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ORIGINAL ARTICLE

Pretreatment with remifentanil, fentanyl, or lidocaine to prevent withdrawal after rocuronium using venous occlusion technique in children and adolescents: a prospective randomized placebo-controlled double-blind study

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Abstract
Background Pain caused by intravenous injection of the muscle relaxant rocuronium bromide is common in children and adolescents. The cause of this unwanted effect is still unclear, and different pretreatment drugs have been administered in attempts to alleviate this side effect, with varying degrees of success.
Purpose This study used a 60-s venous occlusion technique to evaluate the effectiveness of pretreatment with lidocaine, fentanyl, or remifentanil in preventing pain-induced withdrawal caused by intravenous injection of rocuronium bromide during the induction of general anesthesia.
Method One hundred and one child and adolescent patients, ASA I–II, requiring various surgical procedures under general anesthesia with muscle relaxation and mechanical ventilation, were enrolled. Patients were allocated randomly using computer-generated randomization into one of four pretreatment groups: a remifentanil group (1 μg/kg, $n = 25$), fentanyl group (1 μg/kg, $n = 26$), lidocaine 1 % group (0.5 mg/kg, $n = 25$), and normal saline group ($n = 25$). Drug doses were prepared in normal saline to a total volume of 5 ml. Venous occlusion was applied 10 cm above the venous access site. Pretreatment drugs were injected and retained for 60 s at the site of injection by an anesthetist blinded to group allocation. After release of the tourniquet, rocuronium (0.5 mg/kg) was then injected over 5 s, and withdrawal was recorded by another anesthetist blinded to group allocation. Descriptive statistics, analysis of variance, and a chi-squared test were used to statistically analyze the results as appropriate.
Results Compared to normal saline, all other pretreatment groups scored a significantly lower mean of withdrawal response ($P < 0.001$). Lidocaine was superior to both remifentanil ($P < 0.05$) and fentanyl ($P < 0.05$) in suppressing the withdrawal response to rocuronium injection. Remifentanil was superior to fentanyl in suppressing the withdrawal response caused by rocuronium injection ($P < 0.001$).
Conclusion Using a venous occlusion technique for 60 s, lidocaine was found to be most effective in preventing the withdrawal effect caused by rocuronium injection in children and adolescents. Lidocaine was superior to remifentanil which, in turn, was more effective than fentanyl.

Keywords Anesthesia · Fentanyl · Lidocaine · Pain · Remifentanil · Rocuronium bromide

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Introduction

Pain caused by intravenous injection of some anesthetic agents is common [1], and the incidence of pain after rocuronium injection can be as high as 80 % [2–4]. Withdrawal of the wrist and arm, or even generalized movements, may be caused by the pain induced by rocuronium injection after induction of general anesthesia [3, 4]. The mechanism by which rocuronium injection causes

pain is not yet fully understood. Different drugs have been used with and without venous occlusion to prevent the pain caused by rocuronium injection, with variable success rates. These include lidocaine, opioids, ondansetrone, magnesium sulphate, ketamine, and ketorolac [5–10]. Remifentanil has been used by Kim and colleagues [11] to prevent the withdrawal effect caused by rocuronium injection in children.

Despite the preceding loss of consciousness induced by hypnotic drugs, there is still a high incidence of withdrawal of the arm or generalized movements that are presumed to be secondary to pain at the site of rocuronium injection [11]. Although deepening the level of anesthesia may help to reduce this incidence, it may result in a higher incidence of side effects of the hypnotic drugs. The aim of this study was to evaluate the effect of pretreatment with lidocaine, fentanyl, or remifentanil in preventing withdrawal movements caused by intravenous injection of rocuronium after loss of consciousness during the induction of anesthesia using a 60-s venous occlusion technique.

