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Research Paper

Prevention of Propofol Injection Pain in Children: A Comparison of Pre-treatment with Tramadol and Propofol-Lidocaine Mixture

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Abstract

Background: The pain on propofol injection is considered to be a common and difficult to eliminate problem in children. In this study, we aimed to compare the efficacy of pretreatment with tramadol 1 $mg.kg^{-1}$and propofol-lidocaine 20 mg mixture for prevention of propofol induced pain in children.

Methods: One hundred and twenty ASA I-II patients undergoing orthopedic and oto-laryngological surgery were included in this study and were divided into three groups with random table numbers. Group C (n=39) received normal saline placebo and Group T (n=40) received 1 $mg.kg^{-1}$ tramadol 60 sec before propofol (180 mg 1% propofol with 2 ml normal saline) whereas Group L (n=40) received normal saline placebo before propofol-lidocaine mixture (180 mg 1% propofol with 2 ml %1 lidocaine). One patient in Group C was dropped out from the study because of difficulty in inserting an iv cannula. Thus, one hundred and nineteen patients were analyzed for the study. After given the calculated dose of propofol, a blinded observer assessed the pain with a four-point behavioral scale.

Results: There were no significant differences in patient characteristics and intraoperative variables ($p>0.05$) except intraoperative fentanyl consumption and analgesic requirement one hr after surgery among the groups ($p<0.05$). Both tramadol 1 $mg.kg^{-1}$ and lidocaine 20 mg mixture significantly reduced propofol pain when compared with control group. Moderate and severe pain were found higher in control group ($p<0.05$). The incidence of overall pain was 79.4% in the control group, 35% in tramadol group, 25% in lidocaine group respectively ($p<0.001$).

Conclusions: Pretreatment with tramadol 60 sec before propofol injection and propofol-lidocaine mixture were significantly reduced propofol injection pain when compared to placebo in children.

Key words: tramadol, lidocaine, propofol, pain, children.

Introduction

Propofol is a popular intravenous (iv) anesthetic agent providing fast onset and smooth anesthetic induction with rapid recovery. However, the disadvantage of pain or discomfort during iv injection may be as high as 85% in children when given into small vein on the dorsum of the hand (1-3). Although vari-

ous drugs have been used to decrease propofol injection pain such as ketamine, lidocaine, alfentanil, remifentanil, and thiopenthal (4-8), it still represents a clinical problem in children, especially in younger children because of the smaller size of the accessible veins (9). The two most commonly used methods are pretreatment of the vein with lidocaine and mixing propofol with lidocaine immediately before injection (3). However, prior or concomittant administration of lidocaine is not effective in all children (9-11).

Tramadol is a centrally-acting drug, which is effective in the treatment of moderate to severe pain. In addition to its systemic effect, the local anesthetic effect of tramadol has been shown in both clinically and laboratory studies (12,13). According to this action, pretreating the vein with iv tramadol has proved to be effective in preventing propofol injection pain in adults, the incidence of tramadol treated patients was 23% vs 69% in the control group (14). However, to date no published data are available for tramadol on reducing propofol injection pain in children. To the best of our knowledge this is the first study of tramadol on preventing propofol injection pain in pediatric population. As the beneficial effect of tramadol on propofol injection pain in adults is already well known, we aimed to investigate the effect of preatreatment with tramadol on reducing both the incidence and severity of propofol injection pain and how it compared with lidocaine in children.

Materials and Methods

After receiving the Institutional Ethics Committee approval (EC.071.00/2631), written informed consent was obtained from the parents of 120 ASA physical status I or II patients aged 6-13 years, who were scheduled for elective orthopedic and otolaryngological surgery with general anesthesia between November 2010 and June 2011 were enrolled in this study. Exclusion criteria include crying children on arrival in the operating room, emergent cases, presence of hepatic or renal dysfunction, musculoskeletal disorders and known allergies to propofol, tramadol and lidocaine. Patients were also excluded if it was impossible to insert a venous line into the dorsum of the hand.

Preoperative assessment was performed the day before surgery. Prior to surgery, consultant anesthesiology assistants reassured each child. Parents did not accompany the child during anesthetic induction. All children were unpremedicated. When the children arrived in the operating room, routine monitors for heart rate, noninvasive blood pressure (NIBP) and peripheral oxygen saturation was applied. The NIBP cuff was applied on the arm contralateral to that with intravenous access. A 22G iv cannula was inserted into the dorsum of the hand. The cannula was inserted 15 min before induction without the use of local anesthetic because of the lack of availability of topical anesthetic creams. A continous of isomix 1/3 was applied at the maintenance rate according to the children' weight.

