VIA MEDICA

ORIGINAL AND CLINICAL ARTICLES

Anaesthesiology Intensive Therapy
2015, vol. 47, no 4, 297–302
ISSN 1642–5758
10.5603/AIT.2015.0042
www.ait.viamedica.pl

The use of sugammadex for the reversal of vecuronium-induced neuromuscular block following intracranial surgery

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Abstract

Background: Total intravenous anaesthesia with propofol and remifentanil is widely used in neuroanaesthesiology and enables the quick recovery and early neurological assessment of patients. The administration of muscle relaxants carries a risk of residual relaxation following surgery. The administration of a suitable dose of sugammadex reverses the neuromuscular block irrespective of its depth and has none of the side effects associated with acetylcholinesterase inhibitors. The aim of the present study was to evaluate the usefulness of sugammadex for the reversal of vecuronium-induced effects following intracranial surgery.

Method: The study involved 38 women who underwent supratentorial tumour removal. These women were randomly divided into two groups. Total intravenous anaesthesia with propofol and remifentanil using target-controlled infusion was administered according to the Schnider and Minto models, respectively. Endotracheal intubation was performed after the target concentrations of propofol and remifentanil reached 4 μg mL^{-1} and 4 ng mL^{-1}, respectively. Vecuronium (100 μg kg^{-1}) was administered, and no response to TOF stimulation was observed. Relaxation was continued via the continuous infusion of vecuronium (0.8–1.2 μg kg^{-1} min^{-1}) to provide a TOF of 2 throughout the surgery. In group I, neuromuscular conduction was restored with intravenous sugammadex (2 mg kg^{-1}), whereas in group II, no reversal agents were administered.

Results: The times of the return of spontaneous breathing, extubation, eye opening (both spontaneous and in response to a verbal command) were found to be longer in group II than group I.

Conclusion: The use of sugammadex following craniotomy accelerates the achievement of optimal extubation conditions.

Key words: neuromuscular block, reversal agent, sugammadex, craniotomy, target-controlled infusion

Anaesthesiology Intensive Therapy 2015, vol. 47, no 4, 297–302

Total intravenous anaesthesia with propofol and remifentanil is widely used in neuroanaesthesiology. This approach enables the quick recovery and early neurological assessment of patients [1, 2].

The administration of muscle relaxants carries a risk of residual relaxation following surgery. Postoperative residual curarization decreases the sensitivity of chemoreceptors, the ventilatory response to hypoxia and the tones of the laryngeal and pharyngeal muscles and thus increases the risks of aspiration and pulmonary complications [3, 4]. Curarization is particularly dangerous for patients with CNS pathologies in which consciousness and protective reflexes can be compromised due to the underlying disease or the neurosurgical intervention. The administration of sugammadex at a suitable dose enables the reversal of neuromuscular block irrespective of its depth and has none of the side effects associated with acetylcholinesterase inhibitors [5].

The aim of the study was to assess the usefulness of sugammadex in the reversal of the vecuronium-induced effects following intracranial surgery.

METHOD

The study design was approved by the Independent Bioethics Committee of the Medical University of Gdańsk. The study included 38 women who underwent supratentorial tumour removal. These women were randomly divided

into two groups of 19 individuals each. The exclusion criteria were obesity, cardiovascular diseases, diabetes mellitus, and kidney and liver failure.

Forty-five minutes prior to anaesthesia, the patients were orally premedicated with 0.2 mg kg^{-1} midazolam. Anaesthesia was induced and maintained with total intravenous anaesthesia with propofol and remifentanil using target-controlled infusion. Perfusor Space infusion pumps (B. Braun Melsungen AG, Melsungen, Germany) were applied, and the Schnider and Minto models were adhered to for the administrations of propofol and remifentanil, respectively. During the procedure, the target concentrations of propofol and remifentanil in the brain tissue were adjusted such that the haemodynamic parameters did not exceed 20% of the baseline values. Propofol and remifentanil were infused until the final skin sutures were placed. Endotracheal intubation was performed after the target concentrations of propofol and remifentanil reached 4 μg mL^{-1} and 4 ng mL^{-1}, respectively. Vecuronium (100 μg kg^{-1} of) was administered, and no response to TOF stimulation was observed. Muscle relaxation was continued via the continuous infusion of vecuronium (0.8–1.2 μg kg^{-1} min^{-1}) to provide a TOF of 2 during the surgery. Vecuronium was infused until the completion of the surgery. The degree of neuromuscular block was monitored using an acceleromyograph (TOF-Watch, Organon, Dublin, Ireland). The responses of the thumb flexor to ulnar nerve stimulation (a series of 50-mA, 2-Hz stimuli) on the limb unaffected by paresis or paralysis were recorded. To maintain normoventilation (E_TCO_2 within the range of 35–39 mm Hg), the lungs were ventilated with a 1:1 mixture of air and oxygen in a half-closed circular system.

