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Original Article

Lidocaine administration alleviates propofol injection pain

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Abstract: Objective: This study aimed to analyze how to ease propofol injection pain by different administration approaches of lidocaine. Methods: A total of 80 anaesthetized patients in our hospital were divided into four groups, including control group (CG, administered with normal saline), normal saline + propofol group (NPG), lidocaine group (LG), and lidocaine + propofol group (LPG), with 20 patients in each group. The effects of easement of pain were compared among the groups. Results: No statistical difference was found amongst the four groups in terms of heart rate (HR) and SPO2 before, during and after injection as well as mild, moderate and severe pain rates ($P>0.05$). When evaluated by the 4-point method and visual analogue score (VAS), the incidence of injection pain was significantly lower, and the painless rate was significantly higher in the LG and LPG ($P<0.05$), but not statistically different between LG and LPG, CG and NPG ($P>0.05$). The VAS scores yielded by patients in the LG and LPG were lower than the CG's and NPG's ($P<0.05$), but not statistically different between LG and LPG, CG and NPG ($P>0.05$). The incidence of adverse reaction was 10.00% in the LG and 15.00% in the LPG ($P>0.05$). Conclusion: Lidocaine pre-injection and lidocaine+propofol mixed injection are similarly effective in easing propofol injection pain, while injection with normal saline is ineffective.

Keywords: Lidocaine, administration approach, propofol, injection pain, pharmacological action

Introduction

Propofol is a short-acting intravenous anesthetic widely used inside and outside of China. It safely anaesthetizes patients soon after medication and patients can wake up quickly and stably after surgery with all functions well recovered and without serious adverse reactions [1].

However, propofol has disadvantages in clinical application, typically pain to various degrees in the peripheral local vein or along the blood vessel after intravenous injection, which last about 20 seconds [2]. It is found that the incidence of injection pain after intravenous injection of propofol is over 28%, even up to 90%, and may further rise when it is intravenously injected at the superficial opisthenar vein [3]. Although the degree of injection pain varies, it will have adverse psychological effects on patients, and lead to a variety of adverse emotions, which affect patients' compliance and satisfaction with medical activities [4].

At present, how to reduce the pain arising from intravenous injection of propofol has gradually become a key focus. A large number of domestic and foreign studies have tried a variety of methods, including increasing or reducing the drug temperature, diluting the concentration of propofol, adjusting the speed of intravenous injection, blocking the vein, and selecting bulky veins for injection [5-7]. There are also some studies trying to reduce pain with preventive drugs, such as opioids, non-steroidal drugs, or the highly recognized option of combination with lidocaine [8, 9]. In a study, the best ways to reduce the propofol injection pain were found with lidocaine [10], especially when it was injected at the median cubital vein [11]. In previous studies, the treatment of injection pain relief was mostly with the single use of different doses of lidocaine. When the dose of lidocaine reaches 1.5 mg/kg, the conclusion that lidocaine can relieve injection pain through local anesthesia and central analgesia has been confirmed. In fact, there are different specific methods of lidocaine injection used to prevent

propofol injection pain, but there is no consensus on which method is most effective. In this study, a new administration method of 1 mg/kg lidocaine +0.5 mg/kg propofol was proposed, and it is believed that the dosage of lidocaine can be further reduced by increasing the use of propofol compared with previous studies; and here four different methods were compared and analyzed to find the most effective one to reduce propofol injection pain.

Materials and methods

Materials

A total of 80 patients anaesthetized with propofol from January 2019 to December 2019 in Suzhou Kowloon Hospital were included, and randomized into four groups (n=20 respectively), i.e., the Control Group (CG), the normal saline+propofol group (NPG), the lidocaine group (LG) and the lidocaine+propofol group (LPG). Inclusion criteria: patients aged under 18 years, and BMI between 18-30 kg/m^2 were included for a surgery under general anesthesia. They were informed of the study content and signed an informed consent in person or by their direct relatives; the study was approved by the Ethics Committee of Suzhou Kowloon Hospital, Shanghai Jiaotong University School of Medicine. Exclusion criteria: patients allergic to the drug in the studies, demanding emergency surgical treatment or having disorders in their mentality or speech, or severe dysfunctions of liver and kidney, or difficulties in venous channel puncturing were excluded.

Methods

Prior to anesthesia, all patients were prohibited from food and water, and subjected to routine ECG and Bispectral Index (BIS) monitoring. A venous channel was opened on the bulky superficial opisthenar vein, into which, a 22G detaining needle was inserted. During the surgery, patients were provided with oxygen through a mask with a flow rate around 5 L/min.

