

CLINICAL PRACTICE

Effect of sugammadex or neostigmine neuromuscular block reversal on bispectral index monitoring of propofol/remifentanil anaesthesia

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Editor's key points

- The influence of electromyographic (EMG) activity neuromuscular block (NMB) on bispectral index (BIS) is controversial.
- BIS was measured before and after reversal of NMB with sugammadex or neostigmine.
- BIS increased after both agents only in patients with EMG activity.
- This effect should be taken into account when using BIS.

Background. Sugammadex is a modified γ -cyclodextrin with a novel mechanism of action for reversing the steroidal neuromuscular blocking agent rocuronium. Bispectral index (BIS) is an EEG-derived measure which can be sensitive to frontal electromyographic (EMG) artifacts. We compared BIS values before and after sugammadex or neostigmine neuromuscular block (NMB) reversal in patients with or without high EMG activity.

Methods. During stable propofol/remifentanil anaesthesia and rocuronium-induced block, 48 patients were randomly allocated to receive sugammadex 4 mg kg⁻¹ or neostigmine 50 μ g kg⁻¹/glycopyrrolate 10 μ g kg⁻¹, 10 min after the end of surgery.

Results. Five minutes after sugammadex administration, mean BIS 50.1 (10.3) increased ($P=0.018$) to 61.7 (7.9) in 11 patients with high EMG activity. In contrast, BIS 49.3 (4.9) remained at 51.9 (5.4) in 13 patients who had no EMG activity. Fifteen minutes after neostigmine administration, mean BIS 51.9 (8.1) increased ($P=0.007$) to 63.9 (8.1) in 13 patients who had reappearance of muscle activity. However, in 11 patients who had no EMG activity, BIS 52.3 (7.4) remained at 53.3 (6.8). There was no significant difference between the sugammadex and neostigmine groups over time.

Conclusions. We have shown that reversal of NMB with sugammadex or neostigmine increased BIS values dependent on the presence of EMG activity. Thus, the effect of muscle activity reappearance during rocuronium NMB reversal spuriously increasing the BIS value should be taken into consideration when relying on BIS monitoring for evaluating propofol/remifentanil recovery.

Keywords: anaesthesia, depth; measurement techniques, mechanomyography; measurement techniques, neuromuscular block; monitoring, intraoperative; monitoring, neuromuscular function; neuromuscular blocking agents; NM relaxant, reversal

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Sugammadex is a modified γ -cyclodextrin that encapsulates, in a highly selective fashion, neuromuscular blocking agents (NMBAs) vecuronium and rocuronium. Its novel mechanism of action for promptly reversing monoquaternary steroidal NMBAs is completely different from neostigmine and other anticholinesterase agents.¹

Bispectral index (BIS) is a processed EEG measure quantifying the level of interfrequency phase-coherent synchronization in the signal. BIS is derived from an empirical database using a complex proprietary algorithm that combines three subparameters into a single metric: a frequency-domain BetaRatio, a bispectral-domain SynchFastSlow, and a time-domain burst suppression. The BIS algorithm allows the three different

descriptors to dominate sequentially as the EEG changes its character.² Interference by electromyographic (EMG) activity on EEG-derived monitoring has been a matter of concern,^{3 4} and a source of controversy.^{4–11} Thus, we feel that a study looking at the effect of sugammadex or neostigmine NMB reversal, depth of anaesthesia, and influence of EMG is warranted.

The latest commercially available BIS software (version 4.1 in the unilateral BIS and its bilateral 1.4 version, Covidien, Dublin, Ireland) offers modifications of earlier versions. It is presented as being better at detecting and filtering EMG artifacts, with an improved ability to remain appropriately low in the presence of EMG activity that is not associated with true lightening of anaesthesia. We present a study in patients,

with and without high EMG activity, in whom we compared BIS values before and after sugammadex or neostigmine administration. In an attempt to clarify the possible effects of drugs used for reversal of NMBAs on BIS monitoring, we tested the hypothesis that sugammadex or neostigmine administration at stable propofol/remifentanyl anaesthesia and rocuronium NMB would result in an increase in BIS value dependent on the presence of EMG activity.

