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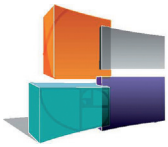

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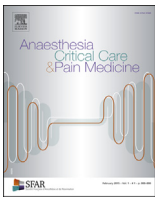

Letter to the Editor

Sugammadex for reversal of neuromuscular blockade in paediatric patients: A two-year single-centre retrospective study

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While the safety of sugammadex as a reversal agent for rocuronium-induced neuromuscular blockade (NMB) has been established in adult surgical patients [1,2], its safety in paediatric patients is less clear because of the paucity of studies in this population [3]. Anaesthesia-related complications play a substantial role in perioperative morbidity in children [4]. No data are available regarding the effects of sugammadex on early complications after general anaesthesia in this age group. We thus analysed the role of sugammadex on postoperative complications in paediatric patients after general anaesthesia. As some sugammadex effects are dose-related [5,6], we compared two doses to evaluate dose-related side effects in children. After approval by the Institutional Ethics Committee of Istituto Giannina Gaslini IRCCS, Genova, Italy, we retrospectively evaluated data from our hospital database, as well as the anaesthesia and medical records of paediatric patients (aged 3–12 years; American Society of Anesthesiologists [ASA] physical status ≤ 3) who underwent general anaesthesia for tonsillectomy and adenoidectomy from January 1, 2016 to December 31, 2017.

Before anaesthesia, anxious children received rectal midazolam (0.1–0.5 mg/kg) and ketamine (2 mg/kg). Anaesthesia was induced with increasing concentrations of inspired sevoflurane or intravenous propofol (2–3 mg/kg). Rocuronium (0.6–1 mg/kg) was administered at induction of anaesthesia to facilitate tracheal intubation. Anaesthesia was maintained using sevoflurane for inhalational anaesthesia or propofol for intravenous anaesthesia; both were titrated to a bispectral index of 40–60. Analgesia was maintained with fentanyl (1–5 μg/kg), remifentanil (0.1–0.3 μg/kg/min), or dexmedetomidine (2 μg/kg). Dexmedetomidine (1–2 μg/kg) or clonidine (1–2 μg/kg) with dexamethasone (0.3 mg/kg) were administered intraoperatively to prevent post-operative nausea and vomiting (PONV) and delirium. To minimise postoperative pain, intravenous paracetamol (15 mg/kg) was administered to all patients. At the end of surgery, intravenous morphine (0.1 mg/kg) or tramadol (1.5 mg/kg) was administered at the anaesthesiologist's discretion. Moderate NMB (≥ 1 twitch [T_1] upon train-of-four [TOF] stimulation) was reversed with sugammadex 2 mg/kg, and deep NMB (absent T_1 and post-tetanic count ≥ 1) was reversed with sugammadex 4 mg/kg. All children were extubated after verifying a TOF ratio > 0.9 by acceleromyography.

The role of sugammadex on anaesthesia-related side effects was evaluated by assessing postoperative complications, defined as adverse events unrelated to the preoperative surgical condition occurring within 30 minutes post-extubation [4]. Complications were classified as neurological (e.g., delirium), respiratory (e.g., airway obstruction, laryngospasm, cough), or cardiovascular (e.g., tachycardia, bradycardia, hypertension, hypotension); PONV; pain; or other [1,2]. The proportions of patients with complications were compared using the Chi-square test. Multiple logistic regression analysis was used to assess associations between the occurrence of complications and a number of factors, including sugammadex dose. All analyses were performed using R version 3.4.0 (2017-04-21). *P*-values < 0.05 were considered statistically significant.

