

PAEDIATRICS

Pretreatment with remifentanyl to prevent withdrawal after rocuronium in children

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Background. Pain from rocuronium injection is a common side-effect reported to occur in 50–80% of the patients. This randomized, double-blind, placebo-controlled study was designed to evaluate the efficacy of pretreatment with i.v. remifentanyl on prevention of withdrawal response during rocuronium injection in paediatric patients.

Methods. After obtaining parental consents, 70 paediatric patients were randomly allocated into two groups to receive either i.v. remifentanyl $1 \mu\text{g kg}^{-1}$ (remifentanyl group, $n=35$) or i.v. saline 5 ml (saline group, $n=35$). Anaesthesia was induced with thiopental sodium 2.5% (5 mg kg^{-1}) and the test drug was injected over 30 s. One minute after the test drug injection, rocuronium 1% (0.6 mg kg^{-1}) was injected over 5 s and the response was recorded. Mean arterial pressure (MAP) and heart rate were recorded on arrival in the operating theatre, before and 1 min after the tracheal intubation.

Results. The overall incidence of withdrawal movements was significantly higher in the saline group (33 patients; 94%) than that in the remifentanyl group (8 patients; 23%) ($P<0.001$). No patient in the remifentanyl group showed generalized movement, whereas 51% of patients in the saline group did. Remifentanyl prevented significant increase in MAP after intubation.

Conclusion. This study demonstrated that pretreatment with remifentanyl $1 \mu\text{g kg}^{-1}$ provided a safe and simple method for reducing the incidence of rocuronium-associated withdrawal movement with haemodynamic stability in children.

Br J Anaesth 2007; **98**: 120–3

Keywords: anaesthesia, paediatric; analgesics opioid, remifentanyl; neuromuscular block, rocuronium; pain, injection

Accepted for publication: September 9, 2006

Pain on rocuronium injection is a common side-effect reported in 50–80% of the patients.^{1–3} Even after loss of consciousness during induction of anaesthesia, rocuronium injection is associated with withdrawal of the arm or generalized movement and such movements are presumed to be secondary to pain at the site of injection.^{2,3}

Pretreatment or mixing with a variety of drugs such as fentanyl and lidocaine has been suggested to attenuate the withdrawal movements related to rocuronium injection pain.^{4–9} Fentanyl was more effective in the prevention of withdrawal response than lidocaine.⁷ Although

withdrawal movements have a tendency to occur more frequently in younger patients,⁴ previous studies were focused mostly on adult patients,^{4–7} and a few studies were on children.^{3,8}

Compared with other opioids such as fentanyl, remifentanyl has the advantage of shortening the induction time and maintaining stable haemodynamics during anaesthesia induction owing to its faster onset and shorter duration.¹⁰ However, there have been no reports on the use of remifentanyl for reduction of withdrawal movements on rocuronium injection in children. This randomized, double-blind,

placebo-controlled study was designed to evaluate the efficacy of pretreatment with i.v. remifentanil to prevention of withdrawal response during rocuronium injection in paediatric patients.

Methods

This study was approved by the institutional review board, and informed parental consent was obtained. The study was conducted prospectively on 70 patients aged between 3 and 10 yr, ASA physical status I or II, undergoing general anaesthesia for elective surgery. Patients were randomly allocated into two groups to receive either i.v. remifentanil $1 \mu\text{g kg}^{-1}$ (remifentanil group, $n=35$) or i.v. saline 5 ml (saline group, $n=35$) using a sealed envelope system. Patients with known allergy to opioids, asthma, neurological deficits, those who received analgesics or sedatives within the previous 24 h, and crying children on arrival in the operating theatre were excluded from this study. Patients, anaesthesia providers and investigators who scored the movements were blinded to the treatment group and an independent researcher prepared the study solution consisting of 5 ml mixture of remifentanil (Ultiva, GlaxoSmithKline®, UK) $1 \mu\text{g kg}^{-1}$ and normal saline in the remifentanil group and 5 ml of normal saline in the normal saline group. The study syringes were stored in ambient temperature.