Before anesthesia induction, 1 mg/kg lidocaine (specification: 2 ml:40 mg:10 pcs., GYZ Zi No.: H11020558, producer: Beijing Yokon Pharmaceutical Co., Ltd.) was administered to patients in the LPG in combination with 0.5 mg/kg propofol (specification: 20 ml:0.2 g, GYZ Zi No.: J20080023, producer: Fresenius Kabi AB); but was replaced by normal saline equal in volume for patients in the NPG; patients in the LG were intravenously injected with 1 mg/kg lidocaine; while for those in the CG, only normal saline equal in volume was provided. With a flowrate of 1 ml/2.5 s, 30 s after residual propofol injection all patients in the four groups were provided with 0.2 mg/kg Cisatracurium (specification: 10 mg, GYZ Zi No.: H20060869, producer: Jiangsu Hengrui Medicine Holdings Limited), 0.4 ug/kg sulfentanyl (specification: 1 ml:50 μg, GYZ Zi No.: H2005-4172, producer: Yichang Humanwell Pharmaceutical Co., Ltd.), and 0.04 mg/kg midazolam (specification: 2 ml:10 mg, GYZ Zi No.: H20-031037, producer: Jiangsu Nhwa Pharmaceutical Co., Ltd.). At 3 min after injection, mechanical ventilation was performed with trachea cannula. The surgery and treatment were conducted by the same metical team and the same methods.

Observation indices

General materials: the four groups were compared for gender, age, height, BMI, BIS, and ASA (American Society of Anesthesiologists) grades.

HR and SPO2: HR and SPO2 were measured by an aneroid electronic sphygmomanometer and a fingertip photoelectric sensor respectively before, during and after injection.

A 4-point assessment method was used for injection pain [12]: patients were given a score of 0 for no pain or discomfort, 1 for mild pain at the arms but no reactions during physical activities, 2 for moderate pain at the arms or when the waist moves mildly or complaints by the patients when they were not inquired about by the doctor, 3 for severe pains actively reported by patients or read from patients' painful expression or unconscious retraction of arms or tears running down their face due to pain. The evaluation was performed during administration. Patients with a score between 1 and 3 were suffering from injection pain.

Injection pain evaluation by VAS: the Visual Analogue Score (VAS) [13] was used to evaluate patients' memory of injection pain immediately after they woke up from the surgery. It was a vernier with 11 scales from 0 (no pain) to 10 (the worst possible pain) to reflect the pain intensity. Patients repositioned the vernier to the corresponding scale when recalling how

Table 1. Intergroup comparison of basic materials ($\bar{x}$ ± s)/[n (%)]

Material		CG (n=20)	NPG (n=20)	LG (n=20)	LPG (n=20)	t/X^2	*P*
Gender	Male	12 (60.00)	11 (55.00)	9 (45.00)	10 (50.00)	1.573	0.149
	Female	8 (40.00)	9 (45.00)	11 (55.00)	10 (50.00)		
Age (y)		38.45±15.69	40.91±16.32	37.49±14.13	41.23±16.86	0.257	0.134
Height (cm)		160.28±10.49	158.79±10.39	165.42±12.75	162.38±11.72	0.859	0.421
BMI(kg/m^2)		23.62±3.28	23.19±3.45	22.18±3.81	22.49±3.64	1.035	0.715
Initial BIS		96.83±1.16	95.78±1.23	96.12±1.07	97.31±1.42	0.857	0.164
ASA grade	I	13 (65.00)	11 (55.00)	9 (45.00)	12 (60.00)	1.827	0.639
	II	7 (35.00)	9 (45.00)	11 (55.00)	8 (40.00)		

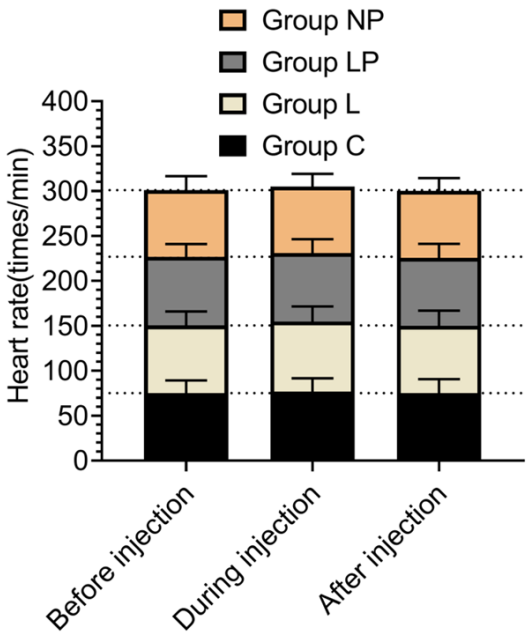

Figure 1. Intergroup comparison of HR. No statistical difference was found amongst the four groups for HR before, during and after injection (P>0.05).

they felt with the worst injection pains. The results were conformed and documented by the medical staff. Patients with a score between 1 and 10 were suffering from injection pain.

