Upsala Journal of Medical Sciences. 2014; 119: 338–342

informa
healthcare

ORIGINAL ARTICLE

Dexmedetomidine pretreatment alleviates propofol injection pain

LIANG HE[1], JUN-MEI XU[2], TAO HE[1], LEI LIU[2] & RONG ZHU[2]

[1]*Department of Anesthesiology, Loudi Central Hospital of University of South China, Loudi 417000, Hunan Province, China, and* [2]*Department of Anesthesiology, The Second Xiangya Hospital of Central South University, Changsha 410011, Hunan Province, China*

Abstract

Objective. The incidence of propofol injection pain during induction of general anesthesia varies from 28% to 90%. This prospective, randomized, double-blind, placebo-controlled study evaluated the effect of dexmedetomidine (DEX) for reducing the incidence and severity of propofol injection pain.

Methods. Patients undergoing elective surgical procedures were randomly allocated into seven groups of 30 patients each. Experimental treatments were intravenously administered over 10 min (total volume 10 mL) prior to intravenous propofol injection, as follows: group I, the control group, was given isotonic saline. Patients in groups II, III, and IV received DEX 0.25 μg/kg, 0.5 μg/kg, or 1.0 μg/kg, respectively, mixed with isotonic saline immediately before propofol injection. Patients in groups V, VI, and VII received DEX as above, but 5 minutes before propofol injection. Propofol consisted of 1% long-chain triglyceride propofol (2.5 mg/kg) injected at 1 mL/s.

Results. Median propofol injection pain score was 0.00 (IQR 0.00–3.00) in patients who received 1.0 μg/kg DEX 5 min before the propofol injection (group VII), and only 1 patient (of 30) in this group received a pain score >2. The median pain score and number of patients with pain scores >2 in group VII were both significantly less than in the control (group I; $p = 0.000$, both). There were no differences in either mean arterial pressure or heart rate at any time point after DEX injection among the groups.

Conclusions. Pretreatment with intravenous DEX 1 μg/kg 5 min prior to injection of long-chain triglyceride propofol is effective and safe in reducing the incidence and severity of pain due to propofol injection.

Key words: *Dexmedetomidine, injection pain, propofol*

Introduction

Propofol is widely administered during anesthetic induction. However, the pain of injection is undesirable, and may cause hand withdrawal and dislodging of the venous cannula (1,2). The incidence of propofol injection pain varies from 28% to 90% (3). Many methods have been used to relieve the pain of propofol injection, such as pretreatment with lidocaine, ondansetron, and methylene blue, but the effectiveness of these methods remains uncertain (4–8).

The alpha-2 adrenoceptor agonist clonidine was found to alleviate the pain of injected propofol effectively (9). Dexmedetomidine (DEX; Jiangsu Singch Pharmaceutical, Lianyungang, Jiangsu province, China) is also an alpha-2 adrenoceptor agonist, but is more selective than clonidine and has analgesic and sedative properties (2). DEX has been evaluated for reducing the incidence and intensity of propofol-induced pain, but reported results are inconsistent (1,2).

We hypothesized that DEX injection before propofol would reduce propofol injection pain. We also studied the effectiveness of different doses of DEX and the time interval between DEX and propofol injection.

Methods

After the approval of the Hospital Ethics Committee of Second Xiangya Hospital of Central South

Correspondence: Rong Zhu, MD, PhD, Department of Anesthesiology, The Second Xiangya Hospital of Central South University, Changsha 410011, Hunan Province, China. E-mail: zhurong0807@hotmail.com

(Received 29 April 2014; accepted 29 June 2014)

ISSN 0300-9734 print/ISSN 2000-1967 online
DOI: 10.3109/03009734.2014.941049

University, 210 patients, aged 18 to 60 years, ASA (American Society of Anesthesiologists) physical classification I to II, and scheduled for minor elective surgery, were included in the study. All patients signed a written informed consent form. Patients were excluded if they had a history of drug abuse, chronic use of any medication, presence of neurological or psychiatric diseases, uncontrolled hypertension, or renal or hepatic insufficiency. Patients were also excluded if they had a known history of hypersensitivity to the study drugs.