Methods

After obtaining Institutional Ethics Committee approval at the University of Jordan Faculty of Medicine (Institutional Approval number 11/2006-2007), this prospective, randomized, placebo-controlled, double-blind study was performed at the University of Jordan Hospital, Amman, Jordan, between January 2009 and December 2010. Written informed consent was obtained from the parents of each child. A 33 % decrease in pain was considered to be a clinically relevant difference when comparing different study drugs. At a study power (β) of 0.8 and a statistical significance level (α) of 0.05, the required sample size was determined to be 100 using G*Power 3.1 software (Psychonomic Society, Inc., Princeton, USA). One hundred and one patients, aged 3–16 years, ASA physical status I–II, undergoing elective surgical procedures under general anesthesia and muscle relaxation, were enrolled in the study. The patients were randomly assigned to one of four groups using computer-generated random numbers. Group 1 ($n = 25$) was given remifentanil (1 μg/kg), group 2 ($n = 26$) was given fentanyl (1 μg/kg), and group 3 ($n = 25$) was given lidocaine 1 %, (0.5 mg/kg). All study drugs were prepared in normal saline (0.9 %) to a total volume of 5 ml. The fourth (control) group ($n = 25$) was given normal saline (0.9 %, 5 ml). The dose of lidocaine was chosen based on its previous safe use in a similar study [4]. As fentanyl has not been studied before in pediatric patients using the venous occlusion technique, we chose to use the more conservative 1 μg/kg dose of fentanyl compared to the higher 2 μg/kg dose used in adults in a previous study [5]. We could not find previous studies describing the use of remifentanil using the venous occlusion technique, and used the 1 μg/kg dose that was safely administered by free flow intravenous injection [11]. An independent researcher prepared the study solutions. The identity of the pretreatment drug was not revealed to the anesthesia provider, the research member who scored the withdrawal response, the adolescent patients, or the parents. Solutions of all study drugs were clear and prepared in equal volumes using the same syringe size and trademark. Concealment of drug identity was ensured by using a plain white label detailing only the drug assignment number from the randomization sequence and the drugs were brought to the theater in sealed envelopes. The drug which had been used for each patient was revealed only after measuring the study outcomes. Exclusion criteria were difficult intravenous access, a history of allergy to the study drugs, and receipt of analgesics or sedation in the preoperative period.

None of our study group patients received premedication or local anesthetic (EMLA) cream at the intravenous cannula insertion site. All patients were monitored with 3-lead ECG, non-invasive blood pressure measurement, pulse oximetry, and capnography. Upon arrival in the operating theater, a 22G intravenous Venflon® cannula (BD Medical, New Delhi, India) was inserted into the dorsum of the hand and checked for function. Lactated Ringer's crystalloid solution was then set up for gravity-driven free flow through the venous catheter.

After baseline measurements of arterial blood pressure and pulse rate, inhalational induction of anesthesia was carried out using sevoflurane in a 50 % oxygen/nitrous oxide gas mixture. After loss of consciousness, a tourniquet in the form of a mercury sphygmomanometer pediatric cuff was applied 10 cm proximal to the intravenous access point and inflated to a pressure of 65 mmHg. The allocated study drug was injected and retained for 60 s by an anesthetist blinded to study drug allocation. Venous occlusion was then released followed by injection of rocuronium bromide (0.5 mg/kg) over 5 s by the anesthetist who had injected the study drug. Using a scale proposed by Shevchenko and colleagues (1: no response, 2: movement at the wrist only, 3: movement/withdrawal involving arm only (elbow/shoulder), 4: generalized response, movement/withdrawal in more than one extremity) [4], patient responses were recorded by an anesthesia registrar who was also blinded to study drug allocation. Mean arterial pressure, heart rate, and oxygen saturation were recorded 1 min before injection of rocuronium and 1 min after injection. Tracheal intubation was carried out 3 min after rocuronium injection and anesthesia was maintained with sevoflurane in a 50 % oxygen/nitrous oxide gas mixture. Patients were observed to monitor adverse effects of study

