

A Comparative Study of Attenuation of Propofol Induced Pain by Lignocaine, Ondansetron, Dexamethasone and Cold Propofol per se.

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Abstract: Background: Pain on injection of propofol is a common problem. Aim of this study was to compare the efficacy of lignocaine, ondansetron, dexamethasone and cold propofol per se as a pretreatment drug for attenuation of pain due to propofol injection. Materials and Methods: Fifty two ASA I and II patients were randomly assigned into four groups (13 in each). Group O received 0.1mg/kg ondansetron, Group L received 0.5mg/kg lignocaine, Group D received 0.1mg/kg dexamethasone, Group T received propofol 1% at 4°C 2mg/kg. Mid forearm was occluded manually before injection of pre-treatment drug and released after 1 min and then propofol was injected over 5 sec. Patients were observed and questioned 15 sec later if they had pain and pain was assessed using four point scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain. Result: The incidence and intensity of pain were significantly less in all groups. We observed mild to moderate pain in Group L, O, D, and T were 31%, 54%, 46% and 77% respectively. The incidence of score 0 was significantly higher in Group L (70%) and Group D (54%) and Group O (46%) than Group T (23%) ($p < 0.05$). Conclusion: Pretreatment with lignocaine 0.5mg/kg, ondansetron 0.1mg/kg, dexamethasone 0.1 mg/kg in preventing pain from propofol injection were better than cold propofol per se.

Keywords: Propofol pain, lignocaine, dexamethasone, ondansetron, cold propofol

1. Introduction

Propofol, a widely used drug for induction, often causes local pain when administered into a peripheral vein. Many patients experience mild to moderate pain or even excruciating pain during propofol injection. Several methods have been described to reduce this pain, of which most effective and common are the use of a larger vein and mixing with lignocaine. Efficacy of various drugs such as lignocaine, tramadol, ketorolac and ketoprofen have been compared in reducing the propofol-induced pain. 5-hydroxytryptamine-3 (5-HT₃) antagonists such as ondansetron, granisetron, ramosetron and palonosetron have been shown to effectively alleviate propofol-induced pain individually. Propofol has been shown to release nitric oxide (NO) from vessels in animals and humans, and the release of nitric oxide has been linked to the generation of pain in the veins in humans. Corticosteroid like dexamethasone alter nitric oxide release has also been demonstrated in several disease conditions. Therefore, the choice of dexamethasone to minimize propofol-induced vascular pain is not only based on its wide clinical utilization but also due to its biological basis. Manufacturer notes that pH value of propofol is 6-8.5 and it can effectively be used between 4-37°C. The aim of this study was to compare the effect of cold propofol at 4°C on severity of injection pain.

2. Methodology

We included 52 patients belonging to American Society of Anesthesiologists (ASA) physical status (PS) 1 and 2, of either sex, aged 18–60 years, weighing between 40 and 80 kg, scheduled for various elective surgical procedures under

general anaesthesia. After obtaining approval from the Ethical Committee and written informed consent from the patients, the study was conducted. The exclusion criteria included patients belonging to ASA 3 and 4, patients with known cardiac disorders, other systemic disorders of lungs and liver, pregnant patients, patients for emergency procedures, those allergic to propofol and lignocaine, those with history of motion sickness, history of PONV, on nasogastric tube and patients with difficult airway.

Patients were randomly divided into one of the four groups using computer-generated random numbers (13 in each group). The drug solution was administered by an anaesthesiologist who was blinded to the constituents of the drug. Group L received 0.5 mg/kg of lignocaine and Group O received 0.1mg/kg of ondansetron, Group D received 0.1mg/kg of dexamethasone and Group T received propofol 1% at 4°C 2mg/kg. All the pre-treatment drugs were made into 2 ml volume with normal saline.

Prior to surgery, the patients underwent thorough pre-anaesthetic check-up and required investigations. Patients were kept fasting for 6 h for solids. In the operation theatre, intravenous (IV) access was established with 18-gauge cannula in suitable vein on non-dominant hand and was infused with Ringer's lactate solution. Vital signs were measured by placing an electrocardiogram, non-invasive blood pressure monitor and pulse oximeter, followed by a 10 min stabilisation period. Patients were given 2 ml of pre-treatment solution IV, containing either lignocaine 0.5 mg/kg (Group L), or 0.1mg/kg of ondansetron (Group O) or 0.1 mg/kg of dexamethasone (Group D) and cold propofol 1% at 4°C 2mg/kg (Group T). Following 5 s of pre-treatment in all four groups, we manually occluded venous drainage at

