Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Prediction of emergence agitation using withdrawal reaction following rocuronium injection in preschool-aged patients undergoing inguinal herniorrhaphy: a preliminary exploratory observational trial

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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Purpose: The development of emergence agitation (EA) is associated with several factors including age, preoperative anxiety, postoperative pain, anesthesia method, and surgery type. No studies have investigated whether the withdrawal reaction following rocuronium injection can predict the occurrence of EA. Therefore, we investigated this relationship in preschool-aged children undergoing inguinal herniorrhaphy, and which grade of withdrawal reaction is appropriate for identifying patients at risk of experiencing EA.

Methods: A total of 40 patients were enrolled in this study. During anesthesia induction, the withdrawal reaction after loss of consciousness following rocuronium injection was assessed using a 4-point scale. After surgery, EA was assessed using the Watcha scale.

Results: There was a correlation between withdrawal reaction and EA on admission to the postanesthesia care unit (PACU). Patients with a severe withdrawal reaction (grade 3) showed a significantly higher incidence of severe EA requiring medication on admission to the PACU.

Conclusion: The findings of this preliminary exploratory observational study suggest that it is possible for withdrawal movement following rocuronium injection during anesthesia induction to reflect pain sensitivity of pediatric patients, which in turn may be useful in identifying those at risk of severe EA on admission to the PACU among preschool children undergoing inguinal herniorrhaphy. Further studies with a larger sample size are required to validate these findings. The exact correlation between pain reaction following rocuronium injection and postoperative pain or pain-related phenomenon should be elucidated.

Keywords: emergence agitation, prediction, rocuronium, withdrawal movement

Introduction

Postoperative emergence agitation (EA) is a clinical condition, marked by crying, agitation, thrashing behavior, and inconsolability during recovery from general anesthesia.[1,2] It increases the risk of self-injury, burden for caregivers, and dissatisfaction of parents.[3,4] To date, various preventive strategies have been primarily focused on reducing the overall frequency and severity of EA.[5,6] There is considerable individual variation in the level of EA.[7,8] Thus, the identification of patients at risk of severe EA may help to further optimize individualized prevention strategies.

The exact mechanism of EA after general anesthesia remains unclear, but several factors are thought to be involved. They include age, preoperative anxiety, postoperative

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Dovepress
http://dx.doi.org/10.2147/TCRM.S154264

pain, the use of halogenated anesthetics, and surgery type.[1,9] Under the same anesthetic and surgery conditions in a similar age group, a previous study found no significant predictors of EA other than anxiety. Pain was thought to be the major cause of EA, but more recent studies have found that EA frequently occurs after nonpainful procedures, suggesting that there must be other mechanisms involved.[4,10] Nonetheless, considerable pain is a potential risk factor for EA because uncomfortable stimuli could be distressing in partially awake or dissociated patients.[10,11] If so, a pain-sensitive temperament might also affect the incidence or severity of EA. Pain sensitivity was reported to be mutually independent of anxiety for predicting postoperative pain.[12] Thus, pain sensitivity itself might be useful as another predictor of EA. For the assessment of pain sensitivity, we focused on clinical pain, specifically the reaction to pain from a rocuronium injection during anesthesia induction. It is well known that rocuronium injections elicit an intense burning pain, and this often appears as a withdrawal movement during anesthesia induction.[13,14] The withdrawal reaction has a wide spectrum of reactions from no response to generalized movement.[14]

The aim of this study was to evaluate if the withdrawal reaction due to rocuronium injection during anesthesia induction correlates with clinical EA in the postanesthesia care unit (PACU) and which grade of withdrawal reaction is appropriate for identifying patients at risk of experiencing EA preoperatively in order to improve clinical management and implement preventative strategies.

Methods

After receiving approval from the institutional review board of Ajou University Hospital (Suwon, South Korea), this study was registered with ClinicalTrials.gov (NCT no: NCT02646722), and written informed consent was obtained from the parents of all patients. We recruited patients from Ajou University Hospital, Suwon, South Korea, from January 2016 to May 2016. Patients with an American Society of Anesthesiologists physical status I or II who were 1–5 years of age undergoing inguinal herniorrhaphy were enrolled in the study. Patients with a history of neurological problems and medications including sedatives and analgesics within 24 h of surgery were excluded. Patients who had a venous line in the forearm that was not 24 gauge were also excluded.