The children were randomly allocated using a table of random numbers to one of three treatment groups. Children in Group C (Group Control) received normal saline placebo 60 sec before propofol (180 mg 1% propofol with 2 ml saline); Group T (Group Tramadol) received 1 $mg.kg^{-1}$ tramadol iv 60 sec before propofol (180 mg 1% propofol with 2 ml normal saline); Group L received normal saline placebo 60 sec before propofol-lidocaine mixture (180 mg 1% propofol with 2 ml %1 lidocaine).

After the injection of the pretreatment drug, propofol (at room temperature) 3-4 $mg.\ kg^{-1}$ was delivered through the iv cannula at an approximate rate of 2 ml per 10 sec by observers until the loss of eyelash reflex. During a ten-second pause after the 25% of the calculated propofol dose had been given, another anesthesiologist who was unaware of the study groups, assessed propofol induced pain using a four point behavioral scale: 1= no pain (no reaction); 2= mild pain (grimace); 3= moderate pain (grimace+cry); 4= severe pain (cry+withdrawal) (9). Then Fentanyl iv 1-2 $\mu g.kg^{-1}$ was administered only after assessment of the pain after propofol injection. Induction of anesthesia was completed with the remaining dose of propofol and tracheal intubation was facilitated with 0.6 $mg.kg^{-1}$ rocuronium. Anesthesia was maintained with sevoflurane and nitrous oxide 50% in oxygen, with controlled ventilation and intermittent fentanyl and rocuronium was given if required. Before the skin closure 10 $mg.kg^{-1}$ paracetamol given intravenously for postoperative analgesia. Within 24 h after the operation, the injection site was checked for pain, edema or allergic reactions by an anesthesiologist who was unaware which drug had been administered.

Statistical Analyses

Statistical analyses were performed by using SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA). The primary endpoint of the study was the number of patients in each group without injection pain. The sample size was determined according to a previous study which was estimated the pain was 66 % after iv 1 % propofol injection (8) with a significance level of α= 0.05 and β= 0.80 and 29 patients in each group was found sufficient. We decided to include 40 patients in each group for the possibility of drop out.

Descriptive statistics are expressed as mean ± SD unless otherwise stated. *Kolmogorov-Smirnov* test was used to determine the distribution of numeric data. Patient demographic data were determined by *analysis of variance* (continous variables: age, weight, eg), as well as χ^2 test (discrete variables: sex, ASA physical status). Pain severity scores were determined by using the *Mann-Whitney test* and the incidence of pain was determined using the χ^2 *test*. A p value of less than 0.05 was considered significant.

Results

One hundred and twenty patients were enrolled in the study but one patient in Group C was drop out from the study because of the difficulty of insertion of iv cannula into the dorsum of the hand. There were no significant differences in age, weight, gender and ASA physical status of the patients and the mean induction dose of propofol, time to loss of eyelash reflex (p>0.05) (Table 1). The patients in tramadol group had less intraoperative fentanyl consumption and postoperative analgesic requirement one hr after surgery than other groups. 11 (27.5 %) patients in tramadol group had received additional fentanyl intraoperatively whereas 25 (64.1 %) in control (p=0.01). and 24 (60 %) patients (p<0.01) in lidocaine group had need fentanyl. According to postoperative analgesic requirement one hr after surgery 5 (12.5 %) patients in tramadol group had received additional fentanyl intraoperatively whereas 30 (76.9 %) in control (p<0.001). and 31 (77. 5%) patients (p<0.001) in lidocaine group had need fentanyl.

The overall incidence of pain during iv injection of propofol in the various groups is shown in Table 2. The incidence of propofol injection pain was 79.4 % (31 of 39) in the control group, 35 % (14 of 40) in tramadol group, 10 % (10 of 40) in lidocaine group. Data analyses showed that both tramadol and lidocaine significantly reduced propofol injection pain more than placebo (p<0.001). Pretreatment with tramadol 1 $mg.kg^{-1}$ were equally effective with lidocaine mixture in attenuating pain during iv injection of propofol and there was no significant difference between these groups (p>0.05).

According to mild pain there was no statistically difference found among groups (p>0.05). In respect to moderate pain 14 (35.9 %) in control group, 6 (17.5 %) in tramadol group and 4 (10 %) patients in lidocaine group had moderate pain. The statistically difference was found only between control and lidocaine group (p=0.012). Severe pain had been experienced by 11 (28.2 %) patients in only control group and it was found statistically significant when compared with both tramadol and lidocaine groups (p<0.001). Additionally, no patient had an experience of severe pain in tramadol and lidocaine groups so there was no statistically significance between these two groups with respect to severe pain.

No complications, such as pain, edema, wheal or flare response were observed at the injection site within the first 24 h after the operation.

Table 1. Demographic data and intraoperative variables of the patients.