Methods

Our study was registered at European Community Clinical Trials Database EudraCT (<https://eudract.ema.europa.eu/>) trial registration number: 2009-016146-97. Our study conformed with the guidelines for 'Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision'.¹² We prepared our report of a prospective clinical consecutive study in conformity with the guidelines of the 'consolidated standards of reporting trials (CONSORT)-statement'.¹³ After Medical University of Graz ethics committee approval (21-196 ex 9/10 at its March 15, 2010, meeting, chaired by P.H. Rehak), all patients who agreed to participate in the study, between March and September 2010, gave written informed consent. Exclusion criteria were BMI <18.5 or >24.9 kg m⁻²,¹² history of alcohol or drug abuse, patients suffering from small joint arthritis, hepatic, renal or neuromuscular disease, patients on medications thought to interfere with neuromuscular transmission or medical conditions that could affect their level of consciousness such as stroke, or dementia.

Forty-eight consecutive ASA I–II patients, aged 18–50 yr,¹² undergoing orthopaedic or general surgical procedures under general anaesthesia were randomly allocated (using a computer-generated program by an external investigator not involved in the study) to receive sugammadex 4 mg kg⁻¹ or neostigmine 50 µg kg⁻¹/glycopyrrolate 10 µg kg⁻¹ 10 min after the end of surgical procedures and noxious stimulation.

A BIS Quatro sensor was mounted on the forehead according to manufacturer's guidelines and connected to a BIS-Vista monitor. The raw EEG signals were band-pass filtered to 2–70 Hz and processed in real time using version 1.4 BIS algorithm. BIS recordings were started after verifying a signal quality index >95% and electrode impedance <5 kΩ. EEG variables were digitally collected and stored on a laptop computer in the once every 5 s mode. BIS values showing sudden artifacts were identified and eliminated in the offline analysis.

The BIS monitor displays the frontal EMG (FEMG) of the 70–110 Hz frequency band in decibel units relative to 0.01 µV logarithmic transformation. The minimal decibel value that the BIS monitor displays is 30 dB, although actual measured lower decibel values can be recorded and retrieved in the offline mode.¹⁴ We chose the level of 35 dB as an indicator of adequate FEMG suppression to discriminate patients with No-EMG, when EMG values, after NMB reversal, were

consistently <35 dB. Patients were considered to have High-EMG, when EMG values were consistently ≥35 dB.

NMB at the adductor pollicis muscle was evaluated using the Relaxometer mechanomyograph (Groningen University, The Netherlands) to quantify the NMB.¹⁵ The force transducer of the Relaxometer was attached to the thumb and the ulnar nerve was stimulated supramaximally at the wrist (pulse width 200 µs, rectangular wave) via surface electrodes with train-of-four (TOF) stimuli (2 Hz for 2 s) at 12 s intervals. First twitch of the TOF (T_1) expressed as the percentage of control response and the TOF ratio ($T_4:T_1$) were used to evaluate NMB. $T_1\%$ and TOF ratio were digitally collected and stored on a laptop computer for the duration of the study.

Midazolam 7.5 mg was given orally 1 h before operation. For induction, a propofol 4 µg ml⁻¹ target-controlled infusion (TCI) using Diprifusor infusion pump (AstraZeneca Pharmaceuticals, Macclesfield, UK), incorporating Marsh pharmacokinetic model,¹⁶ was started after entering patients' anthropometric data. We used remifentanyl 0.1–0.3 µg kg⁻¹ min⁻¹ infusion and propofol ±0.2 µg ml⁻¹ TCI rate adjustments to maintain a stable BIS value of 40–60.¹⁷

Rocuronium 600 µg kg⁻¹ was given for tracheal intubation followed by 200 µg kg⁻¹ top-up doses. The lungs were ventilated mechanically with 40% oxygen in air and adjusted to maintain 30–40 mm Hg end-tidal carbon dioxide. Patients were warmed using a forced-hot-air-blanket to maintain core temperature above 36°C and skin temperature above 32°C. We monitored our study patients for clinical signs of recovery such as spontaneous movement, eyes opening, or spontaneous breathing.

