A Comparative Study of Ramosetron and Lidocaine in the Attenuation of Propofol Induced Pain in Paediatric Patients – A Double Blinded Randomized Study in ESIC Medical College, Kalaburgi

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ABSTRACT

BACKGROUND

The incidence of pain on propofol injection varies between 28 – 90 % during induction and may be severe. Ramosetron has been proved efficacious in reducing propofol pain in adults but not in children, therefore we conducted this double blinded randomized controlled study to determine the effectiveness of ramosetron in attenuating propofol induced pain in children. The purpose of this study was to compare the effectiveness of injection ramosetron, a 5HT3 antagonist and lidocaine, the commonest drug for attenuation of pain caused by injection propofol.

METHODS

This is a randomised double-blinded study. Eighty children of American Society of Anaesthesiologist (ASA) grade I - II, aged 4 - 14 years, undergoing elective surgical procedures under general anaesthesia were randomly assigned to two groups of 40 each. Group PR received 6 µg/kg of ramosetron and Group PL received 0.2 mg/kg of 2 % lidocaine. After injection of study drug, occlusion of venous drainage was done manually by a trained assistant at mid-arm for 60 seconds. After releasing manual occlusion Injection propofol (1 %) 2 mg/kg was administered slowly over a period of 5 seconds. A four point scale was used to assess the severity of pain. The results were analysed by using unpaired student's t - test and chi-square test/Fisher's exact test. P value of < 0.05 was considered statistically significant.

RESULTS

The demographic characteristics were comparable in both groups. The incidence of no pain in Group PR and Group PL was 60 % (N = 24) and 65 % (N = 26) respectively which was comparable. The incidence of mild, moderate and severe pain was comparable in both groups. The overall incidence of propofol injection pain in group PL and group PR was 35 % and 40 % respectively (P = 0.862).

CONCLUSIONS

Intravenous ramosetron at a dose of 6 µg/kg can effectively attenuate the propofol induced pain comparable to 0.2 mg/kg of lidocaine in children.

KEYWORDS

Children, Lidocaine, Propofol Induced Pain, Ramosetron

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BACKGROUND

Propofol is a popularly used anaesthetic agent for induction. The various properties of propofol like rapid induction and rapid recovery makes it as an ideal anaesthetic agent. Yet the pain on injection propofol experienced by the patients may be bothersome to the patients as well as to the anaesthesiologist. The incidence of pain varies between 28 – 90 % during induction of anaesthesia and may be severe.[1] The pain on propofol injection in paediatric patients has been reported to be as high as 30 – 80 %.[2] There have been many attempts to reduce the pain, however, none has achieved the complete elimination of pain.

Various drugs have been evaluated for attenuation of propofol induced pain. Recently introduced drugs include 5-hydroxytryptamine antagonists like ondansetron, granisetron, dolasetron and palonosetron. The 5-hydroxytryptamine antagonists are popularly used as antiemetic agents but recently 5-hydroxytryptamine-3 (5 - HT3) antagonists have been shown to effectively alleviate propofol-induced pain in adults. Ramosetron is a tetrahydro-benzimidazole derivative structurally independent of previously developed antiemetic drugs. Ramosetron is more potent and has longer lasting effects because of a slower rate of dissociation from the target receptor and higher binding affinity.[3-6] Ramosetron has been proved to be effective in attenuating propofol induced pain in adults yet the effectiveness of ramosetron in attenuation of propofol induced pain in paediatric population has not been evaluated till date. Therefore, our study aimed to determine the efficacy of ramosetron in attenuation of propofol induced pain.

The aim of this randomized double-blinded study is to detect effectiveness of ramosetron pre-treatment administration in preventing pain of propofol injection in comparison to lidocaine, which is the most common drug used for attenuation of propofol induced pain. The primary objective of our study was to compare the incidence of pain on injection of propofol in patients receiving ramosetron and lidocaine.