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mid-arm with the help of an assistant. One minute later, the occlusion of venous drainage was released. This was followed by injection of 1% propofol which was drawn immediately before use. One-fourth of the calculated dose was injected over 5 s and 15 s later the patient was assessed for pain during injection of propofol. After induction, patients were intubated and maintained with atracurium (loading dose 0.5mg/kg and maintenance dose 0.1mg/kg) and isoflurane. At the end of surgery, residual neuromuscular blockade was antagonised with 0.05 mg/kg of neostigmine and 0.08 mg/kg of glycopyrolate. Extubation was done when the patients were fully awake and obeying commands. To evaluate the severity of propofol-induced pain, we used a four-point scale [10] with the following values: None (no discomfort at the site of injection, 0 point), mild (the presence of pain without behavioural changes, 1 point), moderate (subjective symptoms or the concurrent presence of behavioural changes, 2 points), and severe (severe pain or the concurrent presence of such responses as making a face, hunching arms or shedding tears, 3 points). Comparison of age, sex, weight and ASA PS between the four groups was obtained by Student's *t*-test. Categorical data are reported as numbers and percentages and are analysed using Chi-square test or Fisher's exact test as appropriate. The value $P < 0.05$ was considered statistically significant.

3. Results

Age, weight, gender and ASA PS of the patients are summarised in Table 1. There was no significant difference in the demographic and baseline characteristics in study groups. Table 2 shows incidence of pain during propofol injection in all groups.

Table 1: Demographic Data

| Patient characteristics | Group L N = 13 | Group O N = 13 | Group D N = 13 | Group T N = 13 |
|-------------------------|-------------------|-------------------|-------------------|-------------------|
| Age (years) | 32.6±15.8 | 34.2±15.4 | 32.6±15.2 | 33.9±15.7 |
| Sex (M/F) | 5/8 | 6/7 | 6/7 | 4/9 |
| Weight (kg) | 56.1±6.15 | 55.3±5.6 | 57.3±6.57 | 55.4±14.5 |
| ASA I/II | 7/6 | 5/8 | 8/5 | 7/6 |

Values are expressed as mean ± standard deviation (SD) or number of patients.

There were no significant differences among groups.

Table 2: Assessment of Pain Score

| Pain score | Group L N (%) | Group O N (%) | Group D N (%) | Group T N (%) |
|------------|------------------|------------------|------------------|------------------|
| 0=no pain | 9 (70) | 6 (46) | 7 (54) | 3 (23) |
| 1=mild | 3 (23) | 5 (39) | 4 (31) | 7 (54) |
| 2=moderate | 1 (07) | 2 (15) | 2 (15) | 3 (23) |
| 3=severe | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

The overall incidence and intensity of pain were significantly less in all groups.

The incidence of mild to moderate pain in Group L, O, D and T were 30%, 54%, 46% and 77% respectively. The incidence of score 0 (no pain) was significantly higher in Group L (70%) followed by Group D (54%) and Group O (46%) then Group T (23%).

4. Discussion

IV injection of propofol causes pain at the site of injection and the pain is often reported as severe or excruciating and it is never been consistently eradicated. The exact mechanism of pain is not well understood but it is believed that immediate vascular pain on propofol injection is carried mainly by myelinated Aδ fibres due to direct irritant effect of the drug [15] by stimulation of venous nociceptive receptors [16]. The delayed pain of injection has a latency of 10–20 s mediated by activation of kallikrein–kinin system [17]. Various studies have been done with variable results. There are several methods to reduce the pain caused by propofol injection including increasing the infusion rate, adding opioids, aspirin and lignocaine, cooling or diluting the propofol, and performing pre-treatment with lignocaine, ephedrine, ondansetron, metoclopramide, nafamostat mesilate, thiopentone or ketamine [8,18]. Various 5-HT₃ receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron, alosetron, tropisetron and Ramosetron) [19] has been studied in reducing propofol-induced pain. 5-HT₃ receptor antagonists bind to opioid μ -receptor thus acting as agonists. In addition, 5-HT₃ receptors are involved in the nociceptive pathway, and this may be the mechanism of these drugs' analgesic effect.

Local anaesthetics contain hydrophilic and hydrophobic structures separated by an intermediate amide or ester linkage. The hydrophilic group is a tertiary or secondary amine, and the hydrophobic group an aromatic moiety. Although ondansetron does not possess this aromatic moiety, it has shown to block sodium channels [18]. Ondansetron has also shown its effect by binding to opioid μ -receptors in humans and exhibit agonist activity [20]. These properties, together with the observation that 5-HT₃ receptors are involved in the nociceptive pathways, explain the anti-nociceptive properties of ondansetron.

Picard P and his colleagues done a systematic review of 56 studies, including 6264 patients and 12 various drugs, showed that IV lignocaine (0.5 mg/kg) can reduce the pain up to 60% [25].