At the end of surgery, we maintained, and recorded, propofol and remifentanyl infusion rates for a 10 min 'stabilization period'. The patients were given sugammadex 4 mg kg⁻¹ or neostigmine 50 µg kg⁻¹/glycopyrrolate 10 µg kg⁻¹ for reversal of NMB when they regained 1–2 TOF responses, as we did not want to unnecessarily prolong the patients' study period. After recovery from NMB, anaesthesia was stopped, the trachea was extubated, and the patient transferred to the post-anaesthesia care unit.

Statistical analysis

Based upon our first 10 consecutive pilot patients in whom mean BIS 48.7 (4.4) increased after sugammadex administration to 54.9 (5.7), an interim power analysis *t*-test ($\alpha=0.05$) showed that a group size of 11 patients would be required to reveal a statistically significant difference with 80% power. The sample size was then increased to ensure an adequate number of patients with and without EMG activity.

We used a paired *t*-test to compare BIS values before and after study drug administration. We used a two-way analysis of variance (ANOVA, group × time) to compare BIS differences between the two groups over time. Dunnett's two-sided multiple-comparison *post hoc* test was used to compare BIS values at different time points. Data were expressed as

means (SD or range). $P < 0.05$ was considered statistically significant.

Statistical analyses were performed using Number Crunching Statistical System 2007 (NCSS Inc., Kaysville, UT, USA) and StatXact (Cytel Software Corporation, Cambridge, MA, USA).

Results

There was no difference between the two groups with respect to patient characteristics (Table 1). During our study monitoring period, three patients showed clinical signs of recovery (spontaneous breathing) after sugammadex. Except for one patient who reported a strange metal or bitter taste, no serious adverse events such as hypersensitivity were detected.

There was no significant difference between the two groups over time for BIS before [49.6 (7.6), 52.1 (7.8)] and after [56.4 (6.7), 58.6 (7.5)] sugammadex and neostigmine were given. After sugammadex, BIS significantly increased in 11 patients who had high EMG activity and remained unchanged in 13 patients with no EMG activity. After neostigmine, BIS significantly increased in 13 patients who had high EMG activity and remained unchanged in 11 patients with no EMG activity (Fig. 1). Dunnett's two-sided multiple-comparison *post hoc* test revealed significant differences between patients with No-EMG and High-EMG starting 5 min after sugammadex and 15 min after neostigmine administration.

Time to 0.8 TOF ratio was shorter ($P = 0.001$) after sugammadex [3.1 (0.4) min] compared with neostigmine [15.4 (5.6) min] administration.

Discussion

We report BIS monitoring of patients who received sugammadex or neostigmine during stable propofol/remifentanyl anaesthesia and rocuronium-induced block. Our main finding that reversal of NMB resulted in a significant BIS

increase in patients who had reappearance of muscle activity could be attributed to NMBA reversal, provoking EMG artifacts spuriously increasing BIS values. Although hitherto sugammadex has been clinically described as an agent with few side-effects, we have shown that sugammadex, and neostigmine albeit with a slower effect, may interfere with BIS monitoring.

The most plausible explanation of our results is that NMB reversal resulted in a spuriously increased BIS value from FEMG artifact signals. EMG activity produces artifact signals that occur within the frequency 'range of interest' of the bispectrum. $EMG_{30-300\text{ Hz}}$ overlaps $EEG_{0-50\text{ Hz}}$, particularly in the fast EEG waves.¹⁸ $EMG_{30-300\text{ Hz}}$ portion could thus simulate the BetaRatio $EEG_{30-47\text{ Hz}}$, one of the BIS component descriptors that would be construed by the BIS algorithm as EEG activity and assigned a spuriously high BIS value.³ Several studies have shown a decrease in BIS values after NMBA administration as NMB stops FEMG signals from spuriously elevating BIS values.^{4, 9-11} Other studies have reported that NMBA have 'no effect' on BIS values when patients have no muscle activity.⁵⁻⁸