Objectives

The aim of the study is to compare the effectiveness of lidocaine and ramosetron in attenuation of propofol induced pain. The primary objective of the study was to compare the incidence of pain scores i.e. no pain, mild, moderate and severe pain on injection of propofol in ramosetron and lidocaine group. The secondary objective was to compare the hemodynamic parameters including heart rate and non-invasive blood pressure.

METHODS

This is a clinical trial undertaken after obtaining institutional ethical committee clearance with IEC NO: ESIC / MC / GLB / IEC / 01 / 2018-19. The study was registered in clinical trial registry – India with reference number as CTRI / 2019 / 10 / 021601. The study duration was from September 1st 2019 to 30th April 2020. The informed written consent was obtained from all parents in the local language understandable by them. Eighty children in the age group of 4 - 14 years of either sex belonging to American society of Anaesthesiologists physical status I - II who underwent elective surgical procedures under general anaesthesia were included in the study. Exclusion criteria included irritable/ un-cooperative/excessive crying child, presence of existing medical illness like anaemia, cardiac conditions, upper airway diseases, ASA grade 3 & 4, parents not consenting for study and known allergies to propofol and lidocaine.

Patients were randomly divided into two groups using computer-generated random numbers. Each group named Group PL-propofol-lidocaine and Group PR - propofol - ramosetron (PR) group had 40 patients. Group PL received 0.2 mg/kg of lidocaine and Group PR received 6 µg/kg of ramosetron as pre-treatment drug. The drug solution was administered by an anaesthesiologist who was blinded to the constituents of the drug.

Thorough pre-anaesthetic evaluation was done day before surgery and standard pre-operative fasting guidelines were followed. Intravenous access was established after the application of EMLA (eutectic mixture of local anaesthetic) cream prior to shifting to the operation theatre. On arrival of the patient in the operating room, appropriate intravenous fluid was connected. The patients were connected to multichannel monitor which recorded heart rate (HR), non-invasive measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), electrocardiogram (ECG), end tidal carbon-dioxide (ETCO2), anaesthetic gas monitor (AGM) and oxygen saturation (SPO2) of all the patients. Patients received pre-treatment drug containing either lignocaine 0.2 mg/kg (Group PL), or 6 µg/kg of ramosetron (Group PR) over a period of 5 s. The manual occlusion of venous drainage was done for one minute at mid forearm by a trained assistant to allow for the action of pre-treatment drugs either ramosetron or lignocaine to begin and enhance their local anaesthetic effect. One minute later, the occlusion of venous drainage was released. This was followed by injection of 1 % propofol 2 mg/kg (diluted in LCT, Troypofol®, Troikaa Pharmaceuticals, Ahmedabad, Gujarat, India) which was drawn immediately. All the drugs injected were at room temperature. One-fourth of the calculated dose was injected over 5 s and, 15 s later the patient was assessed for pain using four-point scale 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). After induction of anaesthesia, patients were intubated with appropriate size of endotracheal tube and were connected to the ventilator after confirming bilateral equal air entry. Anaesthesia was maintained with a non-depolarizing muscle relaxant injection atracurium and isoflurane was maintained at minimum alveolar concentration of 1 (MAC 1). At the end of surgery, residual neuromuscular blockade was

antagonised with 0.05 mg/kg of injection neostigmine and 0.02 mg/kg of glycopyrrolate. Extubation was done after the extubation criteria was fulfilled.

Statistical Analysis

Considering previous studies, the incidence of propofol-induced pain was assumed as 80 % and 50 % reduction was considered significant. Based on the alpha value of 0.05 and a power value of 80 %, our study required 40 patients per group. Comparison of demographic characters like age, sex, weight and ASA PS between the two 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. Results were considered statistically significant when P - value of < 0.05.