Groups	Group Control (n=39)	Group Tramadol (n=40)	Group Lidocaine (n=40)
Age (yr)	8.76±2.38	8.37±2.22	8.46±1.90
Weight (kg)	30.8±9.08	30.9±7.58	29.7±8.39
Gender (M/F)	27/12	26/14	29/11
ASA-PS I/II (n)	38/1	39/1	38/2
Mean induction dose of propofol (mg/kg)	3.5±0.3	3.2±0.6	3.3±0.7
Time to loss of eyelash reflex (s)	38±14	36±15	39±13
Intraoperative additional fentanyl consumption (n)	25†	11*	24 γ
Postoperative Analgesic requirements at 1hr (n)	34§	5*	32 γ
Duration of surgery (min)	42.5±15.4	44.1±13.9	46.2±16.0

Values are shown as number of patients, mean ± SD or number.
ASA-PS American Society of Anesthesiologists physical status.
*: p<0.001; Group T vs Group L
γ : p>0.05; Group C vs Group L
†: p=0.01; Group C vs Group T
§: p<0.001; Group T vs Group C

Table 2. Incidence and severity of pain during iv propofol injection.

Severity of Pain	Group Control (n=39)	Group Tramadol (n=40)	Group Lidocaine (n=40)
No Pain	8 (20.5)	26 (65)*	30 (75) §
Mild	6 (15.4)	8 (20)	6 (15)
Moderate	14 (35.9)	6 (15)	4 (10) †
Severe	11 (28.2)	0 (0) *	0 (0) §
Total Pain	31 (79.4)* §	14 (35) γ	10 (25)

Data are numbers (%).
*: p<0.001; Group C vs Group T
§: p<0.001; Group C vs Group L
γ : p>0.05; Group T vs Group L
†: p=0.012; Group C vs Group L

Discussion

We showed that pretreatment with tramadol 1 $mg.kg^{-1}$ attenuated pain associated with propofol injection. Tramadol 1 $mg.kg^{-1}$ and lidocaine 20 mg premixed with propofol were equally effective in reducing especially severe pain during iv injection of propofol.

Injection pain which is a recognized adverse effect of propofol can be very distressing to patients (15) and still a limitation of this popular iv anesthetic agent. The mechanism of propofol injection pain is still unclear, it has been postulated to be due to either a direct irritant effect given rise to an immediate sensation of pain or an indirect effect via the release of mediators such as bradykinin leading to a delayed onset (16).

The most common practices including iv lidocaine before propofol injection, after mixing with propofol and iv lidocaine given with a tourniquet were all used for preventing propofol injection pain (3,4). The exact mechanism by which lidocaine reduces propofol pain is unknown. However, there is the possibility that lidocaine, a local anesthetic, reversibly blocks peripheral nerve pathways in the arm (17). Besides, the analgesic effect of lidocaine on propofol injections not only based on its local anesthetic effect but also on the decrease in pH of the propofol when given as a lidocaine mixture. Tan LH et al, compared the effects of propofol-lidocaine mixture and lidocaine pretreatment in adults on propofol injection pain and the dose of propofol required for the induction of anesthesia (18). They showed no statistically difference between the groups for propofol induced pain and induction dose of propofol like in our study. Bilotta et al (19) administered 2 $mg.kg^{-1}$ 2% lidocaine or an equivalent volume of saline as a pretreatment in pediatric ICU patients for different invasive procedures. They investigate the effect of lidocaine on both propofol injection pain and propofol induced motor disturbances such as spontaneous dystonic or choreiform movements. They found that lidocaine not only reduced pain and motor disturbances but also reduced propofol requirement. In contrast, in our study we did not show the difference in the required propofol dose, because we used low dose of lidocaine for propofol injection pain but in their study the dose was higher and reduced propofol dose might be related with the high dose of lidocaine. Although this study was not designed to assess the neurologic and motor disturbances of propofol, in contrast to their study, we did not observe any motor disturbances in our study groups. We thought that this might be related to the pain thresholds and the children investigated. These type of neurologic movements were seen higher in infants and small children (20). We only assessed the intensity and severity of pain with a behavioral scale of Cameron et al which was described the withdrawal of the arm as a severe pain (9).

Furthermore, iv retention of lidocaine with a tourniquet was found the best method for reducing pain (3,4). The tourniquet which isolates the arm veins from the rest of circulation presents a useful model for studying the peripheral actions of a drug in the absence of central effect. It is advised that the duration of venous occlusion with a tourniquet which is applied to the forearm could be for a period of 30-120 sec before propofol injection (3,4). But in this study, we did not administer a tourniquet because of not being practical in the pediatric population, therefore we were not rule out the possible central role of tramadol in reducing propofol injection pain.