In group I, the neuromuscular conduction after surgery was restored with intravenous sugammadex (Bridion, MSD, Dublin, Ireland) at a dose of 2 mg kg^{-1}. In group II, no reversal agents were used.

Thirty minutes prior to the completion of surgery, an intravenous infusion of tramadol (100 mg) and metamizole (2.5 g) was initiated to ensure early postoperative analgesia.

The heart rate (HR), systolic (SysBP), diastolic (DiaBP) and mean (MABP) arterial blood pressures and the rectal core temperature were continuously monitored. The body temperature was maintained within the range of 37.5 ± 0.5° C using a warming system.

The values of the parameters were analysed at the following points of anaesthesia: TO (baseline), T1 (initiation of propofol and remifentanil infusion), T2 (target concentrations of propofol and remifentanil reached), T3 (intubation), T4 (one minute after intubation), T5 (two minutes after intubation), T6 (head fixation in the Mayfield head clamp), T7 (one minute after head fixation), T8 (prior to the skin incision), T9 (one minute after the skin incision, T10 (before bone flap removal), T11 (one minute after bone flap removal), T12 (before the opening of the opening),T13 (one minute after meninx opening), T14 (access stage), T15 (tumour resection stage), T16 (before meninx closure), T17 (one minute after meninx closure), T18 (before bone flap insertion), T19 (one minute after insertion), T20 (initiation of the soft integument closure), T21 (completion of the skin sutures), T22 (administration of the sugammadex) T23 (extubation), and T24 (3 minutes after extubation). Moreover, analyses of the total consumptions of propofol, remifentanil and vecuronium, the time of the return of spontaneous breathing return at V_T > 4 mL kg^{-1}, the time to extubation (TOF-R > 0.9), and the times of spontaneous and verbally commanded eye opening were performed.

Table 1. Characteristics of the study population (mean ± SD)

Characteristics	Group I	Group II
Age (years)	52.1 ± 14.1	53.1 ± 18.1
Height (m)	1.66 ± 0.05	1.71 ± 0.06
Body mass (kg)	64.3 ± 19.7	70.8 ± 13.2

The statistical analyses were performed using GraphPad InStat, version 3.10 (GraphPad Software Inc., La Jolla, USA). The results are presented as the means ± the SD. The distributions of the data were examined with the Kołmogorow-Smirnow test. Dunnett's tests were used for the intergroup comparisons, and Mann-Whitney tests were used for intergroup comparisons. $P < 0.05$ was considered statistically significant.

RESULTS

The study groups did not differ in age, height or body weight (Table 1). The distribution of the natures of the proliferative processes is presented in Fig. 1. The distributions of the target concentrations of propofol and remifentanil are provided in Table 2. The statistical analysis did not reveal any significant intergroup differences across the successive stages of anaesthesia.

No inter-group differences in HR, SysBP, DiaBP, MABP or core temperature were observed at the individual observation points (Figs 2–5).

Moreover, there were no differences in the consumptions of propofol, remifentanil or vecuronium (Table 3).

The times of the return of spontaneous breathing, extubation, and spontaneous and verbally commanded eye opening were found to be longer in group II than in group I (Table 4).

DISCUSSION

Data from the Central Brain Tumour Registry of the United States reveal that more than 64 thousand new disease cases occurred in 2011, and 80% of these cases involved

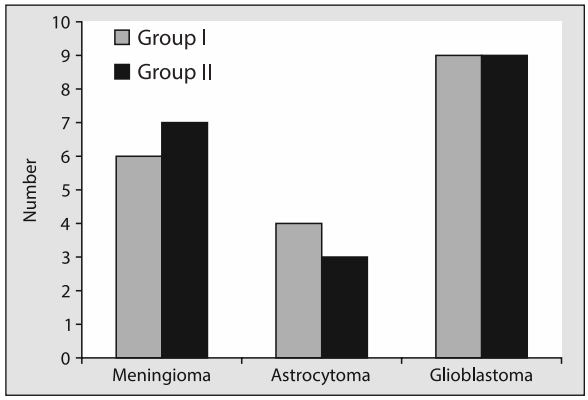

Figure 1. Characteristics of the pathological lesions according to study group

supratentorial localizations [6]. Based on the histopathological natures of the proliferative lesions, meningiomas (35%), glioblastomas (16%), hypophyseal adenomas (14%) and astrocytomas (7%) were distinguished [6].

