic stability between combined or single use of lidocaine and ephedrine, and that there was no synergistic effect of these drugs. Our study found similar findings. It must be kept in mind however that the two studies have different study designs.

Some studies have also given medications combined as admixtures. In a study of 120 patients Austin et al [23] compared vascular pain and hemodynamic effects of three groups (40 patients each): 1ml 1% lidocaine or 15 mg ephedrine or 30mg ephedrine added to 20ml propofol. While they reported no difference in vascular pain, patients receiving 30 mg ephedrine were found to be more stable hemodynamically. To our knowledge, there are no other studies of propofol and ephedrine combination.

Contrary to Austin et al's study [23] we found that propofol-ephedrine-lidocaine admixture not only increased hemodynamic stability but also decreased vascular pain. The admixture used in our study of 20 mg ephedrine and 20 mg lidocaine mixed with 20 ml %1 propofol is similar for ephedrine dose, but our dosage of ephedrine is higher than many previous studies. The discrepancy between our findings and those of previous studies demonstrates the need for larger studies to be performed. Another subject of debate is our finding of higher rate of vascular pain in the lidocaine only group when compared to the lidocaine-ephedrine group.

The lack of a control group and a group where only ephedrine is administered is a limitation of our study. However, our aim was to evaluate the effect of adding ephedrine to lidocaine & propofol admixture, not measuring the effect of lidocaine-less admixture.

Conclusion

Our study has demonstrated a significant decrease in rate of vascular pain and increased hemodynamic stability in patients receiving 20 mg ephedrine added to 20 ml % 1 propofol and 20 mg lidocaine admixture when compared to those who only received the lidocaine-propofol admixture. Studies regarding vascular pain and hemodynamic stability in patients administered propofol remain controversial. Therefore, larger studies are required to confirm our findings.

References

[1]. Skues MA, Prys-Roberts C (1989) The pharmacology of propofol. J Clin Anesth 1(5): 387-400.

[2]. Sethi P, Sindhi S, Verma A, Tulsiani KL (2015) Dexmedetomidine versus propofol in dilatation and curettage: An open-label pilot randomized controlled trial. Saudi J Anaesth 9(3): 258-262.

[3]. Chen L, Wang M, Xiang H, Lin X, Cao D, et al. (2014) Prediction of effect-site concentration of sufentanil by dose-response target controlled infusion of sufentanil and propofol for analgesic and sedation maintenance in burn dressing changes. Burns 40(3): 455-459.

[4]. Mirrakhimov AE, Voore P, Halytskyy O, Khan M, Ali AM (2015) Propofol infusion syndrome in adults: a clinical update. Crit Care Res Pract 2015: 1-10.

[5]. Bennett SN, McNeil MM, Bland LA, Arduino MJ, Villarino ME, et al. (1995) Postoperative infections traced to contamination of an intravenous anesthetic, propofol. N Engl J Med 333(3): 147-154.

[6]. Akeson J (2008) Pain on injection of propofol - why bother? Acta Anaesthesiol Scand 52(5): 591-593.

[7]. Shafer A, Doze VA, Shafer SL, White PF (1988) Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology 69(3): 348-356.

[8]. Nishimoto R, Kashio M, Tominaga M (2015) Propofol-induced pain sensation involves multiple mechanisms in sensory neurons. Pflugers Arch 467(9): 2011-2020.

[9]. Ayatollahi V, Behdad S, Kargar S, Yavari T (2012) Comparison of effects of ephedrine, lidocaine and ketamine with placebo on injection pain, hypotension and bradycardia due to propofol injection: a randomized placebo controlled clinical trial. Acta Med Iran 50(9): 609-614.

[10]. Khezri MB, Kayalha H (2011) The effect of combined ephedrine and lidocaine pretreatment on pain and hemodynamic changes due to propofol injection. Acta Anaesthesiol Taiwan 49(2): 54-58.

[11]. Pagel PS, Warltier DC (1993) Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. Anesthesiology 78(1): 100-108.

[12]. Robinson BJ, Ebert TJ, O'Brien TJ, Colinco MD, Muzi M (1997) Mechanisms whereby propofol mediates peripheral vasodilation in humans. Sympathoinhibition or direct vascular relaxation? Anesthesiology 86(1): 64-72.

