Journal of Anesthesia (2019) 33:311–316
https://doi.org/10.1007/s00540-019-02628-2

ORIGINAL ARTICLE

The analgesic efficacy and duration of lidocaine on vascular pain induced by hypertonic saline infusion: a double-blinded, randomized control trial

Zhiping Song[1] · **Zhen Liu**[1] · **Yang Zhang**[1]

Received: 7 November 2018 / Accepted: 26 February 2019 / Published online: 5 March 2019

Abstract

Purpose To determine the analgesic efficacy and analgesic duration of lidocaine 20 mg and 40 mg on eliminating the vascular pain associated with hypertonic saline infusion.

Method Patients who complained pain during infusion of hypertonic saline were randomized into three groups. They received normal saline (Group C), or lidocaine 20 mg (Group L20), or lidocaine 40 mg (Group L40). An electronic stopwatch was used to record the time to onset ($T1$) and the time to termination ($T2$) of the analgesic effect, and the analgesic duration (AD) was calculated as $T2-T1$.

Results The incidence of pain elimination was significantly higher in both of the lidocaine groups (83.3 and 56.1% in Groups L40 and L20, respectively) than in the saline group (16.3%). Furthermore, lidocaine 40 mg was significantly more effective than 20 mg in eliminating the pain. The analgesic duration was significantly longer in Group L40 than in Group L20 (211.4 ± 50.2 vs. 130.3 ± 39.5 s, $P < 0.001$) and Group C (211.4 ± 50.2 vs. 45.1 ± 14.5 s, $P < 0.001$), and the analgesic duration in Group L20 was significantly longer than in Group C ($P < 0.001$). The incidence of transient tinnitus/dizziness was significantly higher in Group L40 than in Group L20 (19.0 vs. 2.4%, $P < 0.05$).

Conclusion A single bolus of Lidocaine was effective in eliminating the pain induced by hypertonic saline infusion, but just for a short period of time. Lidocaine (without venous occlusion) only provides a short analgesic duration for local vein.

Keywords Lidocaine · Vascular pain · Analgesic duration

Introduction

Vascular pain during the induction period of general anesthesia induced by injection of propofol, rocuronium, etomidate, etc. brings not only pain but also danger to the patients [1]. Pre-injection of lidocaine (without venous occlusion) is a commonly used method to relieve this pain [2, 3]. Lots of studies have confirmed the efficacy of this strategy [4, 5]. However, during peri-anesthesia period, there are other solutions that also evoke local vascular pain. Hypertonic saline is one of them.

In anesthetic practice, fluid preloading before spinal anesthesia is a common method to maintain hemodynamic stability and to prevent hypotension. Hypertonic saline is one alternative to colloid solution or isotonic crystal solution used for preloading. Due to its high osmolality, infusion of hypertonic saline via peripheral vein often causes vascular pain. Usually, after the initiation of infusion, there is a short term of latency and then pain is induced. The intensity of pain is relatively stable if the osmolar concentration present in local vein is stable [6]. Patients may experience the sensation of stinging and compression during infusion of hypertonic saline which is similar to the sensation following the injection of propofol or rocuronium.

Therefore, we hypothesized that a single bolus of lidocaine could also eliminate vascular pain evoked by hypertonic saline infusion. Unlike propofol and rocuronium, hypertonic saline itself has neither hypnotic nor muscle relaxant effect, the vascular pain induced by continuous infusion of hypertonic saline can be used not only for

✉ Zhiping Song
pig.12345@163.com

[1] Department of Anesthesia, First Affiliated Hospital of Nanchang University, No. 17 Yongwaizheng Street, Nanchang, Jiangxi, China

observation of the analgesic efficacy of lidocaine, but also for the determination of its analgesic duration.

The purpose of this study was to determine the analgesic efficacy and analgesic duration of lidocaine 20 mg and 40 mg on eliminating the vascular pain associated with hypertonic saline infusion.