RESULTS

All eighty patients selected for the study completed the study protocol. The patients' demographic characters in ramosetron and lidocaine group were comparable as shown in Table 1. The pain characteristics in both groups are depicted in table 2. The pain scores were comparable in both the groups (P = 0.862). In Group PR the number of patients without pain (no pain) were 24 (60 %) whereas in Group PL the number of patients without pain were 26 (65 %) which was statistically not significant. In ramosetron group, the incidence of mild pain was 25 % (N = 10) and in lidocaine group the incidence of pain was 20 % (N = 8) which was comparable. Similarly, the incidence of moderate pain did not differ in Group PR (N = 4; 10 %) and Group PL (N = 5; 12.5 %). The number of patients with severe pain in group PR and group PL was 2 (5 %) and 1 (2.5 %) respectively which was statistically not significant. The intra-operative heart rate and blood pressure were comparable in both groups.

Data	Group PL (Propofol-Lidocaine)	Group PR (Propofol-Ramosetron)	P-Value
Age (Mean ± SD) (Years)	8.825 ± 3.909	7.525 ± 3.81	0.136
Gender (M/F) §	30/10	33/7	0.412
Weight (Mean ± SD)	19.30 ± 4.74	20.55 ± 4.96	0.41
ASA PS (I/II)	40/0	40/0	-

Table 1. Demographic Data

§-Chi-square applied with X^2=0.672; M =male, F=female; ASA PS-American society of Anaesthesiologists Physical status; SD-standard deviation

Pain Score	Group PR n (%)	Group PL n (%)	P-Value
0 (no pain)	24 (60)	26 (65)	
1 (mild)	10 (25)	8 (20)	X^2 = 0.747;
2 (moderate)	4 (10)	5 (12.5)	P = .862
3 (severe)	2 (5)	1 (2.5)	

Table 2. Comparison of Pain in Both Groups

Group PR: propofol-ramosetron; Group PL- Propofol-lidocaine; n- number;%-percentage

DISCUSSION

Propofol is an intravenous sedative agent used for initiation and maintenance of monitored anaesthesia care (MAC), combined sedation with regional anaesthesia, induction of general anaesthesia and sedation for intensive care unit sedation of intubated patients. Propofol is also used with other sedative agents for total intravenous anaesthesia. Further propofol in popularly used for procedural sedation and conscious sedation in adults and children. Propofol is preferred due to its rapid induction, rapid return of consciousness and minimal residual effects on the central nervous system. Propofol has been accepted worldwide as an ideal general anaesthetic agent in both developed and developing countries.

Although being popular agent, patients might experience severe pain on injection of propofol which may be disturbing both to the patient and to the anaesthesiologist. The experience in children may cause fear and anxiety leading to more distress compared to that of adults. The underlying mechanism of pain on injection of propofol is not fully understood. There have been several schools of thoughts put forward to explain the mechanism of pain associated with injection of propofol. Based on these various hypotheses the different drugs have been tried to attenuate the pain associated with injection of propofol.

The pain caused by propofol is known as angialgia. Propofol induced pain is due to vascular involvement and is immediate and delayed after 10–20 seconds. The immediate pain is due to irritation of vein endothelium whereas delayed pain is due to the release of mediators such a kininogen from kinin cascade. Propofol belongs to phenol group and is irritable to skin, mucous membrane and intima.

The newer hypothesis states that the early pain caused by propofol injection is due to endothelial irritation and the delayed pain is due to stimulation of transient receptor potential (TRP) ankyrin 1 (TRPA1) and TRP vanilloid 1 (TRPV1) receptors. These receptors activate the nerve endings causing release of calcitonin gene related peptide. These neuropeptides cause vascular leakage and dilatation contributing to neurogenic inflammation in the spinal dorsal horn.[7] Since propofol belongs to phenol group it is irritable to skin, mucous membrane, and intima. In children the incidence of pain may be higher because of smaller diameter of veins.