Table 1 Patients' demographic characteristics

	Remifentanyl	Fentanyl	Lidocaine	Normal saline	*P*
Number	25	26	25	25	
M/F	17/8	19/6	18/7	22/3	0.33
Age[a]	8.0 (2.9, 4–15)	8.0 (3.0, 3–15)	8.5 (3.5, 4–16)	8.1 (4.3, 4–16)	0.95
Weight (kg)[b]	26.6 ± 7.7	30.4 ± 13.9	28.5 ± 10.5	28.3 ± 16.0	0.79

[a] Values are mean (SD, range)

[b] Values are mean ± SD

Table 2 Shows the incidence of different withdrawal grades among the four pretreatment groups

Withdrawal response	Remifentanyl ($n = 25$)$^{*\#\dagger}$	Fentanyl ($n = 26$)$^{*\#}$	Lidocaine ($n = 25$)*†	Normal saline ($n = 25$)
No withdrawal	14 (56 %)	1 (4 %)	21 (84 %)	0 (0 %)
Withdrawal response				
Total	11 (44 %)	25 (96 %)	4 (16 %)	25 (100 %)
Wrist	7 (28 %)	7 (27 %)	4 (16 %)	1 (4 %)
Arm only	4 (16 %)	14 (54 %)	0 (0 %)	7 (28 %)
Generalized movement	0 (0 %)	4 (15 %)	0 (0 %)	17 (68 %)

Values are number of patients (percentages)

* $P < 0.001$ compared with normal saline group

$^{\#}$ $P < 0.05$ compared with lidocaine group

† $P < 0.001$ compared with fentanyl group

drugs, including hypotension, hypertension, arrhythmias, muscle rigidity, and allergic manifestations.

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA). Data were summarized using descriptive statistics as frequencies and percentages for categorical variables and mean ± SD for continuous variables. Patients' characteristics were compared using analysis of variance or a chi-squared test as appropriate. The Kruskal–Wallis test was used to compare the incidence of pain among study groups and the Mann–Whitney *U* test was used for multiple comparisons between the independent individual groups. A value of $P < 0.05$ was considered indicative of significant difference.

Results

One hundred and one patients were enrolled in this study. There were no significant differences in demographic data between the four patient groups (Table 1). Overall withdrawal movement upon injection of rocuronium occurred in all patients (100 %) in the saline group, 16 % (4/25) in the lidocaine group, 96 % (25/26) in the fentanyl group, and 44 % (11/25) in the remifentanil group (Table 2). Generalized movements (grade 4) occurred in 68 % (17/25) in the saline group, 15 % (4/26) in the fentanyl group, and none in the lidocaine or remifentanil groups (0 % each). When compared to normal saline, all other three pretreatment groups had significantly lower withdrawal response scores. Lidocaine was superior to remifentanil, which was superior to fentanyl in suppressing withdrawal responses following rocuronium injection.

No patient had any adverse effects caused by administration of the study drugs and hemodynamic changes were within a clinically accepted range.

Discussion

Pain upon intravenous injection of some anesthetic drugs in children and adolescents can cause serious complications. Pulmonary aspiration secondary to gastric regurgitation has been reported as a consequence of the generalized movements induced by this type of pain [12]. Pediatric patients are more likely to undergo accidental loss of venous access due to patient movement [13]. A common pathway in hypotheses about the mechanism of pain induced by intravenous injection of drugs is the stimulation of polymodal nociceptors, leading to release of endogenous pain mediators. This stimulation is speculated to be caused by the unphysiological osmolarity or pH of the drug solution [14]. Although the rocuronium preparation is isotonic, it has a pH of 4, which may explain its association with pain on intravenous injection [14].

Pretreatment drugs used to prevent pain on injection of rocuronium or propofol have been administered either in a

direct intravenous manner [8, 9, 15], or by using a venous occlusion technique [7, 16]. None of the studies carried out in children that used venous occlusion included remifentanil as a study drug. This study may thus be the first to examine using remifentanil with venous occlusion as a possible pretreatment drug to prevent rocuronium-induced injection pain in children and adolescents.