Materials and methods

This study was approved by China Ethics Committee of Registering Clinical Trails (ChiECRCT-20170093), and was registered on the Chinese Clinical Trial Registry (ChiCTR-IOR-17013405). All patients signed an informed written consent form. Inclusion criteria: aged 18–65, American Society of Anesthesiologist (ASA) classes I and II, elective surgery requiring spinal anesthesia, complained vascular pain during infusion of hypertonic saline. Patients with chronic pain, abnormal sensation, neurologic deficits, and history of hypersensitivity to the study drugs were excluded.

A total of 135 patients were randomly assigned to one of the three groups. The control group (Group C) received 2 ml of normal saline intravenously, the Group L20 received lidocaine 20 mg (1%, 2 ml), and the Group L40 received lidocaine 40 mg (2%, 2 ml).

After arrival in the anesthesia preparation room, the patients were monitored, such as ECG, pulse oxygen saturation, and blood pressure. A 22-gauge i.v. cannula was inserted into the vein on the dorsum of the hand. A total of 200 ml hypertonic saline (4%) was used for preloading, and the infusion speed controlled by the electronic pump was 10 ml/min. Anesthesiologist asked the patient to evaluate the pain score (verbal rating scale [VRS]) during the first 2 min of the infusion. The grading criteria of VRS [7] were as follows: 0 = no pain experienced, 1 = mild pain or soreness, 2 = moderate pain, and 3 = severe pain associated with grimacing. Patients with pain score = 0 were excluded. Those subjects with pain score ≧ 1 were allocated randomly to one of the three groups. A resident of the research team opened an opaque envelope containing random allocating information, passed a pre-prepared syringe filled with 2 ml of test solution to the anesthesiologist, and then the resident left the anesthesia preparation room. Therefore, the medical staff and patients in the anesthesia preparation room were blind to the allocation.

An electronic stopwatch was used to record the analgesic effect and duration of the test solution. Immediately after the injection of the 2 ml solution, the stopwatch was activated, and then the patients pressed the "split" button according to their perception of the change in the pain. If the vascular pain was not completely eliminated, they should not to press the button. If the pain was completely eliminated, then pressed the "split" button, and the time recorded on the stopwatch was noted as $T1$ (the time to onset of analgesia after lidocaine); later, if the local pain was felt again, then pressed the "split" button again, and time recorded on the stopwatch was noted as $T2$ (the time to termination of analgesia after lidocaine). Thus, the analgesic duration (AD) could be calculated as $T2 - T1$. The rules for pressing the "split" button were explained to the patients at the day before the surgery, and again when they were delivered into the anesthesia preparation room.

The anesthesiologist reminded the patients with standard words "press the stopwatch if the pain totally disappear", then injected the 2 ml solution into the vein through the nearest port. Immediately after that, another assistant activated the electronic stopwatch, then the patients could press the "split" button according to the rules. Once the patients pressed the button for the first time, the assistant reminded them with standard words "press the button if feels pain again". Previous studies [4, 8, 9] as well as our pilot study showed that lidocaine acted immediately or 10–30 s after injection for reducing local venous pain. Thus, a 60-s time window was chosen for the observation of the first press. The observation was completed if the subjects did not press the button in 60 s after the test solution, or if the subjects pressed the button for the second time, or if the preloading with 200 ml hypertonic saline was accomplished. The adverse events were also observed and recorded in our study.

In our pilot study, the rate of pain total elimination was 50% and 80% in Group L20 and Group L40, respectively. Sample size was selected to detect the difference between the two groups for a Type I error of 0.05 and a power of 0.8. At least 39 subjects would be needed in each group. Therefore, the number of subjects in each group was 45 on assumption of dropout. Statistical analyses were performed using SPSS for Windows software program version 24 (SPSS, Chicago, IL, USA). Data were expressed as mean ± SD, or number of patients (% frequency), or median (range), as appropriate. Demographic and clinical characteristics among the groups were compared using one-way analysis of variance (ANOVA) or the Kruskal–Wallis H test. The incidence of pain elimination was compared using a chi-square analysis with Bonferroni method. $T1$, $T2$ and AD among the three groups were analyzed by one-way ANOVA, and multiple comparisons among the groups were performed by LSD post hoc procedure. The incidence of adverse events associated with lidocaine among the two treatment groups were compared using chi-square analysis or Fisher's exact test as appropriate. The statistical significance was defined as $P < 0.05$.