Newer BIS monitors incorporated algorithms with a higher capability of rejecting most of the FEMG components that could elevate BIS values. Despite publication of the general principles of BIS,² it remains a 'black box' as the details of the BIS algorithms' core technology are only completely known to the manufacturer. It is impossible to precisely determine to what extent the EMG component is excluded, possibly keeping the EMG:EEG 'noise to signal ratio' to $< 1:10$. It is plausible that even in the latest versions, some of the EMG component could still contribute to the BIS value. Despite rejection of the in-phase signals to reduce interference and diminish EMG artifacts, a small discrepancy between the electrode impedances would still allow subharmonic EMG artifacts into the BIS input signal.

Conversely, it has been reported that mean BIS values [31.7 (9.9)] remained unchanged [32.0 (11.9)] 10 min after sugammadex reversal of the rocuronium-induced NMB.¹⁹ The authors concluded that sugammadex had no influence on BIS monitoring. The most likely explanation for the discrepancy with our results is that they analysed all their study patients (those with and without EMG activity) in one group.¹⁹ It is feasible that they included more patients exhibiting low EMG than those with high EMG activity, resulting in no statistically significant difference in BIS values when all their study patients were analysed as one group.

Another possible explanation as to why BIS levels may be increased by sugammadex and neostigmine would be the afferentation (muscles spindle) theory.²⁰ This states that afferent signals generated in muscle stretch receptors reach arousal centres in the brain, via afferent nerve pathways, to induce arousal. By blocking such afferent input signals, NMBA would potentially produce a sedative effect.²⁰ Sugammadex and neostigmine nullifying this effect is another possible explanation of how NMBA reversal could induce arousal.

Table 1 Patient characteristics, stable propofol TCI, and remifentanyl infusion requirements before sugammadex or neostigmine administration. Means (SD or range); BMI, body mass index; TCI, target-controlled infusion; BIS, bispectral index

	Sugammadex group (n=24)	Neostigmine group (n=24)
Male/female	13/11	12/12
Age (yr)	30 (18-46)	34 (18-50)
Weight (kg)	66 (8)	69 (11)
Height (cm)	175 (8)	177 (9)
BMI	21.6 (1.9)	22.0 (1.9)
Propofol TCI ($\mu\text{g ml}^{-1}$)	3.4 (0.3)	3.3 (0.2)
Remifentanyl infusion ($\mu\text{g kg}^{-1}\text{ min}^{-1}$)	0.15 (0.02)	0.14 (0.02)
Total amount of rocuronium (mg)	77 (10.3)	79 (13.1)