El-Radaideh KM et al found similar results with the use of lignocaine. Lignocaine 1%, 4 ml was shown to reduce the pain of propofol injection by 68% [26].

Sunny A and his colleagues observed that lignocaine 50 mg was slightly better than ondansetron 4 mg in attenuating pain associated with propofol injection [27].

Our study also proved that lignocaine is more effective in reducing propofol induced pain as compared to ondansetron. Changing the temperature of administered propofol has produced conflicting results in adults. **McCirrick A and Barker P** observed reduced pain in response to treatment with cold propofol [18,30], and it has been due to the decreased speed of the kinin cascade and the stabilization of local pain mediators at lower temperatures [18]. **Ozturk E and Parmar AK** in their study demonstrated that injection of propofol neither at 4°C nor at 37°C reduce pain on injection [31,32].

Conversely, we found that administration of propofol at 4°C reduced the incidence of injection pain from 70% to 30%.

Various studies have found presence of nociceptive nerve endings in endothelium of veins in human which are potential source of NO and propofol has been shown to release NO in vitro. [33,34]

Our study suggests that administration of dexamethasone as a pre-treatment drug also decrease pain on propofol injection because of above proposed mechanism.

5. Conclusion

Pretreatment with iv lignocaine 0.5mg/kg, ondansetron 0.1mg/kg, dexamethasone 0.1 mg/kg in preventing pain from propofol injection were better than cold propofol per se. Highest satisfactory result achieved with iv lignocaine.

6. Financial Support and Sponsorship

Nil

7. Conflicts of Interest

No

References

- [1] Scott RP, Saunders DA, Norman J. Propofol: Clinical strategies for preventing the pain of injection. *Anaesthesia* 1988;43:492-4.
- [2] Gehan G, Karoubi P, Quinet F, Leroy A, Rathat C, Pourriat JL. Sumalatha, *et al.*: Ramosetron versus ondansetron for propofol-induced pain Optimal dose of lignocaine for preventing pain on injection of propofol. *Br J Anaesth* 1991;66:324-6.
- [3] King SY, Davis FM, Wells JE, Murchison DJ, Pryor PJ. Lidocaine for the prevention of pain due to injection of propofol. *Anesth Analg* 1992;74:246-9.
- [4] Vijayant GA, Tej KK, Avtar S, Anju G. Analgesic effect of lignocaine, tramadol, ketorolac, and ketoprofen in ameliorating propofol induced pain. *J Anaesthesiol Clin Pharmacol* 2005;21:389-93.
- [5] Hwang J, Park HP, Lim YJ, Do SH, Lee SC, Jeon YT. Preventing pain on injection of propofol: A comparison between peripheral ketamine pre-treatment and ketamine added to propofol. *Anaesth Intensive Care* 2009;37:584-7.
- [6] Ishiyama T, Kashimoto S, Oguchi T, Furuya A, Fukushima H, Kumazawa T. Clonidine-ephedrine combination reduces pain on injection of propofol and blunts hemodynamic stress responses during the induction sequence. *J Clin Anesth* 2006;18:211-5.
- [7] He L, Xu JM, He T, Liu L, Zhu R. Dexmedetomidine pretreatment alleviates propofol injection pain. *Ups J Med Sci* 2014;119:338-42.
- [8] 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.
- [9] Dubey PK, Prasad SS. Pain on injection of propofol: The effect of granisetron pretreatment. *Clin J Pain* 2003;19:121-4.
- [10] Singh D, Jagannath S, Priye S, Shivaprakash, Kadli C, Reddy D. Prevention of propofol injection pain: Comparison between lidocaine and ramosetron. *J Anaesthesiol Clin Pharmacol* 2014;30:213-6.
- [11] Ryu HB, Kim SJ. Analgesic effects of palonosetron in the intravenous propofol injection. *Korean J Anesthesiol* 2014;66:99-104.
- [12] Swarika S, Pal A, Chatterjee S, Saha D, Dawar N. Ondansetron, ramosetron or palonosetron: Which is better choice of antiemetic to prevent postoperative nausea and vomiting in patients undergoing lap cholecystectomy? *Anaesth Essays Res* 2011;5:182-6.
- [13] Ye JH, Mui WC, Ren J, Hunt TE, Wu WH, Zbuzek VK. Ondansetron exhibits the properties of a local anesthetic. *Anesth Analg* 1997;85:1116-21.
- [14] Lee JW, Park HJ, Choi J, Park SJ, Kang H, Kim EG. Comparison of ramosetron's and ondansetron's preventive anti-emetic effects in highly susceptible patients undergoing abdominal hysterectomy. *Korean J Anesthesiol* 2011;61:488-92.
- [15] Tan CH, Onsiong MK. Pain on injection of propofol. *Anaesthesia* 1998;53:468-76.
- [16] Eriksson M, Engleson S, Niklasson F, Hartvig P. Effect of lignocaine and pH on propofol-induced pain. *Br J Anaesth* 1997;78:502-6.
- [17] Nishiyama T. How to decrease pain at rapid injection of propofol: Effectiveness of flurbiprofen. *J Anesth* 2005;19:273-6.
- [18] McCrirkick A, Hunter S. Pain on injection of propofol: The effect of injectate temperature. *Anaesthesia* 1990;45:443-4.
- [19] Machu TK. Therapeutics of 5-HT₃ receptor antagonists: Current uses and future directions. *Pharmacol Ther* 2011;130:338-47.
- [20] Gregory RE, Ettinger DS. 5-HT₃ receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. *Drugs* 1998;55:173-89.
- [21] Kim KR, Kang G, Ki MS, Shim HJ, Hwang JE, Bae WK, *et al.* A Randomized, double-blind pilot study of dose comparison of ramosetron to prevent chemotherapy-induced nausea and vomiting. *Biomed Res Int* 2015;2015:523601.
- [22] Ahmed A, Sengupta S, Das T, Rudra A, Iqbal A. Pre-treatment with intravenous granisetron to alleviate pain on propofol injection: A double-blind, randomized, controlled trial. *Indian J Anaesth* 2012;56:135-8.
- [23] Piper SN, Röhm KD, Papsdorf M, Maleck WH, Mattinger P, Boldt J. Dolasetron reduces pain on injection of propofol. *Anesthesiol Intensivmed Notfallmed Schmerzther* 2002;37:528-31.
- [24] Lee HY, Kim SH, So KY. Prevention of microemulsion propofol injection pain: A comparison of a combination of lidocaine and ramosetron with lidocaine or ramosetron alone. *Korean J Anesthesiol* 2011;61:30-4.
- [25] Picard P, Tramèr MR. Prevention of pain on injection with propofol: A quantitative systematic review. *Anesth Analg* 2000;90:963-9.