No children received premedication. They had a 24-gauge intravenous catheter inserted in the back of the hand in the ward or preoperative waiting room before being transferred to the operating room. A parent was allowed to accompany a patient in the operating room. The patients underwent basic monitoring including electrocardiogram, pulse oximetry, and noninvasive blood pressure measurement. Anesthetic induction was performed with 5 mg/kg thiopental sodium. Immediately after the loss of eyelash reflex, rocuronium was injected (0.3 mg/kg) over 5 s, along with mask ventilation with 6 L/min of 100% oxygen for breathing assistance. Then, any withdrawal movement was recorded. Following this, 5 vol% sevoflurane in 6 L/min of 100% oxygen was inhaled. In all, 2 min after the rocuronium injection, the trachea was intubated and anesthesia was maintained with 2%–3% sevoflurane and a 50% oxygen and air mixture. No analgesic was provided before or during anesthesia, and rescue analgesics were administered as required in the PACU. This design was the commonly used perioperative analgesic method for children undergoing very short surgery in our institution, and moreover, children's postoperative pain was reported to be similarly effectively managed by using the "as required" method (pro re nata [PRN]) or fixed scheduled method.[15]

At the end of surgery, the residual neuromuscular blocking agent was reversed with pyridostigmine 0.2 mg/kg and glycopyrrolate 0.008 mg/kg. After extubation, patients were transferred to the PACU. After arrival in the PACU, EA was recorded at 10-min intervals by nurses who were blinded to the presence or absence of a previous withdrawal movement in the patient. If the severity of EA was ≥3 points (Watcha scale, detailed subsequently), 0.5 μg/kg fentanyl was administered. Postoperative adverse events such as nausea, vomiting, bradycardia, and respiratory depression were recorded.

The withdrawal movement was graded using a 4-point scale: 0= no response, 1= movement at the wrist only, 2= movement/withdrawal involving the arm only (elbow/shoulder), and 3= generalized response, movement/withdrawal in more than one extremity.[16] EA was assessed using the Watcha scale: 1= calm; 2= crying, but can be consoled; 3= crying, cannot be consoled; and 4= agitated and thrashing around.[17]

The primary outcome measure of the present study was the EA on admission to the PACU. Because the nature of the study was exploratory, an exact formal calculation of the sample size could not be made. Instead, it was based on a similar survey reported in the literature.[18] Secondary end points included the EA scores at 10, 20, and 30 min after PACU admission and at discharge from the PACU. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). The data were tested for normality using the Shapiro–Wilk test. Data are presented as mean

and standard deviation if normally distributed, median and interquartile range if not normally distributed, and percentage as appropriate. To examine the relationship between the severity of withdrawal movement and EA, the Kendall's tau correlation test and Eta correlation coefficient were used. We determined the optimal cutoff scores for a mild (grade 0–2) and severe (grade 3) withdrawal reaction based on the highest accuracy using a binary classification of the withdrawal group to identify patients at risk of experiencing EA who required medication.[19] For comparison between the mild and severe withdrawal groups as differentiated by the cutoff score, an analysis was conducted using an independent samples *t*-test if normally distributed and a Mann–Whitney *U*-test if not normally distributed to compare continuous variables. A chi-square test and Fisher's exact test were used when appropriate to compare the categorical variables. A *P*-value of <0.05 was considered as statistically significant.

Results

A total of 40 patients were enrolled in this study. The demographic data are presented in Table 1. There was no significant difference in demographic data between the two groups when separated by withdrawal reaction.

There was a significant correlation between the severity of withdrawal movement and EA on admission to the PACU (Kendall's tau =0.29, *P*=0.04). There were no other significant differences for EA scores at other time points, ie, at 10, 20, and 30 min after PACU admission and at discharge from the PACU (Kendell's tau =–0.02, *P*=0.988; Kendell's tau =–0.07, *P*=0.625; Kendell's tau =–0.09, *P*=0.533; and Kendell's tau =–0.01, *P*=0.959, respectively). A Kendall's tau value of <0.3 indicates a weak positive linear correlation. Table 2 and Figure 1 show the association between withdrawal movement and EA. As withdrawal movement increased in patients, so did severe EA.

In all, 27 patients exhibited mild withdrawal (grade 0–2) and 13 patients showed severe withdrawal (3 points). This classification was performed according to the optimal cutoff score to preoperatively identify patients at risk for experiencing EA requiring medication (EA score ≥ 3). A comparison between the mild and severe withdrawal movement groups is presented in Table 3. The incidence of EA requiring medication (EA score ≥ 3) on admission to the PACU in the severe withdrawal group was significantly higher than that in the mild withdrawal group. The time of initial fentanyl administration from the end of surgery was significantly shorter in the severe withdrawal group compared to the mild withdrawal group. However, there was no significant difference in the length of stay and fentanyl consumption in the PACU between the two groups.

Discussion

The results of this study suggest that, in pediatric patients, the withdrawal movement following rocuronium injection during anesthesia induction could be used to predict the occurrence of severe EA on admission to the PACU after recovery from general anesthesia. Patients who demonstrated severe withdrawal movement had a significantly higher incidence of severe EA on admission to the PACU, requiring active intervention.

