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Original Article

Prevention of Withdrawal Movement Associated with the Injection of Rocuronium in Children: Comparison of Paracetamol and Lidocaine

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Abstract

Objective: Pain from rocuronium injection is observed in 50%–80 % of patients. This study aimed to compare the effectiveness of pretreatment with paracetamol and lidocaine in preventing pain-induced withdrawal caused by the intravenous injection of rocuronium during the induction of general anaesthesia in paediatric patients.

Methods: Ninety children were randomized into two groups using a simple drawing from the box method: a paracetamol group (Group P, n=45) and a lidocaine group (Group L, n=45). After anaesthesia induction, venous occlusion was applied by a paediatric cuff inflated to a pressure of 75 mmHg and by 50 mg paracetamol and 0.5 mg kg^{-1} lidocaine was injected in Groups P and L, respectively. Venous occlusion was then released, followed by rocuronium injection (0.6 mg kg^{-1}). Withdrawal was evaluated using a 4-point scale (1, no response; 2, movement at the wrist only; 3, movement/withdrawal involving arm only (elbow/shoulder) and 4, generalized response, movement/withdrawal in more than one extremity).

Results: The incidence of withdrawal movement was 42% and 26% in the Groups P and L, respectively (p=0.120). Although no significant differences were noted in the number of patients who had no withdrawal movement and mild withdrawal movement in Groups P and L, compared with Group L, the incidences of moderate withdrawal movement were significantly higher in Group P (p<0.05). No patient in either group revealed generalized movement.

Conclusion: Using a venous occlusion technique, pretreatment with 50 mg paracetamol can prevent withdrawal movement caused by rocuronium injection in children but is not as effective as lidocaine to prevent moderate withdrawal movement.

Keywords: Rocuronium, withdrawal movement, lidocaine, paracetamol

Introduction

Pain develops in 50%–80% patients during intravenous (i.v.) rocuronium injection (1, 2). Despite loss of consciousness after anaesthesia induction, rocuronium injection can lead to limited movement such as withdrawal of the arm and sometimes generalized movement in the whole body. This withdrawal movement is considered secondary to pain.

Various agents and methods have been used for preventing rocuronium injection pain (2-4). Ketamine, opioids and diphenhydramine are the drugs having been tried. Some techniques such as dilution of rocuronium or heating injection site have also been found to be effective (5, 6). Specific agents are used for managing injection pain and their administration through the venous occlusion technique increases their efficacy. Lidocaine is the most efficient agent used for this purpose.

Paracetamol is an agent with analgesic and antipyretic effects, and it is commonly used in daily clinical practice. There are some studies demonstrating that paracetamol provides its anti-nociceptive effect through both central and peripheral cyclooxygenase-2 inhibition (COX2) (7-9). In a recent study, it was revealed that paracetamol selectively inhibits peripheral prostaglandin synthesis (PGE2) in the experimental acute inflammation model (10). Although paracetamol does not inhibit COX1, COX2 enzymes in vitro at treatment dose, it has been revealed to inhibit COX3, which is accepted as a COX1 variant, in vivo (11). The fact that paracetamol administered via the venous occlusion technique prevents pain because of

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propofol injection suggests that paracetamol has a peripheral effect (12). These studies indicate that paracetamol can also be effective in preventing pain induced by rocuronium injection. Rocuronium injection pain is seen in paediatric patients more frequently than in adult patients (13). Most of studies on the pain caused by rocuronium injection include adult patients and this issue has not been investigated in children adequately.

The aim of this study is to compare the efficiency of i.v. paracetamol administered through the venous occlusion technique with that of i.v. lidocaine for preventing pain caused by i.v. rocuronium injection in children who are scheduled to undergo a surgery under general anaesthesia.

Methods

After receiving the approval from the Ethics Committee of the Ministry of Health Dışkapı Yıldırım Beyazıt Education and Research Hospital (15.12.2014-18/34), we included 90 children scheduled to undergo elective surgery in the study; the children were aged 2–14 years and had an American Society of Anaesthesiologists (ASA) physical status of I–II. Patients having a known allergy to the administered drugs, having neurological and psychiatric problems, having received long-term analgesic treatment and having a thin dorsal vein on the dorsum of the hand were excluded from the study. Written informed consent was obtained from the parents of the children.