Irrespective of the technique used for the induction and conduction of anaesthesia, the lowest possible ICP, the haemodynamic stability of the systemic circulation in response to endotracheal intubation and brain relaxation during neurosurgical interventions in the operating field have to be provided [6, 7].

Propofol combined with one of the synthetic opioids and a non-polarising neuromuscular transmission blocker has been a widely used approach for total intravenous anaesthesia for many years [8, 9]. Target-controlled infusion systems allow for the accurate dosing of propofol and remifentanil for both for the induction and maintenance of anaesthesia. Wakeling *et al*. [10] and Struys *et al*. [11] demonstrated that the target effector site concentration is more strongly correlated with the depth of anaesthesia than the target serum concentration. Due to their beneficial effects on the factors that inhibit intracranial homeostasis in physiological and pathological conditions, propofol and remifentanil are considered the drugs of choice for neuroanaesthesia [12, 13]. Propofol combined with remifentanil ensures the haemodynamic stability of the systemic circulation during the induction and maintenance of anaesthesia as confirmed by numerous studies and our observations [14–17].

Post-craniotomy pain occurs almost instantly after surgery in 70–90% of cases [18]. One of the negative effects of the pharmacokinetics of remifentanil is the considerably earlier development of postoperative pain, which more frequently requires early postoperative analgesia compared with other opioids [8, 14, 18, 19].

In the majority of cases, the current doctrine of management assumes the earliest possible recovery of patients after neurosurgical procedures and the preservation of conditions that ensure haemodynamic stability and pressure-volume balance inside the cranium are the most important factors [6, 7, 9]. Therefore, the restoration of neuromuscular transmission is essential, particularly because following intracranial surgeries, patients can develop cerebral blood flow and nervous tissue metabolism disorders and symptoms of oedema and increased intracranial pressure, which when combined with ventilation failure can lead to decreases in PaO_2 and increases in $PaCO_2$ that are likely to have catastrophic sequelea [6, 7].

One of the elements of general anaesthesia is neuromuscular transmission block. The role of neuromuscular block depth monitoring in everyday clinical practice has been disputed for a decade [20]. In our study, the depth of neuromuscular block was monitored using train-of-four stimulations that were applied during intubation, the conduction of anaesthesia and extubation. The utilized criteria were consistent with the recommendations of Sorin and co-workers [21]. The prevention of residual curarization effects involves the monitoring of relaxation subsidence using acceleromyography and the pharmacological reversal of relaxation with antagonistic agents. An ideal antagonistic agent should be characterised by the quick and total abolition of the relaxant effects regardless of the dose and the depth of block, the lack of side effects, and 100% excretion.

Table 2. Modes of the propofol and remifentanil infusions in the study groups*

		T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	T_{10}	T_{11}	T_{12}	T_{13}	T_{14}	T_{15}	T_{16}	T_{17}	T_{18}	T_{19}	T_{20}
Group I	Propofol μg mL^{-1}	4.0 (0.0)	4.0 (0.0)	2.2 (0.6)	2.3 (0.6)	3.8 (0.6)	3.6 (0.5)	3.3 (0.8)	3.2 (0.8)	2.9 (0.5)	2.9 (0.5)	2.8 (0.5)	2.7 (0.6)	2.6 (0.4)	2.5 (0.6)	2.5 (0.5)	2.5 (0.4)	2.5 (0.4)	2.4 (0.4)	2.4 (0.5)
	Remifentanil ng mL^{-1}	4.0 (0.0)	4.0 (0.0)	0.8 (1.3)	0.7 (1.0)	4.4 (0.9)	4.2 (0.8)	3.8 (1.6)	3.7 (1.3)	3.3 (1.2)	3.2 (1.3)	3.0 (1.4)	2.8 (1.4)	2.5 (0.9)	2.6 (0.9)	2.4 (1.0)	2.3 (1.1)	2.2 1.0	2.3 1.0	2.2 (1.1)
Group II	Propofol μg mL^{-1}	4.0 (0.0)	4.0 (0.0)	2.6 (0.7)	2.5 (0.6)	3.6 (0.6)	3.0 (0.6)	3.1 (1.1)	3.0 (1.0)	3.0 (1.0)	3.0 (1.0)	3.1 (1.3)	3.2 (1.2)	3.3 (1.3)	3.3 (1.2)	3.0 (0.8)	3.0 (0.7)	3.1 (0.7)	3.5 (1.0)	4.0 (1.4)
	Remifentanil ng mL^{-1}	4.0 (0.0)	4.0 (0.0)	1.1 (1.4)	1.0 (1.5)	4.3 (1.1)	4.1 (0.8)	4.2 (1.5)	4.1 (1.3)	3.8 (1.4)	3.8 (1.4)	3.8 (1.2)	4.0 (1.8)	4.2 (1.8)	3.1 (1.7)	2.8 (1.3)	2.8 (1.3)	2.1 (1.3)	2.3 (1.6)	2.7 (2.0)