EA is a common clinical condition in which the emergence from general anesthesia is accompanied by confusion and psychomotor agitation.[20] The exact mechanism of EA after general anesthesia still remains poorly understood.[21–23] In pediatric patients, it may be related to differences in neurodevelopmental characteristics and the variable effect of anesthetics.[24] Nevertheless, pain is still reported to be a potential risk factor affecting the incidence of EA.[10,11] Even though pain and EA might not have a causal relationship, uncomfortable stimuli may be distressing in partially awake or dissociated patients, ie, pain may aggravate the EA phenomenon. Several other risk factors of EA have been proposed, such as preoperative anxiety, preschool age, type of surgery, and anesthetics.[25] Among them, anxiety has yielded conflicting results.[24] A previous study found that pain sensitivity and anxiety were mutually independent predictors of postoperative pain in the same patient population, with pain

Table 1 Patients' demographic data

Variables	Total patients (N=40)	Mild withdrawal (n=27)	Severe withdrawal (n=13)	*P*-value
Age (years)	3 (2–5)	4 (2–5)	3 (2–4)	0.317
Body weight (kg)	14.2 (12.0–17.6)	15 (15.5–21.5)	13.5 (11.0–15.3)	0.141
Height (cm)	95.4 (87.3–109.0)	99.0 (88.0–112.0)	91.0 (85.1–106.2)	0.133
Sex (M/F)	28/12	19/8	9/4	0.941
Operation time (min)	15.0 (15.0–23.8)	15.0 (10.0–20.0)	20.0 (15.0–25.0)	0.156
Anesthesia time (min)	40.0 (35.0–45.0)	40.0 (35.0–45.0)	35.0 (35.0–45.0)	0.563

Notes: Values are reported as median (interquartile range) and number of patients. *P*-values were calculated using the Mann–Whitney *U*-test and Fisher's exact test. All tests were two-sided.
Abbreviations: M, male; F, female.

Table 2 Severity of withdrawal movement following rocuronium injection during anesthesia induction and severity of EA on admission to the PACU

Watcha scale for EA on admission to the PACU	Withdrawal movement following rocuronium injection			
	0	1	2	3
1	4	3	8	3
2	0	2	4	3
3	0	1	1	1
4	1	1	2	6

Notes: Withdrawal movement: 0= no response, 1= movement at the wrist only, 2= movement/withdrawal involving the arm only (elbow/shoulder), and 3= generalized response, movement/withdrawal in more than one extremity. Watcha scale for EA: 1= calm; 2= crying, but can be consoled; 3= crying, cannot be consoled; and 4= agitated and thrashing around.
Abbreviations: EA, emergence agitation; PACU, postanesthesia care unit.

sensitivity having a stronger correlation with postoperative pain than anxiety.[12] Based on this finding, we speculated that pain sensitivity might predict the development and severity of EA, and conducted the present study, which is the first to investigate the association between pain sensitivity and EA. The findings of the current study indicate that patients with higher pain sensitivity are more likely to experience severe EA immediately after surgery. This may imply that the individual responses to postoperative pain in the PACU affect the severity of EA.

Among the methods to assess pain sensitivity, quantitative sensory testing is reported to have a higher predictive strength than demographic and psychological factors, which may predict up to 54% of the variance in postoperative pain

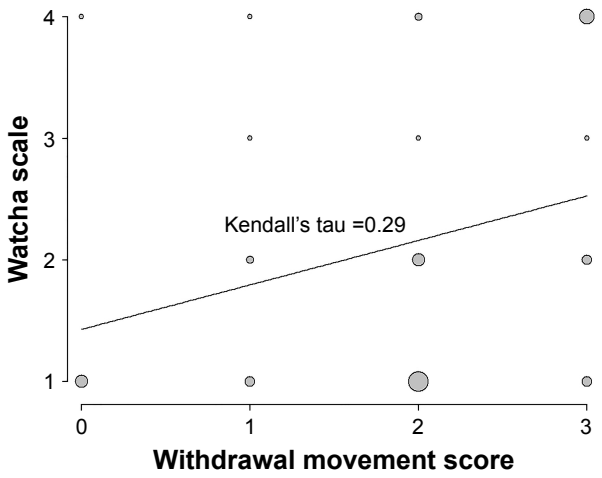

Figure 1 Correlation between the severity of withdrawal movement following rocuronium injection and severity of EA on admission to the PACU.
Notes: The Kendall's tau was estimated as 0.29. The diameters of the plotted circles are proportional to the number of patients.
Abbreviations: EA, emergence agitation; PACU, postanesthesia care unit.