The patients were randomly divided into two groups by a simple drawing-lots method: paracetamol group (Group P) and lidocaine group (Group L).

All patients were administered anaesthesia using the same technique; 0.5 mg kg^{-1} of oral midazolam was administered as a premedication 45 minutes (min) before surgery. Patients' heart rates (HR); systolic, diastolic and mean blood pressures (SBP, DBP, MBP); and peripheral oxygen saturations (SpO_2) were monitored. In anaesthesia induction, i.v. 5–7 mg kg^{-1} thiopental was administered to patients for whom vascular access could be established. Sevoflurane in the mixture of 50/50% O_2/N_2O was administered with the help of a facial mask for patients whose vascular access could not be established.

After anaesthesia induction, the sphygmomanometer cuff was inflated to a pressure of 75 mm Hg for venous occlusion. Then, the patients were administered i.v. 50 mg paracetamol in Group P and i.v. 0.5 mg kg^{-1} lidocaine in Group L. The dose of lidocaine was selected on the basis of a similar study in which it was used safely in paediatric patients (3). In literature, we have not found a study in which paracetamol was used through the venous occlusion technique in paediatric patients. Therefore, the dose of paracetamol was identified on the basis of a study in which peripheral analgesic efficiency was shown in adult patients (12). Venous occlusion was released 60 seconds (sec) later and 0.6 mg kg^{-1} rocuronium bromide was injected within 5 sec. The movements observed in the patients were evaluated by using a 4-score scale (Table 1) (14). Paracetamol and lidocaine injections were prepared at equal volumes (5 mL) and labelled by an anaesthetist blinded regarding the groups. The anaesthetist that evaluated movements after injection was not informed about the groups; thus, double-blinding of the research was preserved. The patients were intubated 3 min after rocuronium injection and anaesthesia was maintained with sevoflurane in the mixture of 50/50% O_2/N_2O.

Injection site was evaluated in terms of rash, oedema and pain for 24 hours (h).

Statistical analysis

The data were statistically analysed by using the Statistical Package for Social Sciences for Windows software version 12.0 (SPSS Inc.; Chicago, IL, USA). Findings were presented as mean ± standard deviation (SD), the number of patients (n) and the frequency of events (%). Student's t-test was used for continuous values (age, weight) and the chi-square test was used for discrete data (gender, pain and the arm withdrawal movement). In all evaluations, the value of $p<0.05$ was considered statistically significant. For determining adequate number of patients, a previously conducted study, in which the rate of painless injection was found to be 48% with lidocaine and 22.5% with paracetamol, was taken as a reference (15). In our study, 43 patients was the calculated minimum sample size required for getting the difference of 25.5% in painlessness, type I error of 0.05 and power of 80% between lidocaine and paracetamol groups.

Results

The groups were similar with regard to patient characteristics (Table 2). In Group P, withdrawal movements because of rocuronium injection occurred in 42% (19/45) of patients. The severity of these movements was mild in 29% (13/45) patients and moderate in 13% (6/45) patients. In Group L, withdrawal movements were observed in 26% (12/45) of patients. The severity of the movement was mild in 24% (11/45) patients and moderate in 2% (1/45) patients. Although there was no difference between the groups in terms of the number of patients with mild withdrawal movements

Table 1. The evaluation of withdrawal movements associated with rocuronium injection pain

Degree	
0 (None)	No movement
1 (mild)	Movement in the wrist
2 (moderate)	Movement in the arm (elbow/shoulder)
3 (severe)	More generalized movement rather than just a single extremity

Table 2. Comparison of patients' characteristics between the groups

	Group P (n= 45)	Group L (n=45)	p
Age (year)	6.5±2.0	6.6±3.1	0.936[t]
Gender (F/M)	22/23	21/24	0.833[χ^2]
Weight	22.7±5.5	22.6±7.9	0.951[t]