No premedication was administered before surgery. Before arrival at the operating theatre, a 24-gauge cannula was inserted in the dorsum of the hand, and its position was confirmed by a free flow of dextrose/saline infusion by gravity. All patients were monitored with electrocardiogram, pulse oxymeter, non-invasive arterial pressure, capnography and end-tidal sevoflurane monitor on arrival at the operating theatre. Mean arterial pressure (MAP) and heart rate (HR) were recorded on arrival at the operating theatre (baseline), before and 1 min after the tracheal intubation. All drugs were administered through the rubber port connected to the i.v. cannula with a free flow of i.v. fluid. After preoxygenation, anaesthesia was induced with 2.5% thiopental sodium 5 mg kg^{-1} followed by free flow of i.v. fluid until loss of consciousness, which was assessed by loss of eye reflex. Mask ventilation was initiated with oxygen, $F_{\text{IO}_2} = 1$, once the patient became unconscious and apnoeic. Ten seconds later, the test drug was injected over 30 s by the blinded investigator. One minute after the test drug injection, rocuronium 1% (0.6 mg kg^{-1}) was injected over 5 s. Patient response was graded by the investigator according to the following scale proposed by Shevchenko and colleagues:³ 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. The investigator also recorded the incidence of coughing and breath holding.

Sevoflurane was started after rocuronium injection and its end-tidal concentration was adjusted to maintain 2.5 vol% in 100% oxygen. The trachea was intubated 2 min after rocuronium injection and their lungs were mechanically ventilated to maintain normocarbida. Anaesthesia was maintained with sevoflurane (end-tidal concentration of 2–4 vol%) in oxygen/nitrous oxide ($F_{\text{IO}_2}=0.5$). Intubation time, which was defined as the time from mouth opening to obtaining an appropriate capnograph trace, was measured in all patients.

Statistical analyses were performed using the statistical package (SPSS 11.0 for windows, SPSS Inc., Chicago, IL, USA). Data are presented as mean (SD) or number of patients. Patients' characteristics were compared with Student's *t*-test or Fisher's exact test where appropriate. Incidence of withdrawal movement was analysed with Fisher's exact test. Haemodynamic variables were analysed using repeated measures ANOVA. To detect a 50% difference in the incidence of withdrawal movement on rocuronium injection at a significant level of 5% and a probability power of 80%, this study required at least 32 patients per group on the basis of power analysis estimating the incidence of 80%. Statistical significance was defined as $P \leq 0.05$.

Results

There was no significant difference in patient characteristics between the two groups (Table 1). Five patients coughed during the induction of anaesthesia only in the remifentanil group, but the difference was not statistically significant.

The incidence and grade of withdrawal movement are listed in Table 2. The overall incidence of withdrawal movements was significantly higher in the saline group

Table 1 Patient characteristics. Values are mean (SD) or number of patients. ET Sevo, end-tidal sevoflurane concentration just before intubation; coughing, coughing patients during the induction of anaesthesia. No significant differences between the groups were noted

	Remifentanil ($n=35$)	Saline ($n=35$)
Sex (M/F)	25/10	23/12
Age (yr)	7.2 (4–10)	6.7 (4–10)
Weight (kg)	25.8 (8.0)	23.2 (6.1)
ET Sevo (%)	2.6 (0.3)	2.6 (0.2)
Intubation time (s)	17.3 (3.0)	16.3 (3.6)
Coughing (n)	5	0

Table 2 Incidence and grade of withdrawal movements associated with rocuronium injection. Values are number of patients (percentage). * $P < 0.05$ compared with saline group