- [26] El-Radaideh KM. Effect of pretreatment with lidocaine, intravenous paracetamol and lidocaine-fentanyl on propofol injection pain. Comparative study. *Rev Bras Anesthesiol* 2007;57:32-8.
- [27] Sunny A, Veerabhadraiah T, Trivikram S. Comparison of pretreatment with lignocaine and ondansetron for pain on injection of propofol during induction of anaesthesia. *Internet J Anesthesiol* 2013;32:1373-6.
- [28] Alipour M, Tabari M, Alipour M. Paracetamol, ondansetron, granisetron, magnesium sulfate and lidocaine and reduced propofol injection pain. *Iran Red Crescent Med J* 2014;16:e16086.
- [29] Ryu J, So YM, Hwang J, Do SH. Ramosetron versus ondansetron for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. *Surg Endosc* 2010;24:812-7.
- [30] Barker P, Langton JA, Murphy P, Rowbotham DJ. Effect of prior administration of cold saline on pain during propofol injection. A comparison with cold propofol and propofol with lignocaine. *Anaesthesia* 1991; 46: 1069-70.
- [31] Ozturk E, Izdes S, Babacan A, Kaya K. Temperature of propofol does not reduce the incidence of injection pain. *Anesthesiology* 1998; 89: 1041.
- [32] Parmar AK, Koay CK. Pain on injection of propofol. A comparison of cold propofol with propofol premixed with lignocaine. *Anaesthesia* 1998; 53: 79-83.
- [33] A. J. Petros, R. G. Bogle, and J. D. Pearson, "Propofol stimulates nitric oxide release from cultured porcine aortic endothelial cells," *British Journal of Pharmacology*, vol. 109, no. 1, pp. 6-7, 1993.
- [34] F. S. Gragasin, S. L. Bourque, and S. T. Davidge, "Propofol increases vascular relaxation in aging rats chronically treated with the angiotensin-converting enzyme inhibitor captopril," *Anesthesia & Analgesia*, vol. 116, pp. 775-783, 2013.
- [35] T. R. L. Romero, G. S. Galdino, G. C. Silva et al., "Ketamine activates the l-arginine/nitric oxide/cyclic guanosine monophosphate pathway to induce peripheral antinociception in rats," *Anesthesia and Analgesia*, vol. 113, no. 5, pp. 1254-1259, 2011.
- [36] M. Nakane and H. Iwama, "A potential mechanism of propofol-induced pain on injection based on studies using nafamostat mesilate," *British Journal of Anaesthesia*, vol. 83, no. 3, pp. 397-404, 1999.