The study included 423 patients, with a median [interquartile range] age and body weight of 6.0 [5–7] years and 17 [15–20] kg. Obstructive sleep apnoea (OSA) was diagnosed in 31.4%. Inhalational anaesthesia was used in 94.6%. The intraoperative medications (with corresponding percentages of patients) were midazolam (5.9%), ketamine (4.5%), dexmedetomidine (64.8%; 22.4% received dexmedetomidine and no opioid), clonidine (29.8%), fentanyl (42.8%), remifentanil (34.8%), rocuronium > 0.6 mg/kg (23.4%; 17.2% received 1 mg/kg), tramadol (25.5%), and morphine (16.8%). All patients received dexamethasone, paracetamol, and sugammadex. Sugammadex was administered at 2 mg/kg in 278 patients and 4 mg/kg in 145 patients. There were no significant differences in patient or most anaesthetic characteristics between patients receiving 2 mg/kg or 4 mg/kg of sugammadex. Rocuronium > 0.6 mg/kg was more common in patients receiving sugammadex 4 mg/kg than in those receiving 2 mg/kg (49% vs. 10.1%; $P < 0.001$). Overall median surgical and anaesthetic times were 20 [15–23] minutes and 27 [22–32] minutes, respectively. Compared with moderate NMB, deep NMB was associated with a shorter surgical time (14 [10–15] min vs. 20 [20–25] min, $P < 0.001$) and anaesthetic time (21 [19–24] minutes vs. 30 [27–35] minutes, $P < 0.001$).

At least one postoperative complication occurred in 50.8% of patients. No significant differences in rates of one or more complications were observed across age groups or between patients receiving sugammadex 2 mg/kg or 4 mg/kg (50.4% vs. 51.7%, respectively, $P = 0.838$). The postoperative complications (with corresponding percentages of patients) were delirium (25.8%), airway obstruction (19.4%), laryngospasm (16.1%), cough (0.9%), tachycardia (0.7%), bradycardia (5.7%), hypertension (3.1%), PONV (10.2%), pain (5%), pruritus (0.5%), and rash (0.2%). The rates of all complications did not differ between patients receiving sugammadex 2 mg/kg or 4 mg/kg: delirium (26.6% vs. 24.1%,

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Table 1
Multiple logistic regression analysis.

Variable Dependent	Variable Independent	Regression model OR (95%CI)	*P*-value	Variable Independent	Regression model OR (95%CI)	*P*-value
Total complications	gender (M)	1.44 (0.95–2.16)	0.0821	clonidine	0.10 (0.02–0.52)	0.0058
	OSA	2.04 (1.30–3.21)	0.0019	dexmedetomidine	0.12 (0.02–0.57)	0.0077
	fentanyl	2.11 (1.16–3.81)	0.0138	midazolam	0.43 (0.18–1.05)	0.0632
	morphine	1.61 (0.88–2.92)	0.1210			
Delirium	OSA	1.73 (1.07–2.78)	0.0247	weight	0.94 (0.89–1.00)	0.0538
				morphine	0.32 (0.14–0.72)	0.0057
				clonidine	0.19 (0.06–0.54)	0.0021
				dexmedetomidine	0.24 (0.09–0.64)	0.0045
Airway obstruction	weight	1.11 (1.04–1.19)	0.0016	age	0.67 (0.54–0.83)	0.0003
	ASA	1.98 (1.19–3.29)	0.0082			
	fentanyl	2.41 (1.42–4.09)	0.0011			
	morphine	1.86 (0.95–3.63)	0.0703			
Laryngospasm	OSA	1.67 (0.95–2.91)	0.0731	age	0.85 (0.71–1.03)	0.0975
	remifentanil	1.93 (1.12–3.33)	0.0180			
	morphine	1.92 (0.98–3.75)	0.0567			
	Sugammade x4 mg/kg	1.54 (0.88–2.67)	0.125			
Hypertension	TIVA	6.40 (1.41–29.00)	0.0161	ASA	0.26 (0.06–1.08)	0.0638
				dexmedetomidine	0.08 (0.02–0.37)	0.0010
Bradycardia	TIVA	9.34 (2.47–35.30)	0.0009			
	fentanyl	2.28 (0.81–6.41)	0.1170			
	Sugammade x4 mg/kg	2.05 (0.85–5.92)	0.1070			
PONV	morphine	51.5 (15.6–170.0)	<0.0001			
	fentanyl	7.33 (2.82–19.10)	<0.0001			
	tramadol	3.63 (1.11–11.9)	0.0330			
Pruritus, rash	fentanyl	33.4 (3.60–310.0)	0.0020	weight	0.75 (0.55–1.03)	0.0751
	TIVA	9.17 (0.59–141.00)	0.1120	surgery	0.86 (0.72–1.03)	0.1100