Results

Subject enrollment and analysis are illustrated in Fig. 1. With written consent, 166 subjects were enrolled in this study. Thirty-one subjects were excluded before

randomization for two reasons, including failure in inserting i.v. cannula on the dorsum of hand, pain score = 0 during the infusion of the hypertonic saline. As such, a total of 135 patients were randomized to the three groups. Five subjects did not receive the assigned intervention because the study drug or personnel was unavailable. Four subjects

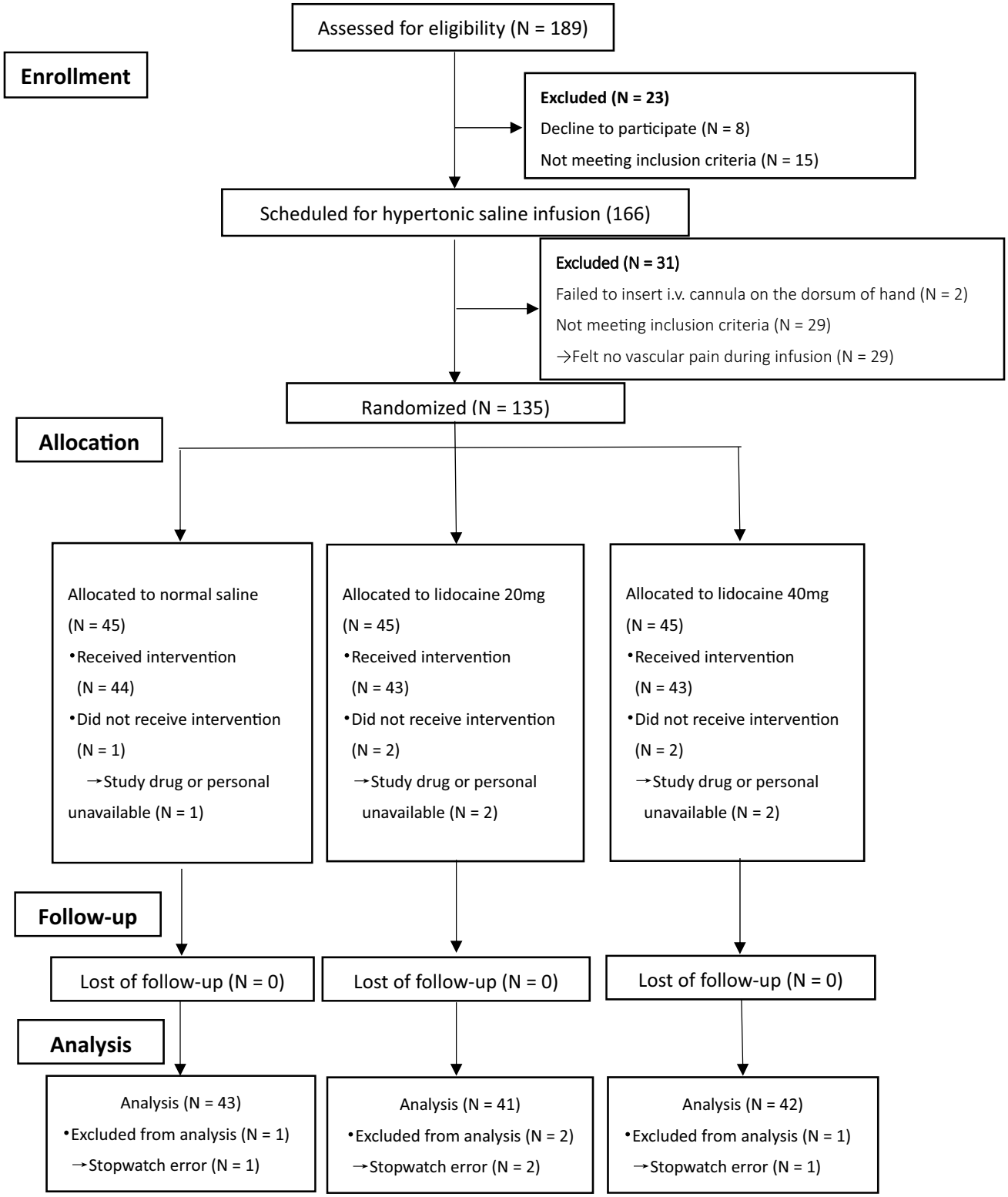

Fig. 1 Study and data analysis flowchart

Table 1 Demographic and clinical characteristics of patients

	Group C ($n=43$)	Group L20 ($n=41$)	Group L40 ($n=42$)	P value
Age (years)	43.3 ± 7.9	46.8 ± 7.7	45.2 ± 7.6	0.116
Weight (kg)	57.3 ± 8.1	56.2 ± 7.4	55.3 ± 8.7	0.497
Height (cm)	160.7 ± 6.9	163.2 ± 6.1	163.2 ± 5.6	0.115
Gender (M/F)	19/24	22/19	19/23	0.638
ASA				0.732
I	33	32	35	
II	10	9	7	
Pain score				0.409
1	33	26	31	
2	8	13	9	
3	2	2	2	

Data are presented as mean ± SD or as number of patients

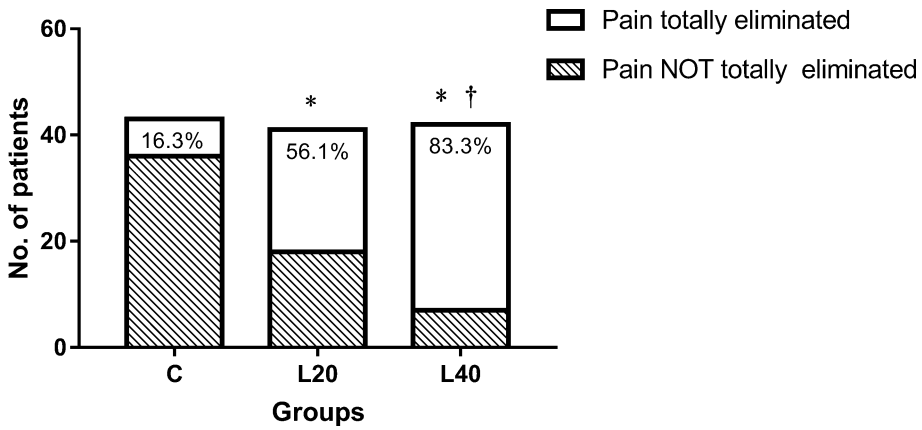

Fig. 2 The incidence of pain elimination in each group. *$P<0.05$ compared with Group C. †$P<0.05$ compared with Group L20

were excluded from analysis due to faulty operation on the stopwatch. Finally, 126 subjects received the assigned intervention and were included in the analysis.

The three groups were comparable with respect to age, weight, height, gender, ASA physical status, and pain scores (Table 1).

The number of patients who pressed the "split" button was 7, 23 and 35 in Group C, Group L20 and Group L40, respectively. All the patients who pressed the button pressed it twice. The incidence of pain elimination of lidocaine groups was significantly higher than that of Group C. Lidocaine 40 mg was significantly more effective than lidocaine 20 mg (Fig. 2).

The data of $T1$, $T2$ and AD are illustrated in Table 2. $T1$ in Group L40 was significantly earlier than that in Group C and Group L20. $T2$ in lidocaine groups was significantly later than that in Group C, and $T2$ in Group L40 was significantly later than that in Group L20. Additionally, AD in the two treatment groups was significantly longer than that in Group C, and lidocaine 40 mg provided significantly longer AD than lidocaine 20 mg.