Adverse reactions related to lidocaine: the incidences of lip and tongue numbness, tinnitus, dizziness, nausea and vomiting, and drowsiness were recorded and compared between the LG and LPG after injection with lidocaine.

Statistical analysis

Statistical analysis was performed with SPSS 22.0. In case of numerical data, it was expressed as Mean ± Standard Deviation, comparison studies were carried out through independent-samples *t* test. In the case of nominal data expressed as [n (%)], comparison studies were carried out through chi-squared test for intergroup comparison. Intragroup comparison at multiple points was performed through ANVOA analysis and F test. For all statistical comparisons, significance was defined as P< 0.05.

Results

Basic materials

The four groups were not statistically different in the proportions of male and female patients, proportions of patients at ASA grade III, average age, height, BMI and initial BIS (P>0.05) (**Table 1**).

HR and SPO2

The HR and SPO2 before, during and after injection were (75.26±10.19) times/min and (95.46±2.18)%, (76.23±11.28) times/min and (95.86±1.29)%, (75.13±11.39) times/min and (95.36±1.03)% in the CG; (74.19±11.43) times/min and (96.02±1.96)%, (74.18±10.67) times/min and (97.02±1.55)%, (74.68±10.53) times/min and (96.27±1.08)% in the NPG; (75.18±11.27) times/min and (96.31±1.47)%, (77.91±12.47) times/min and (96.37±1.17)%, (74.89±12.48) times/min, (96.05±1.04)% in the LG; and (76.49±10.18) times/min and (95.76±1.83)%, (76.24±11.22) times/min and (94.38±1.41)%, (75.63±11.84) times/min and (95.09±1.07)% in the LPG (P>0.05) (**Figures 1** and **2**).

Incidence of injection pain

Evaluated by the 4-point method and VAS method, the incidences of injection pain were significantly lower in the LG and LPG (P<0.05),

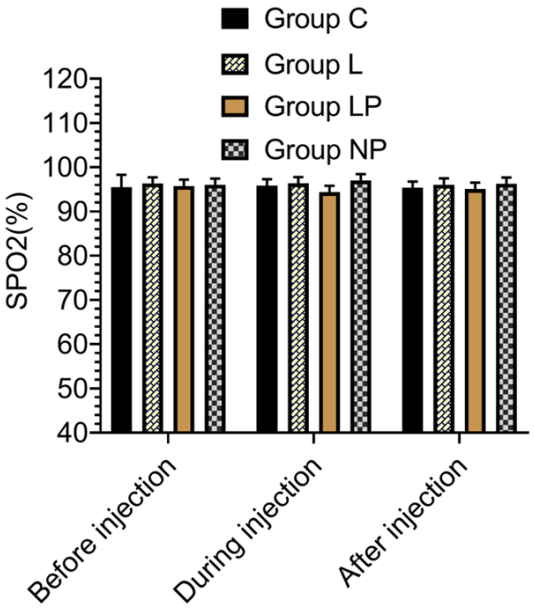

Figure 2. Intergroup comparison of SPO2. No statistical difference was found amongst the four groups for SPO2 before, during and after injection (P>0.05).

Table 2. Intergroup comparison of incidence of injection pain [n (%)]

Group	n	4-point method	VAS
CG	20	13 (65.00)	15 (75.00)
NPG	20	12 (60.00)	13 (65.00)
LG	20	4 (20.00)	5 (25.00)
LPG	20	3 (15.00)	3 (15.00)

but not statistically different between the LG and the LPG, the CG and the NPG (P>0.05) (**Table 2**).

Results of 4-point method for injection pain

Patients reporting no pain, mild pain, moderate pain, and severe pain were 7, 2, 3 and 1 respectively, in the CG; 8, 3, 3 and 2 respectively, in the NPG; 16, 2, 2 and 0 respectively, in the LG; and 17, 2, 1 and 0 in the LPG. The painless rates of LG and LPG were significantly higher than that of the CG and NPG. No statistical difference was found between LG and LPG (P>0.05), CG and NPG (P>0.05) for painless rate, and amongst the four groups for mild, moderate and severe pain rates (P>0.05) (**Table 3** and **Figure 3**).