Various pharmacological and non-pharmacological methods have been described for attenuation of propofol induced pain. The non-pharmacological strategies to reduce the incidence of pain on injection include cooling or warming propofol, diluting the propofol solution or injection in to large vein like ante cubital vein. The pharmacological strategies include use of different group of drugs like lidocaine, low dose ketamine, non-steroid anti-inflammatory drugs (NSAIDs), opioids like fentanyl, remifentanil, alfentanil, antiemetic agents like metoclopramide, inhalational agents like nitrous oxide and sevoflurane. The other drugs that have been evaluated include alpha 2 receptor antagonists like dexmedetomidine and clonidine with variable results.

Use of medium chain triglycerides (MCT) or low chain triglycerides (LCT) propofol also has been tried to reduce the propofol induced pain but no significant reduction of pain has been observed both in adults and paediatrics. Even non lipid formulations like triglyceride free microemulsion propofol formulation utilizing non-ionic surfactant and cosurfactant to emulsify propofol in water has been introduced to overcome the pain associated with propofol pain. Similarly, another lipid free preparation of propofol has been developed containing sulfobutylether-β cyclodextrin and water, but it does not reduce pain on injection. All these methods have tried to minimise the propofol pain on injection with variable results.

One of the studies has shown that propofol characteristically causes vascular pain that occurs in response to prostanoids, particularly PG E2.[7] According to Faerber et al.[8] serotonin (5 - HT3) receptors are located in the nerve terminals and sensory nerve endings of neurons releasing pain mediators such as substance P. Therefore, use of 5 hydroxy tryptamine receptor antagonists might help in attenuating the pain associated with injection propofol.

The use of lidocaine to prevent the propofol injection is the most common and popular method used by most of the anaesthesiologists. The exact mechanism by which lidocaine reduces propofol pain is unknown. However, there is the possibility that lidocaine, a local anaesthetic, reversibly blocks peripheral nerve pathways in the arm. Besides, the analgesic effect of lidocaine on propofol injections not only based on its local anaesthetic effect but also on the decrease in pH of the propofol when given as a lidocaine mixture. Lidocaine has been used in different ways. Venous occlusion with lidocaine for 60 s is an effective method in relieving propofol-induced pain. The use of tourniquet to the arm for 30-120 seconds before administration of injection propofol has been used for studying peripheral action of drug.[9] Different doses of lidocaine have been studied to attenuate the pain on propofol injection. Few studies showed that lidocaine pre-treatment at the dose of 10 mg and 20 mg effectively attenuated the propofol induced pain.[10-13] In another study,[14] the optimum dose of lidocaine to attenuate the pain on propofol injection was 0.1 mg/kg in adults. Similarly in children, lidocaine at a dose of 10 mg mixed with propofol was found to significantly reduce the incidence of pain on propofol injection.[15] However, another study found 0.2 mg/kg of lidocaine in children to be effective dose to attenuate the pain on propofol injection due to higher volume of distribution in children.[16] A quantitative systematic review compared three different methods of using lidocaine. First was bolus dose of lidocaine in one group, second was mixing lidocaine with propofol and third was using lidocaine after venous occlusion with tourniquet. The authors reported that venous occlusion with tourniquet was effective method to reduce the propofol induced pain on injection.[2] Hence in our study we used 0.2 mg/kg of lidocaine which was considered effective to attenuate the pain on propofol injection in children. However, the tourniquet was not used in our study as in children it may not be because of two reasons. Firstly, the tourniquet itself in children may cause pain and secondly because of not being practical in paediatric population.

In the present study, lidocaine group showed 65 % (N = 26) of the patients to be free of pain on injection of propofol whereas the incidence of mild pain was 20 % (N = 8). This is in consistent with the study by Borazan et al.[17] where in the authors reported that 75 % (N = 30) of the patients were free of pain on propofol injection and the incidence of mild pain was 15 % (N = 6) in patients receiving 20 mg of lidocaine. In our study the overall incidence of propofol injection pain in lidocaine group was 35 % and 40 % in ramosetron group which was statistically not significant. Inconsistent to our study Kwak et al.[18] also reported the incidence of painful injection of propofol mixed with lidocaine to be 40 %. However, the authors quoted this incidence to be higher and unacceptable. Hence the authors suggested that the combination of alfentanil and lidocaine is significantly effective in reducing the propofol injection pain rather lidocaine alone.