Table 2 $T1$, $T2$, and AD of each group in those patients with pain eliminated

	Group C ($n=7$)	Group L20 ($n=23$)	Group L40 ($n=35$)
$T1$ (s)	9.4 ± 1.4	8.8 ± 1.8	7.7 ± 2.0*,†
$T2$ (s)	54.6 ± 14.1	139.1 ± 39.0§	219.1 ± 49.8§,‡
AD (s)	45.1 ± 14.5	130.3 ± 39.5§	211.4 ± 50.2§,‡

Data are expressed as mean ± SD

$T1$ time to onset of analgesia, $T2$ time to termination of analgesia, AD analgesic duration

*$P<0.05$ compared with Group C

§$P<0.001$ compared with Group C

†$P<0.05$ compared with Group L20

‡$P<0.001$ compared with Group L20

The adverse events were also observed and recorded in our study. One patient in Group C was observed to have transient redness on the local vein during the infusion of the hypertonic saline. A total of eight (19.0%) subjects in Group L40 complained transient tinnitus or/and dizziness after injection of lidocaine, which was significantly

($P < 0.05$) more than that in Group L20 [only one (2.4%) subject complained transient tinnitus]. There were no other complications.

Discussion

It is generally accepted that pain following i.v. injection/infusion of irritating agents is mediated via nociceptors in the venous wall [10]. These nociceptors are assumed to respond to the unphysiological osmolality or PH of solutions as well as to endogenous mediators such as bradykinin [6, 11]. The mechanisms of vascular pain caused by hypertonic saline remain uncertain. In this study, i.v. infusion of 4% sodium chloride solution with the osmolality of 1.37 osmol/kg evoked vascular pain in most of the patients enrolled. Probably due to the individual variations in the thresholds [10], a small proportion of the patients did not feel the pain during the infusion and were excluded.

The results of the present study showed that the incidence of pain elimination was 56.1% in group L20 and 83.3% in Group L40. Intravenous injection of lidocaine (without venous occlusion) was effective in reducing vascular pain associated with infusion of hypertonic saline. A dose-dependent effect of lidocaine in attenuating vascular pain was present. These results were consistent with previous studies on investigating the effect of lidocaine pretreatment (without venous occlusion) on vascular pain caused by injection of propofol, rocuronium, etomidate, etc. [4, 12–16].

The mechanisms of intravenous lidocaine on alleviating vascular pain may be sophisticated [17]. In the treatment groups, the immediate onset of analgesia implied that local anesthetic effect of lidocaine played an important role in alleviating vascular pain. However, there is abundant evidence suggesting intravenous lidocaine can exert analgesic effects through central nervous system [18]. Lidocaine inhibits the glycinergic system, some potassium and calcium channels, as well as the N-methyl-D-aspartate (NMDA) receptors [19]. Additionally, lidocaine may even act directly through opiate receptor stimulation [20, 21]. A recent study suggests intravenous lidocaine decreases the excitability of spinal dorsal horn by inhibiting glutamate release from presynaptic terminals and hyperpolarizing postsynaptic neurons by shifting the membrane potential of dorsal horn neurons [22]. Accordingly, the results of this study might be caused not only by conduction blockade in the peripheral nerves but also by the other mechanisms in the central nervous system.

In this study, using a stopwatch, we investigated the time to onset and the time to termination of the analgesic effect, as well as the analgesic duration. The immediate onset of analgesia after lidocaine was not surprising, because the painful sensation was originated from free afferent nerve endings between media and intima, therefore was vulnerable to pharmacologic intervention [6]. The analgesic duration of local anesthetic agents mainly depends on the local blood circulation. Due to the abundant blood stream in the venous lumen, intravenous administration may be the way with the shortest duration of local anesthetic effect. The blood stream may partially explain the shortness of analgesic duration. The short duration of analgesic effect from this study implied that a single bolus of lidocaine is not an ideal strategy for relieving vascular pain associated with hypertonic saline infusion.