Values are presented as mean ± standard deviation and number. No difference was found between the groups. χ^2: chi-square test, t: Student's t-test. F: female; M: male

Table 3. The distribution of the severity of withdrawal movement according to the groups

Severity of withdrawal movement	Group P (%) (n=45)	Group L (%) (n=45)	p
0	26 (58)	33 (73)	0.600[χ^2]
1	13 (29)	11 (24)	0.634[χ^2]
2	6 (13)	1 (2)	*0.045[χ^2]
3	0	0	
(1+2+3)	19 (42)	12 (26)	0.120[χ^2]

Values are presented as the number of patients and percentage (%). Severity of withdrawal movements 0: no movement, 1: movement only in the wrist, 2: movement only in the arm (elbow/shoulder), 3: more generalized movement rather than just a single extremity. *No difference was found between the groups in terms of the frequency of 2nd degree withdrawal movements. χ^2: chi-square test.

and without withdrawal movements, the number of patients with moderate withdrawal movements was higher in Group P than in Group L (p=0.045) (Table 3). In the comparison of the groups with regard to the severity of withdrawal movements, no significant difference was found between the groups (p=0.102). In both groups, no patient had generalized movement.

In the evaluation performed 24 h after the intervention, no pain, rash, swelling or allergic reaction was detected in any patient.

Discussion

Paracetamol prevented withdrawal movements induced by rocuronium injection in 58% paediatric patients. However, it was not found to be as effective as lidocaine for preventing moderate withdrawal movements.

It was demonstrated in previous studies that pain associated with i.v. injection of anaesthetic agents and withdrawal movements because of this pain led to problems during anaesthesia induction. Generalized movements in unconscious patients have caused gastric regurgitation and pulmonary aspiration have been reported as well (16). In paediatric patients, the loss of established vascular access and subcutaneous fat tissue thickness require re-cannulation of thin vessels and this can lead to difficulties (17).

The mechanism of pain caused by rocuronium injection is not exactly known, but various mechanisms have been proposed. Pain that occurs during the injection of anaesthetic agents is perceived by polymodal nociceptors that innervate the peripheral veins. Drugs having non-physiological osmolality or pH values cause pain more frequently and with high severity. Injection pain can result from direct irritant effect created in the vein wall by these agents (18). Painfulness of rocuronium injection, an isotonic and sterile solution, has been attributed to its acidic pH (18). It has been reported that aminosteroid neuromuscular blockers directly activate C nociceptors; pain occurs because of the subsequent release of calcitonin gene-related peptide and PGE2 (19).

The venous occlusion technique reveals the peripheral effect of an agent without its central effect, similar to the case in Bier block (20). Some agents such as lidocaine, tramadol and ondansetron have been used with this technique for preventing pain induced by rocuronium and propofol (2, 12). Among these agents, lidocaine is the most efficient one used for this purpose.

The early onset of rocuronium-induced pain, its burning nature, its short duration and its lack of recurrence during repeated injections suggest that this pain is associated with local irritant effect; thus, the local anaesthetic effect of lidocaine can be useful for preventing this pain. Cheong et al. (21) used 10 and 30 mg lidocaine for preventing rocuronium injection pain; they demonstrated that both doses prevented rocuronium injection pain, but 30 mg lidocaine was more effective. In another study conducted on 250 adult patients, 30 mg lidocaine used via the venous occlusion technique prevented pain in 72% patients (2). Abu-Halaweh et al. (3) performed a study including 100 paediatric patients and compared 0.5 mg kg^{-1} lidocaine, fentanyl, remifentanil and physiological saline solution. Their results showed that lidocaine prevented rocuronium injection pain at the rate of 84%. In our study, we used a lidocaine dose consistent with that reported in literature with the venous occlusion technique. Our results showed that 73% patients did not have withdrawal movements with 0.5 mg kg^{-1} lidocaine, whereas 24% patients had mild movement.