Grade of withdrawal movements	Remifentanil ($n=35$)	Saline ($n=35$)
1 (No withdrawal)	27 (77%)*	2 (6%)
2 (Wrist withdrawal)	6 (17%)	2 (6%)
3 (Arm only)	2 (6%)*	13 (37%)
4 (Generalized movement)	0 (0%)*	18 (51%)

Table 3 Mean arterial pressure and heart rate during anaesthesia induction. Values are mean (SD). MAP, mean arterial blood pressure; HR, heart rate; baseline, on arrival in the operating theatre. * $P < 0.05$ compared with baseline value within the group, † $P < 0.05$ compared with saline group

	Group	Baseline	Before intubation	1 min after intubation
MAP (mm Hg)	Saline	79.1 (7.6)	83.3 (17.4)	107.5 (13.1)*
	Remifentanyl	75.6 (7.8)	58.7 (7.2)*†	78.6 (15.8)†
HR (beats min ⁻¹)	Saline	91.3 (9.6)	111.9 (13.9)*	130.9 (13.2)*
	Remifentanyl	93.8 (11.2)	95.7 (11.7)†	114.0 (14.0)*†

(33 patients; 94%) than that in the remifentanyl group (8 patients; 23%) ($P < 0.001$). Although the incidence of withdrawal movement grade 2 (wrist withdrawal) was higher in the remifentanyl group than that in the saline group, the difference was not statistically significant. The incidences of withdrawal movement grade 3 (arm only) and 4 (generalized movement) were significantly higher in the saline group than those in the remifentanyl group. No patient in the remifentanyl group showed generalized movement, whereas 51% of patients in the saline group did.

MAP and HR during anaesthesia induction are listed in Table 3. MAP and HR were significantly lower in the remifentanyl group than the saline group before and after tracheal intubation. MAP was significantly decreased in the remifentanyl group before intubation and was significantly increased after intubation in the saline group compared with baseline values. Compared with baseline, HR was significantly increased after intubation in both groups.

Discussion

This study demonstrated that remifentanyl significantly reduces the incidence of rocuronium-induced withdrawal movements and provide haemodynamic stability during the induction of anaesthesia in paediatric patients without delaying anaesthesia. Several reports using different drugs with or without tourniquet technique have been recently published to prevent withdrawal reactions during rocuronium injection.⁴⁻⁹ However, none of them have used remifentanyl and most of them were done in adult patients.

In children, preventing withdrawal movements during rocuronium injection is important because once it is dislodged, it can be a time consuming ordeal to re-cannulate tiny vessels through extensive s.c. fat. In addition, Lui and colleagues¹¹ reported on a child who has developed pulmonary aspiration secondary to gastric regurgitation after generalized spontaneous movements during rocuronium injection. Previous study on paediatric patients by Liou and colleagues⁸ used small-dose ketamine (0.2 mg kg⁻¹) to reduce rocuronium-induced withdrawal movement. They reported that there was 56% reduction of withdrawal movement by ketamine pretreatment and 8% of patients developed generalized movement in the ketamine group. In this study, there was 71% reduction

in the incidence rate of withdrawal movement (≥ 2 response) by remifentanyl pretreatment and no patient exhibited generalized movement in the remifentanyl group.

Although various mechanisms responsible for pain on rocuronium injection have been postulated, the exact mechanism is still unclear.^{9 12 13} Rocuronium is supplied in an isotonic solution with a pH of 4 and this relative low pH was reported as a possible cause of injection pain.¹³ However, low pH is unlikely to be the cause of injection pain because patients receiving normal saline buffered to pH 4 did not complain of pain.² In addition, Tuncali and colleagues¹⁴ reported that dilution of rocuronium to 0.5 mg ml⁻¹ with 0.9% NaCl eliminated the pain during i.v. rocuronium injection in awake adult patients. They reported that pH and osmolalities of the solutions were not different among the groups.