The shortness of analgesic duration of lidocaine for vascular pain in present study was also in consistency with previous findings. Studies on propofol-induced vascular pain suggest that lidocaine 20 mg is effective in alleviating the pain when it is injected "immediately" or 10 s before propofol [8, 9, 23]. However, another study found that lidocaine 20 mg did not reduce the pain when it was injected 2 min before propofol [12]. This contradiction probably suggests that the analgesic duration of lidocaine 20 mg for propofol injection pain is less than 2 min. Additionally, studies on rocuronium-induced pain indicate that the analgesic efficacy of lidocaine 40 mg may decrease 2 min after injection [24, 25]. Therefore, when using lidocaine pre-injection strategy for relieving injection pain, a reasonable timing should be important. The analgesic efficacy may be underestimated if the time interval between lidocaine and propofol/rocuronium is inappropriate. However, the findings (including $T1$, $T2$ and AD) from our study cannot directly be utilized to the management of pain induced by propofol/rocuronium, since the mechanisms of pain are different [26–30] which probably leads to the differences in the characteristics (intensity, duration, etc.) of the pain.

In this study, we adopted normal saline as a control. Data in Group C showed that normal saline 2 ml could eliminate pain in 16.3% of the subjects. Since the intensity of vascular pain is associated with osmotic concentration [6], this result might be mainly due to the dilution effect. A bolus of normal saline could immediately reduce the osmolality in the local vein, but this dilution effect was soon nullified by the continuously infused hypertonic saline. This might explain the fast onset and short duration of the analgesia for alleviating the pain in Group C. Additionally, the findings from Group C implied that this dilution effect also played a role in the analgesic efficacy in the two treatment groups, since the lidocaine solution in this study was of physiologic osmolality.

There were some limitations in this study. First, the intensity of vascular pain itself fluctuated. Although the hypertonic saline was infused at a constant rate, the local venous blood flow might fluctuate. Thus, the osmolality in local vein might not be constant during the infusion causing the fluctuation in the pain intensity. Second, we only investigated two dosages of lidocaine. With the worry of higher

incidence of neurologic adverse reactions, a larger dosage of lidocaine was not involved in this study. Next, the results from this study suggested that further studies are required to find out better strategies and drugs for alleviating the pain associated with hypertonic saline infusion.

In conclusion, a single intravenous injection of lidocaine (both 20 mg and 40 mg) was effective in eliminating the vascular pain evoked by hypertonic saline infusion, but just for a short period of time. Lidocaine (without venous occlusion) only provides a short analgesic duration for local vein.