Paracetamol has been reported to inhibit PGE2 release in tissues such as the lung, the spleen and the brain (7). There are some studies having investigated the effect of the peripheral analgesic effect of paracetamol on preventing propofol and rocuronium injection pain (12, 15). In the study of Canbay et al. (12), which included 150 adult patients, it was found that 50 mg paracetamol administered with the venous occlusion technique was as effective as lidocaine in preventing propofol injection pain; in addition, it was stated that this might be associated with the inhibiting effect of paracetamol on the release of peripheral PGE2 and COX2.

Ateş et al. (22) compared 50 mg paracetamol, administered through the venous occlusion technique, with lidocaine

in 150 adult patients and they reported that paracetamol was as effective as lidocaine for preventing rocuronium injection pain. They explained this effect to be associated with the relationship between the local mediator release and rocuronium injection pain, causing paracetamol to result in the alleviation of acute pain. In another study, Jeon et al. (23) found that the use of 50 mg paracetamol with the technique is as effective as lidocaine for preventing withdrawal movements induced by rocuronium injection pain. On the other hand, in our study, 50 mg paracetamol administered through the venous occlusion technique was not as effective as lidocaine in preventing moderate withdrawal movements associated with rocuronium injection pain. In the study of Ateş et al. (22), venous occlusion lasted for 120 sec after paracetamol injection, but anaesthesia induction was administered earlier. On the other hand, in the study of Jeon et al. (23), venous occlusion after paracetamol injection lasted for 120 sec; however, induction was performed with thiopental after removal of occlusion, following this followed by the injection of rocuronium was injected. In our study, the same efficiency was not obtained because the occlusion time was shorter. In addition, another reason may be that Jeon et al. (23) gave thiopental before rocuronium administration. In this manner, might have escaped into the systemic circulation, resulting in the emergence of its central effects.

Opioids such as fentanyl and remifentanil and agents such as ketamine and lidocaine have been used for avoiding rocuronium injection pain. The results of research about the effect of remifentanil on rocuronium injection pain are contradictory. According to the findings of a study using the venous occlusion technique that compared lidocaine, remifentanil and fentanyl in children, remifentanil was not found to be as effective as lidocaine. On the other hand, in another study, remifentanil was compared to physiological saline solution in children; the results revealed that remifentanil prevented injection pain in 77% patients (3, 23, 24). In the same study, fentanyl was not found to be effective in preventing rocuronium injection pain (3). Paracetamol is an analgesic and antipyretic drug that is safely used in paediatric patients, and it can be considered as an alternative for preventing rocuronium injection pain.

The absence of a control group can be considered as a limitation of our study, but we thought that it would not be ethical not to stop the injection pain in paediatric patients. Considering the complications that could develop because of the withdrawal movements associated with pain, the use of paracetamol for preventing withdrawal movements induced by rocuronium injection pain was compared with the use of lidocaine, the efficiency of which was supported by literature.

Conclusion

Fifty milligrams of paracetamol administered through the venous occlusion technique prevents withdrawal movements because of the pain caused by rocuronium injection in 58% paediatric patients. However, paracetamol is not as efficient as lidocaine in preventing moderate withdrawal movements.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital (12.15.2014 Number: 18/34).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

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References

1. Reddy MS, Chen FG, Ng HP. Effect of ondansetron pretreatment on pain after rocuronium and propofol injection:a randomised, double-blind controlled comparison with lidocaine. Anaesthesia 2001; 56: 902–5. [CrossRef]
2. Memis D, Turan A, Karamanlioglu B, Sut N, Pamukçu Z. The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol and fentanyl. Anesth Analg 2002; 94: 1517-20. [CrossRef]
3. Abu-Halaweh SA, Aloweidi AK, Qudaisat IY, Al-Hussami MO, Al Zaben KR, Abu-Halaweh AS. 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. J Anesth 2014; 28: 886-90. [CrossRef]
4. Jung KT, Kim HJ, Bae HS, Lee HY, Kim SH, So KY, et al. Effects of lidocaine, ketamine, and remifentanil on withdrawal response of rocuronium. Korean J Anesthesiol 2014; 67: 175-80 [CrossRef]
5. Tuncali B, Karci A, Tuncali BE, Mavioglu O, Olguner CG, Ayhan S, et al. Dilution of rocuronium to 0. 5 mg/mL with 0. 9% NaCl eliminates the pain during intravenous injection in awake patients. Anesth Analg 2004; 99: 740-3. [CrossRef]
6. Mahajan C, Rath GP, Bithal PK, Prabhakar H, Yadav R, Dube SK. Local warming at injection site helps alleviate pain after rocuronium administration. J Anesth 2010; 24: 845-8. [CrossRef]
7. Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). Nature 1972; 240: 410-1. [CrossRef]
8. Abbott FV, Hellemans KG. Phenacetin, acetaminophen and dipyrone: analgesic and rewarding effects. Behav Brain Res 2000; 112: 177-86. [CrossRef]
9. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J 2008; 22: 383-90. [CrossRef]