[13]. Terada N, Takubo I, Fujinaka W, Takatori M (2014) [Effectiveness of local cooling and lidocaine administration for prevention of pain upon injection of propofol]. Masui 63(8): 836-840.

[14]. Fujii Y, Itakura M (2008) Comparison of lidocaine, metoclopramide, and flurbiprofen axetil for reducing pain on injection of propofol in Japanese adult surgical patients: a prospective, randomized, double-blind, parallel-group, placebo-controlled study. Clin Ther 30(2): 280-286.

[15]. Gharavi M, Sabzevari A, Ghorbanian E, Sajadi R, Akhondi M (2014) Effect of lidocaine volume and concentration on preventing incidence and severity of propofol injection pain. Iran Red Crescent Med J 16(3): e16099.

[16]. Li M, Zhao X, Zhang L, Niu X, Guo T, et al. (2015) Effects and safety of magnesium sulfate on propofol-induced injection pain, a meta-analysis of randomized controlled trials. Int J Clin Exp Med 8(5): 6813-6821.

[17]. Rahimzadeh P, Faiz SH, Nikoobakht N, Ghodrati MR (2015) Which one is more efficient on propofol 2% injection pain? Magnesium sulfate or ondansetron: A randomized clinical trial. Adv Biomed Res 4: 56.

[18]. Zhang L, Bao Y, Shi D (2014) Comparing the pain of propofol via different combinations of fentanyl, sufentanil or remifentanil in gastrointestinal endoscopy. Acta Cir Bras 29(10): 675-680.

[19]. Lee JH, Jung SY, Kim MH, Cho K (2014) The effect of dexmedetomidine on propofol injection pain. Korean J Anesthesiol 67(Suupl): S30-S31.

[20]. He L, Xu JM, He T, Liu L, Zhu R (2014) Dexmedetomidine pretreatment alleviates propofol injection pain. Ups J Med Sci 119(4): 338-342.

[21]. McCrirrick A, Hunter S (1990) Pain on injection of propofol: the effect of

injectate temperature. Anaesthesia 45(6): 443-444.
[22]. Gilani MT, Bameshki A, Razavi M (2014) Efficacy of ephedrine in the prevention of vascular pain associated with different infusion rates of propofol. Anesth Essays Res 8(3): 345-348.
[23]. Austin JD, Parke TJ (2009) Admixture of ephedrine to offset side effects of propofol: a randomized, controlled trial. J Clin Anesth 21(1): 44-49.
[24]. Cheong MA, Kim KS, Choi WJ (2002) Ephedrine reduces the pain from propofol injection. Anesth. Analg 95(5): 1293-1296.
[25]. Agarwal A, Dhiraaj S, Raza M, Singhal V, Gupta D, et al. (2004) Pain during injection of propofol: the effect of prior administration of ephedrine. Anaesth Intensive Care 32(5): 657-660.
[26]. Hynynen M, Korttila K, Tammisto T (1985) Pain on i.v. injection of propofol (ICI 35 868) in emulsion formulation. Short communication. Acta Anaesthesiol Scand 29(6): 651-652.
[27]. King SY, Davis FM, Wells JE, Murchison DJ, Pryor PJ (1992) Lidocaine for the prevention of pain due to injection of propofol. Anesth Analg 74(2): 246-249.
[28]. Agarwal A, Ansari MF, Gupta D, Pandey R, Raza M, et al. (2004) Pretreatment with thiopental for prevention of pain associated with propofol injection. Anesth Analg 98(3): 683-686.
[29]. Agarwal A, Raza M, Dhiraaj S, Pandey R, Gupta D, et al. (2004) Pain during injection of propofol: the effect of prior administration of butorphanol. Anesth Analg 99(1): 117-119.
[30]. Smith I, White PF, Nathanson M, Gouldson R (1994) Propofol. An update on its clinical use. Anesthesiology 81(4): 1005-1043.
[31]. Galgon RE, Strube P, Heier J, Groth J, Wang S, et al. (2015) Magnesium sulfate with lidocaine for preventing propofol injection pain: a randomized, double-blind, placebo-controlled trial. J Anesth 29(2): 206-211.