* The data are presented as the means (SD)

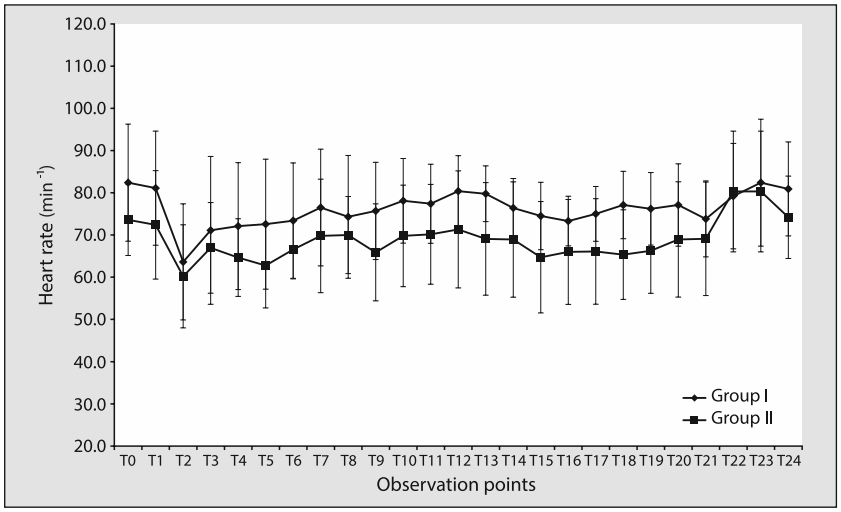

Figure 2. Mean heart rates (the bars indicate the standard deviations)

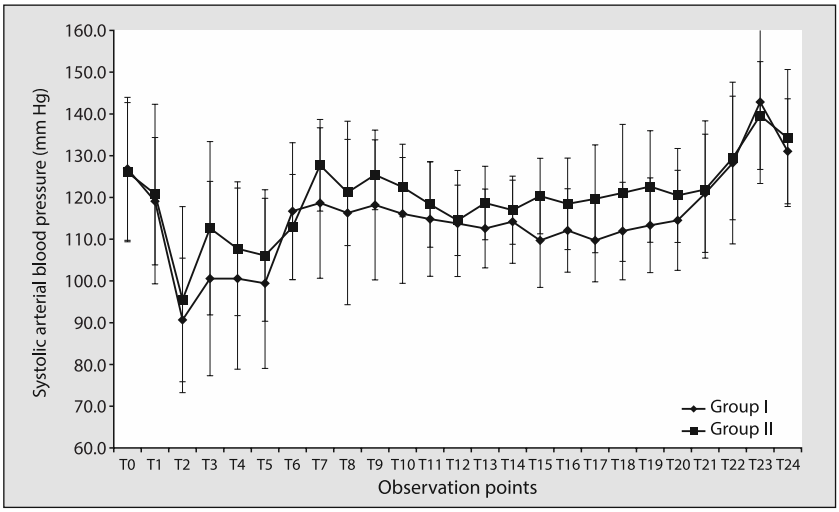

Figure 3. Mean systolic arterial blood pressures (the bars indicate the standard deviations)

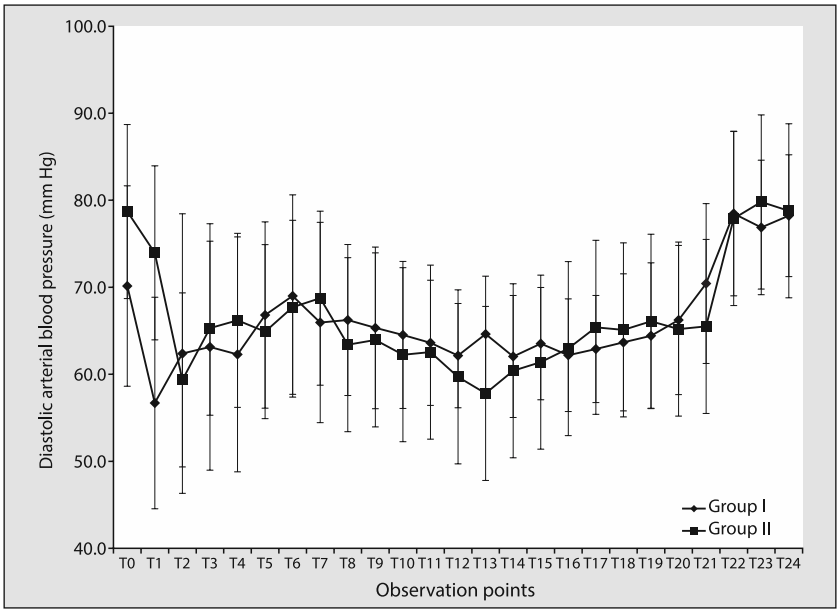

Figure 4. Mean diastolic arterial blood pressures (the bars indicate the standard deviations)