Before surgery (24 h) the patients did not receive analgesics or sedatives. Upon arrival to the operating room, a 20-gauge cannula was inserted into the dorsum of the patient's hand and connected to a T-connector for drug administration. Standard ASA monitors were attached, including non-invasive arterial pressure, electrocardiography, and pulse oximetry.

Patients were randomly allocated to seven groups (I–VII; $n = 30$ each) using a computer-generated table with random numbers (Table I). Patients in group I, the control group, were given 10 mL of isotonic saline intravenously over 10 min via a micro-infusion pump. Patients in groups II, III, and IV received DEX (200 μg/2 mL; Singch Pharm, Lianyungang, China) 0.25 μg/kg, 0.5 μg/kg, or 1.0 μg/kg, respectively, mixed with isotonic saline over 10 min (final volume, 10 mL), and then 1% long-chain triglyceride (LCT) propofol (propofol 1%; Fresenius Kabi, Beijing, Beijing municipality, China) was immediately injected intravenously. Patients in groups V, VI, and VII were given DEX 0.25 μg/kg, 0.5 μg/kg, or 1.0 μg/kg, respectively, mixed with isotonic saline, over 10 min (final volume, 10 mL). Five minutes later, 1% LCT propofol was injected. All groups received 2.5 mg/kg of 1% LCT propofol, injected at a rate of 1 mL/s.

All study medications were prepared in a 10-mL syringe that was covered with black tape by an anesthesiologist who was not involved in the study. All study drugs were maintained at room temperature and were used within 30 min after preparation. Another anesthesiologist, who was unaware of the group assignment, assessed the intensity of pain after propofol injections. The assessing anesthesiologist used a specially designed composite pain scale described by Rochette and colleagues (7) to evaluate the level of propofol injection pain. The pain score is based on assessments of patients' motor and verbal reactions, from the time of propofol injection to loss of consciousness (Table II). Pain is graded on a 0–6 scale, with a score >2 considered unacceptable (8). Mean arterial pressure (MAP) and heart rate (HR) were recorded immediately before injection of the study drug, and then every 5 min until propofol injection. All patients received 1% LCT propofol 2.5 mg/kg (Fresenius Kabi, Beijing, Beijing municipality, France) at a rate of 1 mL/s with different pretreatments.

For the design of this study, an estimation of the required minimum sample size was determined based on a previous report that pain caused by propofol injection was experienced by 70% of adults (8), and an assumption that a pretreatment with DEX would cause a 50% reduction in the injection pain. With a probability of less than 5% of making a type I error, (i.e. significance level $\alpha = 0.05$) and the probability of less than 10% of making a type II error (accepting a null hypothesis that is false, $\beta = 0.10$), we were required to enroll at least 24 patients in each group; we recruited 30 patients in each group.

Statistical analyses were performed using Statistical Product for Social Sciences (SPSS) software v. 18.0. The continuous normally distributed data (age and weight) are described as mean ± standard deviation and compared using one-way ANOVA. Changes in HR and BP over time were tested for normality using the mean ± standard deviation and then compared

Table I. Experimental treatment groups.

Group		Drug and dose	Time to propofol injection
Control	I	Isotonic saline	Immediately before
Treatment	II	DEX 0.25 μg/kg	Immediately before
Treatment	III	DEX 0.50 μg/kg	Immediately before
Treatment	IV	DEX 1.00 μg/kg	Immediately before
Treatment	V	DEX 0.25 μg/kg	5 minutes
Treatment	VI	DEX 0.50 μg/kg	5 minutes
Treatment	VII	DEX 1.00 μg/kg	5 minutes

Table II. Scoring system for propofol injection pain (8).