References

1. Morishima T, Sobue K, Arima H, Tanaka S, So M, Ando H, Katsuya H. Profound pain due to propofol injection triggered myocardial ischemia in a patient with a suspected pheochromocytoma. Anesth Analg. 2003;96(2):631.
2. Picard P, Tramer MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg. 2000;90(4):963–9.
3. Dunn LK, Durieux ME. Another win for lidocaine, another loss for magnesium? Anesth Analg. 2018;127(3):591–3.
4. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, Pace NL, Apfel CC. Perioperative Clinical Research C. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ. 2011;342:d1110.
5. Kwak HJ, Kim JY, Kim YB, Min SK, Moon BK, Kim JY. Pharmacological prevention of rocuronium-induced injection pain or withdrawal movements: a meta-analysis. J Anesth. 2013;27(5):742–9.
6. Klement W, Arndt JO. Pain on i.v. injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. Br J Anaesth. 1991;66(2):189–95.
7. McCrirrick A, Hunter S. Pain on injection of propofol: the effect of injectate temperature. Anaesthesia. 1990;45(6):443–4.
8. Lee TW, Loewenthal AE, Strachan JA, Todd BD. Pain during injection of propofol. The effect of prior administration of thiopentone. Anaesthesia. 1994;49(9):817–8.
9. Ganta R, Fee JP. Pain on injection of propofol: comparison of lignocaine with metoclopramide. Br J Anaesth. 1992;69(3):316–7.
10. Arndt JO, Klement W. Pain evoked by polymodal stimulation of hand veins in humans. J Physiol. 1991;440:467–78.
11. Kindgen-Milles D, Klement W, Arndt JO. The nociceptive systems of skin, paravascular tissue and hand veins of humans and their sensitivity to bradykinin. Neurosci Lett. 1994;181(1–2):39–42.
12. Xing J, Liang L, Zhou S, Luo C, Cai J, Hei Z. Intravenous lidocaine alleviates the pain of propofol injection by local anesthetic and central analgesic effects. Pain Med. 2018;19(3):598–607.
13. Lang BC, Yang CS, Zhang LL, Zhang WS, Fu YZ. Efficacy of lidocaine on preventing incidence and severity of pain associated with propofol using in pediatric patients: a PRISMA-compliant meta-analysis of randomized controlled trials. Medicine (Baltimore). 2017;96(11):e6320.
14. Jeong M, Yoon H. Comparison of the effects of lidocaine preadministration and local warming of the intravenous access site on propofol injection pain: randomized, double-blind controlled trial. Int J Nurs Stud. 2016;61:209–18.
15. Safavi M, Honarmand A, Sahaf AS, Sahaf SM, Attari M, Payandeh M, Iazdani A, Norian N. Magnesium sulfate versus Lidocaine pretreatment for prevention of pain on etomidate injection: a randomized, double-blinded placebo controlled trial. J Res Pharm Pract. 2015;4(1):4–8.
16. Prabhakar H, Singh GP, Ali Z, Kalaivani M, Smith MA. Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults. Cochrane Database Syst Rev. 2016;2:CD009346.
17. Beaussier M, Delbos A, Maurice-Szamburski A, Ecoffey C, Mercadal L. Perioperative use of intravenous lidocaine. Drugs. 2018;78(12):1229–46.
18. Weibel S, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, Eberhart LH, Poepping DM, Afshari A, Kranke P. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. Br J Anaesth. 2016;116(6):770–83.
19. van der Wal SE, van den Heuvel SA, Radema SA, van Berkum BF, Vaneker M, Steegers MA, Scheffer GJ, Vissers KC. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. Eur J Pain. 2016;20(5):655–74.
20. Hirota K, Okawa H, Appadu BL, Grandy DK, Lambert DG. Interaction of local anaesthetics with recombinant mu, kappa, and delta-opioid receptors expressed in Chinese hamster ovary cells. Br J Anaesth. 2000;85(5):740–6.
21. Cohen SP, Mao J. Is the analgesic effect of systemic lidocaine mediated through opioid receptors? Acta Anaesthesiol Scand. 2003;47(7):910–1.
22. Kurabe M, Furue H, Kohno T. Intravenous administration of lidocaine directly acts on spinal dorsal horn and produces analgesic effect: an in vivo patch-clamp analysis. Sci Rep. 2016;6:26253.
23. Lyons B, Lohan D, Flynn C, McCarroll M. Modification of pain on injection of propofol. A comparison of pethidine and lignocaine. Anaesthesia. 1996;51(4):394–5.
24. Ahmad N, Choy CY, Aris EA, Balan S. Preventing the withdrawal response associated with rocuronium injection: a comparison of fentanyl with lidocaine. Anesth Analg. 2005;100(4):987–90.
25. Cheong KF, Wong WH. Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment. Br J Anaesth. 2000;84(1):106–7.
26. Nishimoto R, Kashio M, Tominaga M. Propofol-induced pain sensation involves multiple mechanisms in sensory neurons. Pflugers Arch. 2015;467(9):2011–20.
27. Baek SB, Shin MS, Han JH, Moon SW, Chang B, Jeon JW, Yi JW, Chung JY. Rocuronium bromide inhibits inflammation and pain by suppressing nitric oxide production and enhancing prostaglandin E2 synthesis in endothelial cells. Int Neurourol J. 2016;20(4):296–303.
28. Zhang XM, Wang Q, Wang WS, Wang M. Large vein injection alleviates rocuronium-induced pain in gynaecologic patients. Anaesth Crit Care Pain Med. 2017;36(4):233–5.
29. Blunk JA, Seifert F, Schmelz M, Reeh PW, Koppert W. Injection pain of rocuronium and vecuronium is evoked by direct activation of nociceptive nerve endings. Eur J Anaesthesiol. 2003;20(3):245–53.
30. Desousa KA. Pain on propofol injection: causes and remedies. Indian J Pharmacol. 2016;48(6):617–23.