experience.[26] Moreover, it has been demonstrated that an increased pain score for supra-threshold noxious stimulation has a better predictive value than pain thresholds.[26,27] Furthermore, authentic pain stimuli reflect pain tolerance more closely than pain threshold,[28] suggesting that they can be utilized as a representative of supra-threshold noxious stimuli. In human beings, the peripheral veins are innervated by polymodal nociceptors, which mediate the signal transmission for the injection pain of certain agents.[29] It is unclear which levels of pain processing, ranging from the nociceptors to the brain, contribute to the individual differences in pain perception and sensitivity.[30] However, a recent study reported that propofol injection pain was a predictor for postoperative pain levels.[31] In this study, we used withdrawal movement, which occurs when rocuronium is injected intravenously during anesthesia induction. Rocuronium injection is associated with a strong burning pain, which elicits brisk flexion of the elbow and wrist, even after loss of consciousness.[16,32] In this study, the rocuronium injection took place at the beginning of manual ventilation immediately after the loss of eyelash reflex, so psychological and cognitive effects on the pain reaction might have been depressed. Thus, it is unclear whether the observed movement accurately measured the individual responses to standardized pain stimuli measured in the conscious state.[33] However, a previous study suggested that the patient's response to pain after anesthesia induction has a significant relationship with preoperative pain tolerance.[28] These findings support our assumption that the withdrawal reaction is associated with the patients' pain-related symptoms and EA in this study.

When the scores for withdrawal movement were divided into two categories based on our analysis of clinical feasibility, the optimal cutoff grade was 3, rather than the median. This might be because the scale for withdrawal movement was an ordinal scale with irregular intervals. Our findings suggest that, when using withdrawal movement to predict EA, cases with a severe withdrawal reaction following rocuronium injection must be considered for administration of medications that may ameliorate or prevent EA on admission to the PACU. However, clinical usefulness may be limited because its prediction was confined to EA on admission to the PACU and there was no significant difference in fentanyl consumption in the PACU.

The findings of this study should be interpreted in the context of the following limitations. First, postoperative pain using a pediatric pain scale was not evaluated. Hence, this study has a limitation in that the actual relationship of withdrawal movement with EA after excluding the effect

Table 3 EA according to mild and severe withdrawal reactions

Variables	Mild withdrawal (n=27)	Severe withdrawal (n=13)	*P*-value
EA severity ≥3	6 (22.2%)	7 (53.8%)*	0.048
Interval from the end of surgery to initial fentanyl administration (min)	19 (16.25–27.75)	9.5 (4.25–18.5)*	0.045
Cases of fentanyl use	15 (55.6%)	10 (76.9%)	
Fentanyl consumption (μg/kg)	0.5 (0–0.5)	0.5 (0.5–0.5)	0.383
Duration of stay in PACU (min)	40 (40–44)	40 (40–40)	0.562

Notes: Values are reported as median (interquartile range) and number (proportion) of patients. *P*-values were calculated using the Mann–Whitney *U*-test, and all tests were two-sided. *$P<0.05$ compared to the mild withdrawal group.
Abbreviations: EA, emergence agitation; PACU, postanesthesia care unit.

of postoperative pain on EA could not be investigated. Second, only a simple 4-point scale (Watcha scale) was used for assessing the EA instead of the Pediatric Anesthesia Emergence Delirium scale, which is the most commonly used validated scale for quantification of EA.[34] Third, the results were obtained from a small number of patients. The nature of this study was exploratory, and therefore, an exact power analysis was not performed. Although we did find a significant difference in the incidence of EA requiring medication (EA score ≥3) in the severe withdrawal group compared to the mild withdrawal group, as well as a correlation between withdrawal movement and EA, the study lacks sufficient power. Fourth, EA may have been affected by other confounding factors. For example, anxiety is known to be associated with pain sensitivity and independently can predict postoperative pain.[12] The age-related differences in characteristics of blood vessels may have affected the results, although we did not observe statistically significant differences between age groups. Furthermore, we did not verify that the anesthetic depth after the injection of thiopental sodium was the same between patients, which could also represent a confounding factor. Fifth, the clinical usefulness of withdrawal movement may be limited because its prediction was confined to EA on admission to the PACU and there was no significant difference in fentanyl consumption in the PACU.

Conclusion

The findings from this preliminary exploratory study suggest that it is possible for withdrawal movement following rocuronium injection during anesthesia induction to reflect pain sensitivity of pediatric patients, which in turn may be useful in identifying those at risk of severe EA on admission to the PACU among preschool-aged patients undergoing inguinal herniorrhaphy. Further studies with a larger sample size are required to validate these findings. The exact correlation between pain reaction following rocuronium injection and postoperative pain or pain-related phenomenon should be elucidated.

Disclosure

The authors report no conflicts of interest in this work.

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