In addition to the nervous system, opioid receptors are distributed throughout body tissues including the vascular endothelium [17]. The mechanism of the local analgesic effect of opioids, however, can also be through nonspecific membrane conduction-blocking effects that are shared by many other compounds [18, 19] this second mechanism is supported by the observation that the local anesthetic action of opioids is not reversed by naloxone [20]. By preventing the central spread of opioid drugs, venous occlusion will provide better pharmacokinetic conditions for their action and make any observed effect exclusively local. The results of this study agree with previous studies using this technique in showing the local anesthetic effect of opioids.

Our results agree with those reported by Memis et al. [7], which showed the superiority of lidocaine over fentanyl when using the venous occlusion technique in adult patients. Under such conditions, the two drugs were retained locally for the same length of time. However, when the two drugs were administered freely without venous occlusion, fentanyl was found to be more effective than lidocaine, as shown by Ahmad et al [15]. Their finding that efficacy depends on administration technique suggests that the central effect of fentanyl is as important as the peripheral effect of lidocaine in preventing pain on rocuronium injection.

The superiority of remifentanil over fentanyl in our study can be explained by the 1-min venous occlusion technique that we used. Remifentanil has a faster onset of action than fentanyl (1 vs. 3–5 min, respectively). The faster onset of action of remifentanil can be explained by its alkaline pKa (8.4) compared to that of fentanyl (7.09). At physiological pH, remifentanil is 90 % non-ionized, compared to 33 % for fentanyl. The 1-min venous occlusion time limit in our study is thus unfavorable for fentanyl to establish its local effect. Another factor is the conservative dose (1 μg/kg) of fentanyl that we used. A 2-μg/kg dose would be expected to produce a faster onset and more intense analgesic effect, and would be likely to change the ranking of fentanyl among the study drugs. However, as fentanyl had not been studied before using the venous occlusion technique in pediatric patients, we chose the more conservative 1-μg/kg dose. Studies comparing remifentanil with fentanyl pretreatment administered without venous occlusion showed inconsistent results about the superiority of remifentanil over fentanyl in controlling pain caused by rocuronium injection [5, 21]. This is likely due to the lack of dose standardization and differences in the timing of rocuronium administration after the pretreatment drugs.

The use of lidocaine for the prevention of pain caused by the injection of some anesthetic drugs is well established in the literature [6]. As the local concentration of lidocaine at the intended site of action will be decreased by venous blood flow, the venous occlusion technique will provide more optimal conditions for its action, which has an onset time of around 45–90 s.

Combinations of lidocaine and ketamine administered with venous occlusion have recently shown promise in reducing the pain caused by propofol injection [22]. This method has the advantage of decreasing individual drug doses and side effects, as reported by Chaudhary and colleagues [22]. Studies adopting this method for using opioid drugs to control rocuronium injection-induced pain in pediatric patients are recommended.

Limitations of our study include the use of fentanyl at only 1 μg/kg, which is lower than the 2 μg/kg dose used in a previous study [5]. Since our study used the venous occlusion technique, we opted to use the more conservative 1-μg/kg dose, but this could be a reason why fentanyl scored lower than other drugs in preventing withdrawal responses in our study. Another limitation is the possibility of tourniquet-induced pain as the cause of limb withdrawal. In a conscious adult volunteer study, tourniquet pain was reported after a mean of 31 min using pressures of 300 and 400 mmHg with lower limb exsanguination. Although we applied the tourniquet for only 1 min in our study, [23] the possibility of pain cannot be ruled out completely, as no similar studies were carried out in pediatric age groups.

Conclusion

Our results are consistent with those of previous studies with respect to the effectiveness of lidocaine and fentanyl in preventing movements due to the pain caused by rocuronium injection. Remifentanil (1 μg/kg) was superior to fentanyl (1 μg/kg) in preventing these movements using the venous occlusion technique. Although it was generally less effective than lidocaine, remifentanil was comparable to it in preventing generalized movements.

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