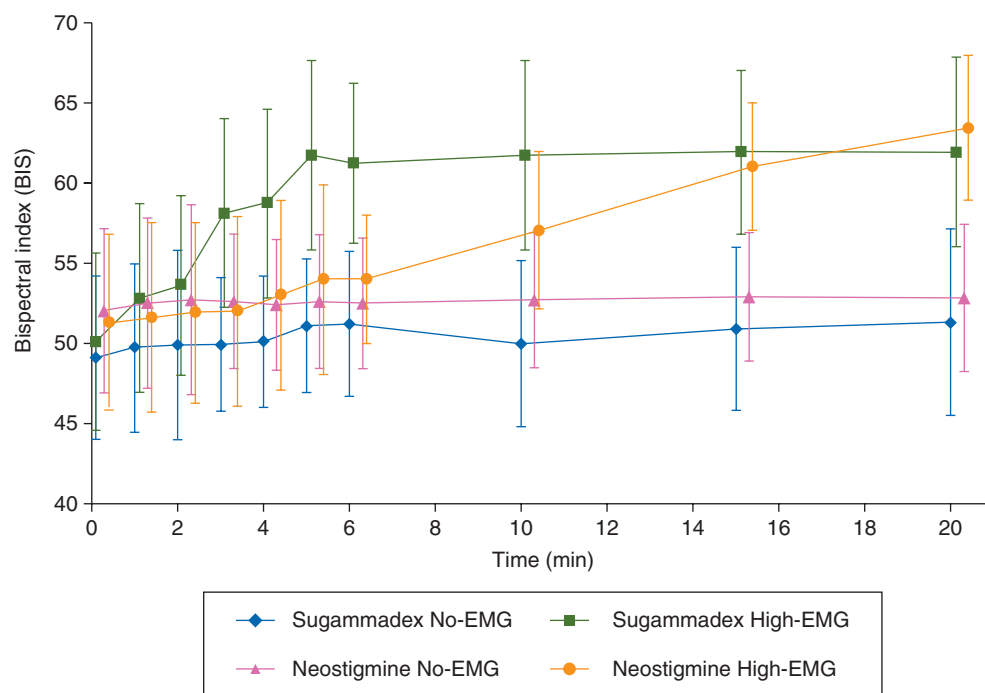


Fig 1 Mean (SD) BIS after sugammadex and neostigmine administration in the No-EMG and High-EMG patients.

Our study has its limitations, as our study design did not allow us to study the interaction of muscle relaxation and noxious stimulation on the depth of anaesthesia. Increasing degrees of NMB have been shown to progressively attenuate the effect of noxious stimulation on BIS monitoring.⁸ However, reversing patients during noxious surgical stimulation would have been unethical.

We have demonstrated that the possible effect of NMBAs reversal on the quantitation of depth of anaesthesia debate is not restricted to sugammadex, as we present a similar, albeit slower, effect on BIS monitoring with neostigmine. Previously, neostigmine antagonism of atracurium-induced NMB was shown to significantly increase BIS by 7.1 (7.5).⁷ Our findings of similar effects by sugammadex and neostigmine on BIS monitoring in patients with pre-existing EMG activity indicate that the BIS increase is related to NMB reversal in general and is not related to a drug-specific effect.

There are concerns that sugammadex cyclodextrin can encapsulate other drugs.²¹ A possible mechanism for increased BIS after sugammadex BIS values could be encapsulation of propofol or remifentanyl by sugammadex. However that does not seem likely as BIS values showed a similar increase after neostigmine in patients with high EMG activity.

An increase in BIS after NMBA reversal does not necessarily imply enhanced arousal from general anaesthesia as BIS does not necessarily indicate an adequate depth of anaesthesia.^{22 23} A low BIS value can be obtained during sleep,

and an increase in BIS occurs shortly after subjects wake up.²⁴ It is possible that patients were simply awake through the preceding part of monitoring, but could only show signs of it when they recovered muscle tone. In two previous studies, 30/157 (19.1%)²⁵ and 18/88 (20.4%)²⁶ patients showed signs of arousal (coughing, movement, and bucking) after sugammadex administration. That this was due to light anaesthesia masked by NMB could not be verified, as BIS was not used in the first study,²⁵ and in few patients in the second study.²⁶ This raises the question of the clinical relevance of our observations. One clinical message is that a high or increasing BIS value after reversal of NMB may not always indicate actual or impending wakefulness.

In our study, patients had slightly longer recovery from NMB after sugammadex than previously reported.²⁷ We propose that this could be attributed to the difference in neuromuscular monitoring technique—TOF-Watch acceleromyography²⁸ compared with mechanomyography²⁹ according to the GCRP consensus conference recommendations and guidelines.¹²

In conclusion, we have demonstrated that during stable propofol/remifentanyl anaesthesia and rocuronium-induced block, sugammadex or neostigmine administration significantly increased BIS value depending on the presence of EMG activity. The possibility of the reappearance of muscle activity during NMB reversal increasing BIS should be taken into consideration when using BIS monitoring for the evaluation of recovery from propofol/remifentanyl anaesthesia.

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Declaration of interest

None declared.

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