		Score
Motor events	No movement	0
	Slight hand withdrawal	1
	Marked withdrawal, rubbing, trying to tear off the line	2
	General restlessness	3
Verbalization scale	No vocalization	0
	Purposeless moaning	1
	Explicit protest	2
	Screams, cries	3
Total		0–6

Table III. Demographics of each group (n = 30, each)[a].

	Control	Treatment groups					
	I	II	III	IV	V	VI	VII
Age, y	37.5 ± 8.5	37.3 ± 9.8	36.7 ± 10.6	39.0 ± 10.9	42.6 ± 9.9	37.5 ± 8.5	37.5 ± 8.5
Male/female, *n*	17/13	15/15	14/16	16/14	17/13	18/12	17/13
Weight, kg	53.3 ± 5.1	52.6 ± 6.0	55.1 ± 6.1	56.2 ± 5.9	54.7 ± 5.5	55.3 ± 7.0	53.6 ± 6.4
ASA I/II, *n*	19/11	20/10	20/10	18/12	17/13	19/11	18/12

[a]All patients completed the present study. There were no statistically significant differences among the seven groups with regard to age, weight, gender, or ASA class ($p > 0.05$).

using two-way repeated measures ANOVA followed by *post hoc* Bonferroni correction. Pain scores are expressed as median (interquartile range (IQR)) and compared using the Kruskal–Wallis test. Categorical data such as gender, ASA status, and the number of patients having pain scores >2 were expressed as number, percent, or both, and were compared using the chi-square test or Fischer's exact test as appropriate. Whenever statistically significant discrepancies appeared, group I was compared separately with others to analyze the differences with the Bonferroni correction when appropriate. A corrected p value of 0.05/6 was considered significant.

Results

All patients completed the study. There were no statistically significant differences among the seven groups with regard to age, weight, gender, or ASA class ($p > 0.05$) (Table III).

There was no difference in median propofol injection pain scores among groups I (3.00 (IQR 2.00–4.00)), II, III, V, and VI. However, the median pain score of group IV (2.00 (IQR 0.00–3.00)) was significantly lower than that of group I ($p = 0.003$), and the median propofol injection pain score of group VII was 0.00 (IQR 0.00–3.00), which was significantly lower than that of group I ($p = 0.000$).

The incidence of pain scored >2 was 17/30 in the control group I (Figure 1). There were no differences in this incidence rate among groups I, II, III, IV, V, and VI. However, the incidence of pain scored >2 in group VII was 1/30, which was the lowest among all the groups and was significantly lower than that of group I ($p = 0.000$).

There were no differences between the groups as regards MAP and HR at any time point after DEX injection ($p > 0.05$, detailed data not shown).

Discussion

This prospective, randomized, double-blind, placebo-controlled study was carried out in order to evaluate the effect of DEX for reducing the incidence and severity of propofol injection pain. Besides the control group (given isotonic saline vehicle),

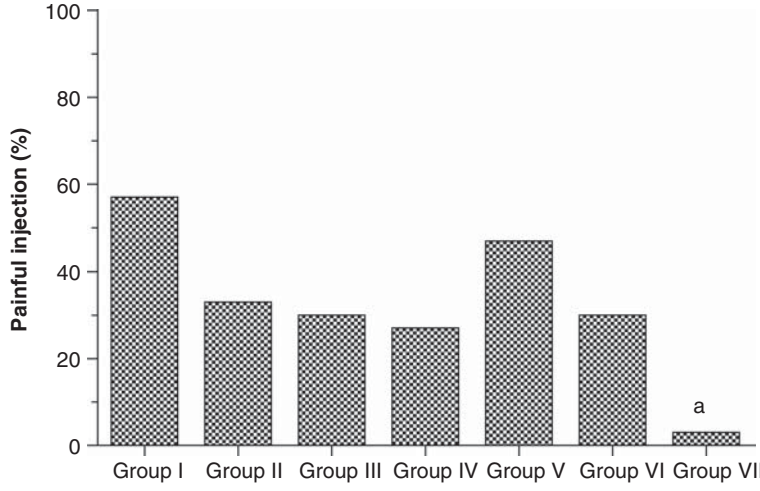

Figure 1. Percentages of patients experiencing pain scored >2. [a]Compared with group I, $p = 0.000$.