Results of VAS for injection pain

The VAS was (6.65±2.73) for the 15 patients with injection pain in the CG, (5.84±2.67) for the 13 patients with injection pain in the NPG, (3.28±1.24) for the 5 patients with injection pain in the LG, and (3.12±1.16) for the 3 patients with injection pain in the LPG. The VASs obtained by patients in the LG and LPG were significantly lower than that of the CG and NPG (P<0.05), while LG and LPG, CG and NPG were not statistically different (P>0.05) (**Figure 4**).

Adverse reactions related to lidocaine

As lidocaine was not used in the CG and NPG, adverse reactions were only assessed for patients in the LG and the LPG, and the incidence was 10.00% (2/20) and 15.00% (3/20), respectively (P>0.05) (**Table 4**).

Discussion

In terms of pharmacology, propofol can activate GABA receptors directly, inhibit NMDA receptors, and regulate calcium influx through slowing down the calcium channels [14]. It has been found that GABA is the most important inhibitory neurotransmitter in the central nervous system, and propofol can effectively reduce the severity of brain injury after local ischemia through its effects on GABA receptors [15]. Along with its extensive clinical application, propofol has been gradually reported with other effects besides anesthetics, including antianxiety and antioxidation, stopping vomiting, regulating immune activity, and inhibiting inflammatory levels, etc. [16, 17]. Studies have also found that propofol can regulate the formation of nephroprotection proteins and ultimately protect the nerves through inhibiting inflammatory response and apoptosis [18].

Injection pain is a common adverse reaction after intravenous injection of propofol. Regardless of its transiency or mildness in most cases, a small number of patients with low pain thresholds or high sensitivity to stimulation will have individually different adverse effects due to injection pain and become anxious, nervous, or even struggle during injection, which may affect the whole process, effectiveness and safety. According to studies, injection pain exists as the worst memory for anesthetized patients before they go to sleep, and will have an impact on the hemodynamics, anesthesia effect and safety [19]. Lidocaine is widely considered as an effective, affordable, quickly responding and structurally stable amide local

Table 3. Results of 4-point method for injection pain [n (%)]

Group	n	No pain	Mild pain	Moderate pain	Severe pain
CG	20	7 (35.00)	2 (10.00)	3 (15.00)	1 (5.00)
NPG	20	8 (40.00)	3 (15.00)	3 (15.00)	2 (10.00)
LG	20	16 (80.00)	2 (10.00)	2 (10.00)	0 (0.00)
LPG	20	17 (85.00)	2 (10.00)	1 (5.00)	0 (0.00)

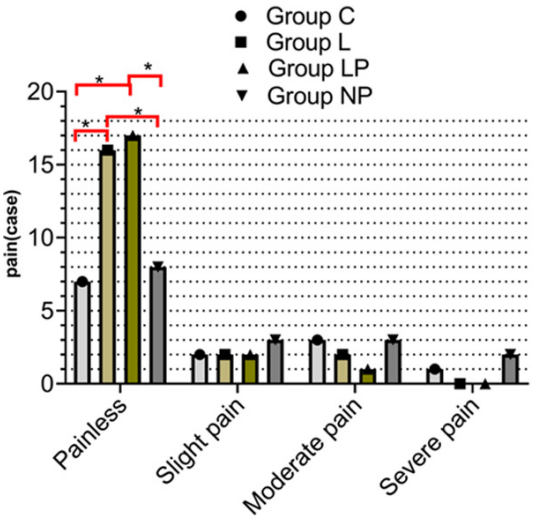

Figure 3. Intergroup comparison of pains evaluated by the 4-point method. The four groups were not statistically different in the number of patients with mild, moderate and severe pains (P>0.05); the number of patients with no pain were significantly higher in the LG and the LPG as compared with that of the CG and NPG (P<0.05). *P<0.05 for intergroup comparison.