Tramadol, is a centrally acting weak μ-receptor agonist, inhibits noradrenaline re-uptake as well as promotes seratonin release and can be used to treat moderate and severe pain (21-24). In addition to its systemic effect, the local anesthetic effect of tramadol on peripheral nerves has been shown in both clinically and laboratory studies (13,24,25). More complete data have been produced the effect of tramadol on the release of monoaminergic neurotransmitters in the central nervous system and its agonist action at peripheral and central opioid receptors. Desmolues and co-workers (25) have confirmed in humans that the analgesic effect of tramadol is apportioned between the opioid and monoaminergic components. Pang et al (26) observed a local anesthetic effect with intradermal injection of tramadol and lidocaine. Jou et al (12) suggested that tramadol affects sensory and motor nerve conduction by a similar mechanism to that of lidocaine which acts on the voltage dependent sodium channel leading to axonal blockage.

Opiates were shown to exert peripheral analgesic action in addition to their well known central effects, a clear cut discrimination between peripheral and central analgesics is debatable (27). The analgesia produced by both peripheral and central mechanisms may be additive or even synergistic. Moreover, peripheral opioid receptors have been described and shown to mediate analgesic effect when activated by opioid agonists (28,29). It was suggested that both peripheral and central actions could be at the basis of the antiinflammatory effects of the tramadol (29). It, in fact, exerts a dual mechanism action due to binding μ opioid receptor and potentiation of the monoaminergic system. Therefore, the antiinflammatory action of tramadol could be at least in part, related to its opioid

effect. Accordingly, it appears that tramadol is not a single-mechanism analgesic.

Pharmacokinetics of tramadol in adults and children is reported to be similar when administered intravenously (30). It has been used as an alternative agent to traditional opioids for pain relief in pediatric population with the recommended dose of 1-2 $mg.kg^{-1}$ for children as we used in our study without increasing adverse events in the pediatric population (31).

Different opioids have been used to reduce propofol pain both in adults and children. Hiller and Saarnivaara (11) compared three different doses of alfentanil one min prior to propofol with 10 mg lidocaine premixed with propofol in children. They found the incidence moderate to severe pain was 4 % in lidocaine group, 40 %, 16 % and 20 % in the groups receiving 10, 15, 20 $\mu g.kg^{-1}$ alfentanil respectively. Al-Refai and coworkers (32) compared remifentanil, alfentanil, lidocaine premixture with placebo and they found that three drugs were all effective in reducing propofol pain in children. Another study of Batra and coworkers (7) showed also the effect of remifentanil especially when give 0.5 $\mu g.kg^{-1}$. In our study, incidence of moderate pain was 15 % in tramadol group and 10 % in lidocaine group whereas 35.9 % in the control group and severe pain was found 28.2 % also. No patient in both tramadol and lidocaine group had experience of severe pain.

In another study of children, Kaabachi et al (33) compared the effects of ketamine-propofol and lidocaine-propofol mixture in children and they showed that both of them were effective but lidocaine was better than ketamine on propofol injection pain. In our study, we also found both tramadol and lidocaine were effective in reducing pain but clinically lidocaine seems to be better analgesia than tramadol though statistically no significant. We suggested that this clinical difference might be related with the different actions of the studied drugs.

Pang et al (14) showed that 50 mg tramadol given as pretreatment following a venous occlusion with a tourniquet for one min significantly reduced propofol injection pain in adults compared with lidocaine 60 mg or placebo group. They found the overall incidence of pain was 23 % in tramadol, 9 % in lidocaine and 69 % in the control group and suggested that tramadol reduced propofol pain due to its peripheral analgesic action which was demonstrated with the use of a tourniquet for one minute. As mentioned before tournique is not used in the current study therefore we could not be explained the analgesic effect of tramadol here with merely peripheral analgesic action of this drug. Besides, it was known that tramadol has a dual effect and it does not have a single mechanism on analgesia. We thought that in this study tramadol might be exerted its effect not only with a peripheral action but also with an action on cental monoaminergic system which may be contributed to its analgesic effect.

In conclusion, it was shown in this study that pretreatment with iv tramadol to be equally effective in relieving propofol injection pain compared to lidocaine mixed with propofol and it is also useful for intraoperative and postoperative analgesia when relatively such these minor operations are undertaken. Further studies comparing tramadol with other opioids that have been shown to reduce propofol injection pain are needed in pediatric population, especially dose ranging studies.

Competing Interests

None of the authors has any personal or financial relationship with the potential to inappropriately influence (bias) his or her actions or this manuscript; no financial or other potential conflicts of interest exist regarding this manuscript (includes involvement with any organization with a direct financial, intellectual, or other interest in the subject of the manuscript).

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