treatments consisted of 0.25, 0.5, or 1.0 μg/kg DEX, each delivered either immediately before or 5 minutes prior to LCT propofol injection. We found that pretreatment with 1 μg/kg DEX 5 min before propofol reduced the incidence and severity of pain due to propofol injection.

Various other pretreatments have also been evaluated, such as parecoxib with venous occlusion (10), tourniquet-controlled lidocaine (4), ondansetron (5), intravenous methylene blue (6), alfentanil and lidocaine (11), and a small dose of ketamine (12). A recent systematic review and meta-analysis showed that propofol infusion via the antecubital vein and pretreatment with lidocaine in conjunction with venous occlusion were the two most efficient interventions to reduce pain on injection of propofol (13). However, some unexpected adverse side effects have been associated with the two methods. For some patients undergoing short-time surgery with general anesthesia, propofol infusion via a hand vein is more convenient than via an antecubital vein. Tourniquets are the most common compressive devices for venous occlusion, but can cause tourniquet-induced hypertension or even ischemia-reperfusion injury (14–17). Therefore, venous occlusion before propofol injection may be contraindicated in patients with moderate to severe hypertension.

DEX has been demonstrated to have significant analgesic effects (18–23). Although the mechanisms of the analgesic effect of DEX have not been fully elucidated, many studies have shown that DEX acted by inhibiting the release of substance P from the dorsal horn of the spinal cord (24,25). A recent study reported that DEX effected strong analgesia through inhibition of the spinal ERK1/2 signaling pathway (26). These studies suggest that DEX has an important role in nociceptive transmission at the spinal level. Boehm et al. (27) demonstrated in rats that when DEX was administered intraperitoneally, the onset of profound analgesia was not reached until 5–10 min after the injection. So, when an infusion of DEX was administered, a time interval was allowed for equilibrium of DEX concentrations between the plasma and effect sites.

So far, there have been only a few studies investigating the inhibiting effect of DEX on the pain of propofol injection, and the question of its efficacy remains controversial. Ayoğlu et al. (1) demonstrated that pretreatment with 0.25 μg/kg DEX was not effective in reducing propofol injection pain (1). Yet the research done by Turan and his colleagues (2) contradicted this, showing that pretreatment with 0.25 μg/kg DEX decreased propofol injection pain as effectively as pretreatment with lidocaine 0.50 mg/kg (2).

Our study demonstrated that the reduction of propofol injection pain through pretreatment with DEX depended on the DEX dose, and 0.25 or 0.5 μg/kg DEX could not reduce the intensity and incidence of propofol injection pain. However, when the pretreatment dose of DEX was increased to 1.0 μg/kg, the incidence rate of pain scores >2 decreased from 17/30 to 1/30. Results of other studies demonstrating analgesic effects of DEX are in accord with ours. For example, Park et al. (28) demonstrated that DEX had a dose-dependent analgesic effect in rat models, and Ebert and colleagues (29) showed that increasing concentrations of DEX in humans resulted in a progressive increase in analgesic effect.

Another finding in our study was that the interval between DEX and propofol infusion influenced the analgesic effect of DEX on propofol injection pain. DEX was most effective when 1 μg/kg was injected 5 min before propofol injection. It is possible that, given this time interval, DEX concentrations at the spinal level increased enough to result in an analgesic effect.