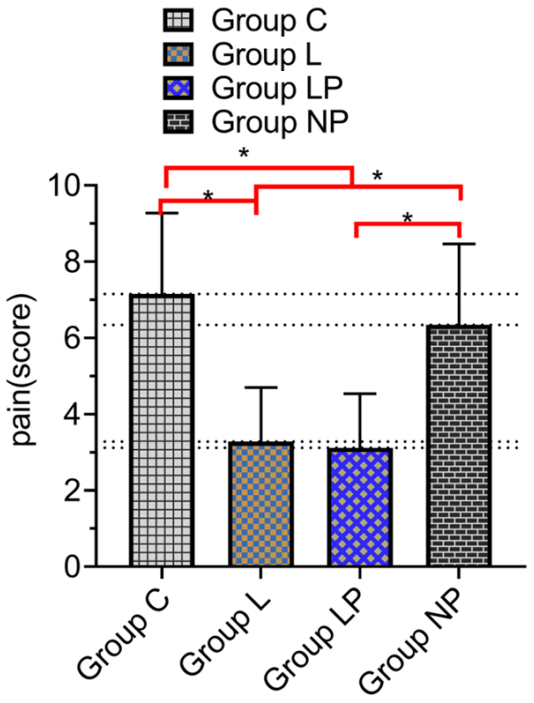

Figure 4. Intergroup comparison of VAS. The VASs were significantly lower in the LG and LPG when compared with that of the CG and the NPG (P<0.05), but not statistically different between the NPG and the CG, the LPG and the LG (P>0.05). *P<0.05 for intergroup comparison.

anesthetic to alleviate the propofol injection pain, and is seldom reported with allergic reaction. Instead, it is highly safe and can be discharged from the body quickly through the metabolism [20].

This study included four groups for comparative analysis. All injections were done through the opisthenar veins in consideration of its higher incidence of injection pain according a number of studies [21] and to facilitate observation and analysis. Furthermore, the propofol was intravenously dripped under room temperature and at a constant speed to effectively eliminate the interference from injection speed, temperature and angiotasis, and to ensure the reliability of results. A 30 s interval was kept between intravenous injection of propofol and lidocaine because the period from 15 s to 30 s after lidocaine injection is the optimal time window for propofol injection according to previous studies [22]. Besides, the lidocaine was used at a dose of 1.0 mg/kg, which was significantly lower than the toxic dose of 5 ug/ml (blood concentration), in order to ensure drug safety. No statistical difference was observed amongst the four groups in HR and SPO2 before, during and after injection, and the incidence of adverse reactions related to lidocaine was 10.00% in the LG and 15.00% in the LPG (P>0.05), indicating that patients' vital signs were not affected whatever the drug administration approach was, and drug safety was guaranteed if propofol was combined with lidocaine. The stable maintenance of the patient's vital signs during the peri-injection period was due to the satisfactory effect of anesthesia. Although, if the patient felt pain during the peri-anaesthesia period, the pain threshold was increased under the anesthesia effect, but the level was not reached affecting the heart rate and other signs. The study also reported lower incidences of injection pain and VASs in the LG and LPG as compared with that of the CG and the NPG (P<0.05) but no statistical difference between the LP and the LPG, the CG and the NPG

Table 4. Comparison of incidences of adverse reactions between LG and LPG [n (%)]

Group	Lips and tongue numbness	Tinnitus	Dizziness	Drowsiness	Nausea and vomiting	Total incidence
LG (n=20)	0 (0.00)	0 (0.00)	1 (5.00)	0 (0.00)	1 (5.00)	2 (10.00)
LPG (n=20)	1 (5.00)	0 (0.00)	0 (0.00)	1 (5.00)	1 (5.00)	3 (15.00)
X^2						0.229
P						0.633

(P>0.05), indicating that lidocaine can effectively control the occurrence and severity of propofol injection pain when injected in advance or with propofol, while no satisfactory effects were observed when normal saline was applied independently or with propofol. According to the 4-point method, the four groups had differences in mild, moderate and severe pain rates, which however was not statistical (P>0.05) possibly due to the limited number of samples in this study. The difference amongst the four groups in the painless rate revealed the preventative role of lidocaine in propofol injection pain. The alleviation in injection pain when propofol was mixed with lidocaine can be explained. After administration, propofol can activate the Kallikrein system, dilate and make vessels more transparent. The addition of lidocaine makes the process of penetrating through the vascular wall much easier so that propofol can reach the free nerve endings to block pain [23]. According to some studies, the mixture of propofol and lidocaine managed to safely maintain stable properties for 6h without the risk of pulmonary embolism [24]. However, some studies also reported that the stability of propofol was compromised by lidocaine, and the risk of pulmonary embolism may rise [25]. To make more definitive conclusions, future studies will be more comprehensive and detailed.

In conclusion, similar alleviation effects of propofol injection pain can be achieved by lidocaine pre-injection or mixture with propofol, while normal saline doesn't work. This study proved that lidocaine can alleviate propofol injection pain regardless of some defects, including limited number of samples and insufficient intensive study of the action mechanism of lidocaine, which will be solved in the future studies.

Disclosure of conflict of interest

None.

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