Ramosetron has been used as a part of premedication before induction of anaesthesia to prevent post-operative nausea and vomiting. It is a more potent anti-emetic compared to other 5HT3 antagonists' drugs like ondansetron and granisetron. Since our study intended to evaluate the effectiveness of ramosetron alone, as pre-treatment in attenuating propofol injection pain no other drug was injected prior to injection propofol. One of the meta-analysis study concluded that 5-HT_3 receptor antagonists can effectively reduce the incidence and severity of propofol injection pain and may become good alternatives to lidocaine in attenuating propofol injection pain.[19] In accordance to this Ye et al.[20] in their study stated that ondansetron, a 5-HT3 receptor antagonist, has multifaceted actions as a sodium channel blocker and μ opioid receptor agonist, and therefore may potentially be used to alleviate pain produced by a drug similar to propofol. These properties, together with the observation that 5-HT3 receptors are involved in the nociceptive pathways, have been postulated to explain the anti-nociceptive properties of ondansetron. Descending monoaminergic pathways from brainstem are known to able to influence nociceptive signalling in the dorsal horn of the spinal cord. Such descending influences are both facilitatory and inhibitory in nature. Suzuki and colleagues[6] showed that the descending influences are predominantly facilitatory, and act via spinal 5-HT3 receptors (expressed on nerve terminals of small diameter afferents), revealing a role for selective 5-HT3 receptor antagonists like ondansetron and granisetron in relieving pain. Similarly other 5-HT3 receptor antagonists such as granisetron, dolasetron, ramosetron, and palonosetron are also successfully used for preventing the propofol pain injection.[21] Despite that the 5-HT3 receptor antagonist ondansetron and ramosetron share their mechanism of action, they have different chemical structures and exhibit differences in affinity for the receptor, dose response and duration of effect.

The results of our study showed that ramosetron effectively reduced the pain caused by injection of propofol similar to lidocaine although the results were statistically not significant. The number of patients with no pain in ramosetron group were 24 (60 %) which was statistically not significant. The incidence of mild pain in group PR was

25 % and the incidence of moderate pain in group PR was 15 % which were comparable to the lidocaine group. Similarly, the incidence of severe pain in group PR and group PL was comparable (5 % versus 2.5 %). Similar reports were reported by Lee et al.[22] in the groups pre-treated with ramosetron 0.3 mg or combination with ramosetron and lidocaine 20 mg (60 % and 38 %, respectively). In a study conducted by Singh et al.[23] the incidence of pain was 65 %, 35 %, and 30 % in the placebo (saline), lido lidocaine 40 mg, and ramosetron 0.3 mg, groups respectively. In another study by Zahoor et al.[24] The propofol induced pain was assessed at 0, 5, 10, 15 and 20 sec intervals after propofol injection. The comparison of lidocaine and ramosetron groups showed statistically non-significant results (P = 0.557), both being equally effective in attenuating propofol pain at 10 and 15 seconds of injection.

CONCLUSIONS

Our study showed that pre-treatment with ramosetron 6 µg/kg effectively attenuated the pain associated with propofol injection which was comparable to the use of 0.2 mg/kg of lidocaine. Besides ramosetron has an added advantage of preventing post-operative nausea and vomiting.

Limitations

The dose of ramosetron 6 µg/kg is a similar dose used for the purpose of anti-emesis in children.[25] As studies and data available in this context are rare, we used the anti-emetic dose and we recommend further studies on the evaluation of effective dose of ramosetron in children for attenuation of propofol induced pain on injection.

Since Ramosetron is a recently developed potent 5-HT3 receptor antagonist and is studied extensively only in adults by various authors, the references quoted in discussion part includes the studies in adults. Therefore, we further recommend studies in children to evaluate the effectiveness of ramosetron in attenuation of propofol induced pain.

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