Pretreatment with DEX has been reported to cause significant hemodynamic adverse side effects (30). However, a recent study showed that DEX at doses of 0.5 μg/kg or 1 μg/kg can be safely used preoperatively, with stable hemodynamics (31). Koroglu et al. (32) found that administration with a high dose of DEX (a bolus of 2–3 μg/kg over 10 min, or infusion of 1.5–3.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) provided adequate sedation in most of the children aged 1–7 years, without hemodynamic changes or adverse sequelae, and no specific treatment required. In our study, none of the patients who received DEX 0.25, 0.5, or 1 μg/kg infusion developed bradycardia or hypotension. Therefore, we believe 1 μg/kg DEX is safe for the general population.

In conclusion, 1 μg/kg DEX given intravenously 5 min before administration of intravenous LCT propofol (2.5 mg/kg) is an effective and safe way to reduce the intensity and incidence of propofol injection pain.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Ayoğlu H, Altunkaya H, Ozer Y, Yapakçi O, Cukdar G, Ozkoçak I. Does dexmedetomidine reduce the injection pain due to propofol and rocuronium? Eur J Anaesthesiol. 2007;24:541–5.
2. Turan A, Memis D, Kaya G, Karamanlioglu B. The prevention of pain from injection of propofol by dexmedetomidine and comparison with lidocaine. Can J Anaesth. 2005;52:548–9.