Other possible mechanisms postulated as the cause of rocuronium injection pain are the release of local mediators such as kinins that directly irritate the venous nociceptors;¹⁵ and the allogenic effect of aminosteroidal neuromuscular blocking drugs, which may attribute to a direct activation of C-nociceptors.¹⁶ Regardless of the mechanism, it is likely that pretreatment with remifentanyl has resulted in a deeper level of anaesthesia that increases the pain threshold and thus explains the decreased incidence of withdrawal movements.

The venous occlusion technique has been used to treat rocuronium injection pain.^{3 6} The application of venous tourniquet is useful for drugs with local anaesthetic properties such as lidocaine,^{3 6} ondansetron⁵ or tramadol.⁵ But this technique is not suitable for drugs with central action such as morphine and fentanyl because it prevents the delivery of these drugs to the effect-site. In this study, the tourniquet technique was not used under the assumption that remifentanyl reduces the rocuronium injection pain via central analgesic effect. Ahmad and colleagues⁷ suggested that pretreatment with opioids is only effective if adequate time is allowed for the onset of analgesia, whereas pretreatment with drugs with local anaesthetic properties is effective both when it is administered immediately before or with a venous occlusion technique. Time consuming factor is not a problem in case of remifentanyl as effect-site concentration of remifentanyl peaks at 1 min. In this study, remifentanyl was administered 1 min before rocuronium injection, which did not delay anaesthesia as other opioids such as fentanyl did. On the other hand, it is possible that the site of action of remifentanyl in reducing pain is peripheral because opioid receptors are found not only in the dorsal root ganglia and the central terminal of primary afferent nerves, but also in peripheral sensory nerve terminals. If remifentanyl has the peripheral effects, the application of venous technique or administration immediately before rocuronium injection might be more effective in reducing the withdrawal movements. Therefore, further research to study the effect of pretreatment technique may be needed.

Five patients in remifentanyl group coughed during anaesthesia induction even though remifentanyl was diluted and injected slowly over 30 s in this study. Although coughing did not result in low saturation nor interfere with mask ventilation, remifentanyl must be injected slowly with caution. The exact mechanism for this tussive effect of opioids is still unclear. The incidence of coughing in children is also unknown because previous studies were focused mostly on adult patients.^{17,18} The incidence of remifentanyl-induced cough in our study was 14%, which is lower than that in a previous study on adults by Phua and colleagues.¹⁸ They reported that fentanyl $1.5 \mu\text{g kg}^{-1}$, via peripheral line, provoked cough in 28% of adult patients. However, the number of patients in this study was too small to confirm the incidence in child and further investigation is needed.

The dose of remifentanyl was decided on the basis of a previous study by O'Hare and colleagues.¹⁹ They reported that remifentanyl $0.5 \mu\text{g kg}^{-1}$ was ineffective in controlling the increase in HR and arterial pressure after intubation but the 1.0 and $1.25 \mu\text{g kg}^{-1}$ doses were effective in controlling the response during rapid sequence induction of anaesthesia. However, as the use of the $1.25 \mu\text{g kg}^{-1}$ dose was associated with a decrease in systolic arterial pressure to <90 mm Hg in 7 of 20 patients, remifentanyl $1 \mu\text{g kg}^{-1}$ was used in our study. As for the haemodynamic effect of remifentanyl during anaesthesia induction, MAP significantly decreased before intubation, but it was clinically insignificant because no patients had showed a MAP below 50 mm Hg. Furthermore, MAP in remifentanyl group did not change after tracheal intubation, whereas that in the saline group was significantly increased. These results are consistent with a previous study by O'Hare and colleagues.¹⁹ As an induction agent, we used thiopental instead of propofol because compared with thiopental pain on injection occurs significantly more commonly with propofol despite the addition of lignocaine, which may have affected the result of this study.²⁰

In conclusion, this study demonstrated that pretreatment with remifentanyl $1 \mu\text{g kg}^{-1}$ provided a safe and simple method for reducing the incidence of rocuronium-associated withdrawal movement with haemodynamic stability in children.

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