Table shows the results of multiple logistic regression analysis performed to determine the relationship between one dependent variable (postoperative complications) and independent variables (e.g. demographic parameters, surgical and anaesthesiological variables). Using the Akaike information criterion, backward/forward stepwise regression analysis was performed to choose the best model for each complication. All output data with their *P*-value are reported. *P*-value < 0.05 was considered statistically significant. Total complications: all complications observed. Multiple logistic regression analysis did not provide output data with OR (95%CI) for observed cough and tachycardia. OR: odds ratio (95% confidence interval, CI). TIVA: total intravenous anaesthesia. OSA: obstructive sleep apnoea. ASA: American society of anaesthesiologists physical status; PONV: postoperative nausea and vomiting.

$P = 0.640$), airway obstruction (18.7% vs. 20.7%, $P = 0.698$), laryngospasm (14.4% vs. 19.3%, $P = 0.210$), cough (0.7% vs. 1.4%, $P = 0.609$), tachycardia (1.1% vs. 0.0%, $P = 0.323$), bradycardia (4.7% vs. 7.6%, $P = 0.268$), hypertension (3.2% vs. 2.8%, $P = 1.00$), PONV (11.2% vs. 8.3%, $P = 0.319$), pain (4.0% vs. 6.9%, $P = 0.238$), pruritus (0.4% vs. 0.7%, $P = 1.00$), or rash (0.0% vs. 0.7%, $P = 0.343$). No hypotension, hypersensitivity, or bleeding was observed.

Multiple logistic regression analysis showed that OSA and fentanyl use were associated with an increased likelihood of postoperative complications (Table 1). Centrally-acting α_2-adrenergic agonists – dexmedetomidine and clonidine – were associated with a reduced likelihood of postoperative complications. Respiratory complications after adenoidectomy and tonsillectomy may result from various anaesthetic and surgical factors. Airway obstruction was significantly associated with ASA, higher weight, and fentanyl use, whereas laryngospasm was significantly associated with remifentanil. There was a trend toward an increased likelihood of laryngospasm with the higher sugammadex dose, although the difference was not statistically significant. Laryngospasm was most likely due to stimulation of laryngeal reflexes during awakening from general anaesthesia [7], rather than sugammadex itself [8]. There was also a non-significant trend toward increased likelihood of bradycardia with sugammadex 4 mg/kg, which is a known side effect, particularly at doses above those recommended for clinical practice [5].

This study is limited primarily by its retrospective nature. Despite the large number of patients, the study remains underpowered to make definitive conclusions about the safety of sugammadex, and further studies are thereby necessary. However, our experience suggests that, even when administered at high doses, sugammadex is well tolerated in the paediatric population.

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Author contributions

A. Simonini: Conceptualization; Data curation; Investigation; Methodology; Validation; Writing-review and editing

E. Brogi: Conceptualization; Data curation; Investigation; Methodology; Validation; Writing-review and editing

M.G. Calevo: Formal analysis; Methodology; Supervision; Writing-review and editing

M. Carron: Conceptualization; Formal analysis; Methodology; Supervision; Roles/Writing-original draft; Writing-review and editing

All authors contributed substantially to the conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, or revising it critically for important intellectual content. All authors gave final approval of the version to be published.

Presentation

Data for this study were not presented previously.

Disclosure of interest

Carron M and Simonini A have received payments for lectures from MSD, Italy. The other authors declare that they have no competing interest.

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