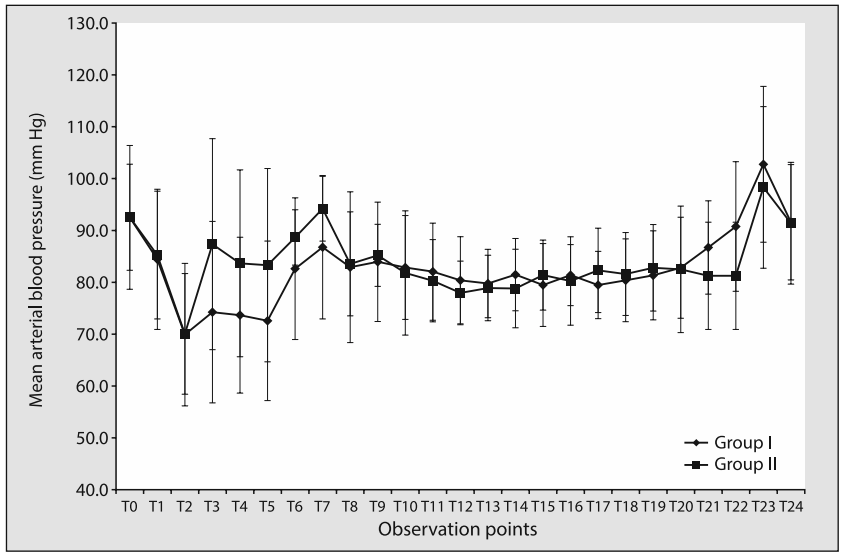

Figure 5. Mean arterial blood pressures (the bars indicate the standard deviations)

Table 3. Comparison of the consumptions of anaesthetic agents between the study groups*

Agent	Group I	Group II
Induction dose of propofol (mg)	109.4 ± 21.2	127.5 ± 21.2
Induction dose of remifentanil (μg)	85.9 ± 21.2	95.4 ± 18.4
Total dose of propofol (mg)	1410 ± 405	1490 ± 390
Total dose of remifentanil (μg)	1226.7 ± 405	1338 ± 412
Total dose of vecuronium (mg)	14.6 ± 3.4	15.1 ± 2.9

The data are presented as the means ± SD

These criteria are fulfilled by sugammadex [22]. Used in a dose of 2 mg kg^{-1}, sugammadex shortened the time to reach optimal extubation conditions. The times to the restoration of complete conduction following deep block induced with rocuronium or vecuronium are dose-dependent [23]. Sugammadex at 2 mg kg^{-1} restored complete conduction following vecuronium-induced block within 2.7 minutes, whereas neostigmine at a dose of 50 μg kg^{-1} requires 17.9 minutes [24]. The discrepancies with our observations likely resulted from the use of different methods of anaesthesia and procedures. Due to its high cost, the use of sugammadex is limited to certain indications [22]. Paton and colleagues [25] noted the potential economic benefits that result from the markedly shorter time required for the care of patients who receive sugammadex compared to patients who are administered neostigmine and glycopyrrolate.

CONCLUSION

The use of sugammadex used after craniotomy accelerates the achievement of optimal extubation conditions.

ACKNOWLEDGMENTS

1. The authors declare no financial disclosure.
2. The authors declare no conflict of interest.

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Table 4. Intergroup comparisons of the times of anaesthesia and the returns of clinical markers of neuromuscular block*

Time (minutes)	Group I	Group II	*P*
Duration of anaesthesia	108.5±21.2	125.5±21.3	$P > 0.05$
Return of spontaneous breathing	5.8 ± 3.8	13.2 ± 2.9	$P > 0.05$
Extubation (TOF-R > 0.9)	9.9 ± 2.3	16.8 ± 3.4	$P > 0.05$
Eye opening to verbal command	10.4 ± 5.6	19.1 ± 3.6	$P > 0.05$
Spontaneous eye opening	13.2 ± 4.9	21.4 ± 4.5	$P > 0.05$

* The data are presented as the mean ± the standard deviation

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Received: 1.04.2015
Accepted: 2.07.2015