3. Koo SW, Cho SJ, Kim YK, Ham KD, Hwang JH. Small-dose ketamine reduces the pain of propofol injection. Anesth Analg. 2006;103:1444–7.
4. Walker BJ, Neal JM, Mulroy MF, Humsi JA, Bittner RC, McDonald SB. Lidocaine pretreatment with tourniquet versus lidocaine-propofol admixture for attenuating propofol injection pain: a randomized controlled trial. Reg Anesth Pain Med. 2011;36:41–5.
5. Ambesh SP, Dubey PK, Sinha PK. Ondansetron pretreatment to alleviate pain on propofol injection: a randomized, controlled, double-blinded study. Anesth Analg. 1999;89:197–9.
6. Salman AE, Salman MA, Saricaoglu F, Akinci SB, Aypar Ü. Pain on injection of propofol: a comparison of methylene blue and lidocaine. J Clin Anesth. 2011;23:270–4.
7. Rochette A, Hocquet AF, Dadure C, Boufroukh D, Raux O, Lubrano JF, et al. Avoiding propofol injection pain in children: a prospective, randomized, double-blinded, placebo-controlled study. Br J Anaesth. 2008;101:390–4.
8. Macario A, Weinger M, Truong P, Lee M. Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. Anesth Analg. 1999;88:1085–91.
9. Yoshikawa T, Wajima Z, Ogura A, Inoue T, Ogawa R. Orally administered clonidine significantly reduces pain during injection of propofol. Br J Anaesth. 2001;86:874–6.
10. Ghai B, Makkar JK, Bala I, Wig J. Effect of parecoxib pretreatment and venous occlusion on propofol injection pain: a prospective, randomized, double-blinded, placebo-controlled study. J Clin Anesth. 2010;22:88–92.
11. Kwak HJ, Min SK, Kim JS, Kim JY. Prevention of propofol-induced pain in children: combination of alfentanil and lidocaine vs alfentanil or lidocaine alone. Br J Anaesth. 2009;103: 410–12.
12. Zhao GY, Guo Y, Bao SM, Meng LX, Zhang LH. Prevention of propofol-induced pain in children: pretreatment with small doses of ketamine. J Clin Anesth. 2012;24:284–8.
13. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ. 2011;342:1–18.
14. Hughes SF, Hendricks BD, Edwards DR, Middleton JF. Tourniquet-applied upper limb orthopaedic surgery results in increased inflammation and changes to leukocyte, coagulation and endothelial markers. PLoS One. 2010;5:1184–6.
15. Lu Y, Zhang Y, Dong CS, Yu JM, Wong GT. Preoperative dexmedetomidine prevents tourniquet-induced hypertension in orthopedic operation during general anesthesia. Kaohsiung J Med Sci. 2013;29:271–4.
16. Lee DH, Jee DL, Kim SY, Kim JM, Lee HM. Magnesium sulphate attenuates tourniquet-induced hypertension and spinal c-fos mRNA expression: a comparison with ketamine. J Int Med Res. 2006;34:573–84.
17. Bostankolu E, Ayoglu H, Yurtlu S, Okyay RD, Erdogan G, Deniz Y, et al. Dexmedetomidine did not reduce the effects of tourniquet-induced ischemia-reperfusion injury during general anesthesia. Kaohsiung J Med Sci. 2013;29:75–81.
18. Cortinez LI, Hsu YW, Sum-Ping ST, Young C, Keifer JC, Macleod D, et al. Dexmedetomidine pharmacodynamics: Part II: crossover comparison of the analgesic effect of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology. 2004;101:1077–83.
19. Cheung CW, Ng KF, Liu J, Yuen MY, Ho MH, Irwin MG. Analgesic and sedative effects of intranasal dexmedetomidine in third molar surgery under local anaesthesia. Br J Anaesth. 2011;107:430–7.
20. Yuen VM, Irwin MG, Hui TW, Yuen MK, Lee LH. A double-blind, crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. Anesth Analg. 2007;105:374–80.
21. Solanki SL, Bharti N, Batra YK, Jain A, Kumar P, Nikhar SA. The analgesic effect of intrathecal dexmedetomidine or clonidine, with bupivacaine, in trauma patients undergoing lower limb surgery: a randomised, double-blind study. Anaesth Intensive Care. 2013;41:51–6.
22. Ohtani N, Yasui Y, Watanabe D, Kitamura M, Shoji K, Masaki E. Perioperative infusion of dexmedetomidine at a high dose reduces postoperative analgesic requirements: a randomized control trial. J Anesth. 2011;25:872–8.
23. Park HJ, Kim YH, Koh HJ, Park CS, Kang SH, Choi JH, et al. Analgesic effects of dexmedetomidine in vincristine-evoked painful neuropathic rats. J Korean Med Sci. 2012;27: 1411–17.
24. Erdivanli B, Altun M, Sezen OK, Colakoğlu SA. Anti-nociceptive, analgesic and pathohistological effects of intrathecal dexmedetomidine and bupivacaine in rats. Rev Bras Anestesiol. 2013;63:183–7.
25. Jackson KC 3rd, Wohlt P, Fine PG. Dexmedetomidine: a novel analgesic with palliative medicine potential. J Pain Palliat Care Pharmacother. 2006;20:23–7.
26. Zhang H, Zhou F, Li C, Kong M, Liu H, Zhang P, et al. Molecular mechanisms underlying the analgesic property of intrathecal dexmedetomidine and its neurotoxicity evaluation: an in vivo and in vitro experimental study. PLoS One. 2013;8: 1–8.
27. Boehm CA, Carney EL, Tallarida RJ, Wilson RP. Midazolam enhances the analgesic properties of dexmedetomidine in the rat. Vet Anaesth Analg. 2010;37:550–6.
28. Park JK, Cheong SH, Lee KM, Lim SH, Lee JH, Cho K, et al. Does dexmedetomidine reduce postoperative pain after laparoscopic cholecystectomy with multimodal analgesia? Korean J Anesthesiol. 2012;63:436–40.
29. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000;93:382–94.
30. Arcangeli A, D'Alò C, Gaspari R. Dexmedetomidine use in general anaesthesia. Curr Drug Targets. 2009;10:687–95.
31. He L, Xu JM, Dai RP. Dexmedetomidine reduces the incidence of fentanyl-induced cough: a double-blind, randomized, and placebo-controlled study. Ups J Med Sci. 2012;117: 18–21.
32. Koroglu A, Demirbilek S, Teksan H, Sagir O, But AK, Ersoy MO. Sedative, haemodynamic and respiratory effects of dexmedetomidine in children undergoing magnetic resonance imaging examination: preliminary results. Br J Anaesth. 2005;94:821–4.