10. Lee YS, Kim H, Brahim JS, Rowan J, Lee G, Dionne RA. Acetaminophen selectively suppresses peripheral prostaglandin E2 release and increases COX-2 gene expression in a clinical model of acute inflammation. Pain 2007; 129: 279-86. [CrossRef]
11. Simmons DL, Botting RM, Robertson PM, Madsen ML, Vane JR. Induction of an acetaminophen-sensitive cyclooxygenase with reduced sensitivity to nonsteroid antiinflammatory drugs. Proc Natl Acad Sci USA 1999; 96: 3275-80. [CrossRef]
12. Canbay O, Celebi N, Arun O, Karagoz AH, Saricaoğlu F, Ozgen S. Efficacy of intravenous acetaminophen and lidocaine on propofol injection pain. Br J Anaesth 2008; 100: 95-8. [CrossRef]
13. Borgeat A, Kwiatkowski D, Ruetsch YA. Spontaneous movements associated with rocuronium injection: the effects of prior administration of fentanyl. J Clin Anesth 1997; 9: 650-2. [CrossRef]
14. Shevchenko Y, Jocson JC, McRae VA, Stayer SA, Schwartz RE, Rehman M, et al. The use of lidocaine for preventing the withdrawal associated with the injection of rocuronium in children and adolescents. Anesth Analg 1999; 88: 746-8. [CrossRef]
15. Uzun S, Erden IA, Canbay O, Aypar U. The effect of intravenous paracetamol for the prevention of rocuronium injection pain. Kaohsiung J Med Sci 2014; 30: 566-9. [CrossRef]
16. Lui JT, Huang SJ, Yang CY, Hsu JC, Lui PW. Rocuronium induced generalized spontaneous movement caused pulmonary aspiration. Chong Gung Med J 2002; 25: 617-20.
17. Solomowitz BH. Intravenous cannulation: a different approach. Anesth Prog 1993; 40: 20-2.
18. Kelment W, Arndt JO. Pain on i.v. injection of some anesthetic agents is evoked by the unphysiological osmolarity or pH of their formulations. Br J Anaesth 1991; 66: 189-95. [CrossRef]
19. 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: 245-53. [CrossRef]
20. Koppert W, Sittl R, Schmelz M. The Bier block as an experimental tool to differentiate peripheral and central effects of analgesics on people. Schmerz 2000; 14: 69-76. [CrossRef]
21. Cheong KF, Wong WH. Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment. Br J Anaesth 2000; 84: 106-7. [CrossRef]
22. Ateş G, Köse EA, Öz G, Apan A. Pain effect of paracetamol pretreatment on rocuronium-ınduced ınjection pain: a randomized, double-blind, placebo-controlled comparison with lidocaine. J Clin Anal Med 2014; 5: 507-10. [CrossRef]
23. Jeon Y, Baek SU, Park SS, Kim SO, Baek WY, Yeo JS. Effect of pretreatment with acetaminophen on withdrawal movements associated with injection of rocuronium: a prospective, randomized, double-blind, placebo controlled study. Korean J Anesthesiol 2010; 59: 13-6. [CrossRef]
24. Kim JY, Kim JY, Kim YB, Kwak HJ. Pretreatment with remifentanil to prevent withdrawal after rocuronium in children. Br J Anaesth 2007; 98: 120-3. [CrossRef]