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# Pediatric Anesthesia

## The effects of mivacurium induced neuromuscular block on Bispectral Index and Cerebral State Index in children under propofol-anaesthesia – a prospective randomized clinical trial

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Key Words:	electroencephalogram, bispectral index, cerebral state index, children, propofol, neuromuscular block

**Title**

**The effects of mivacurium induced neuromuscular block on Bispectral Index and Cerebral State Index in children under propofol-anaesthesia – a prospective randomized clinical trial**

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**Running title:**

EMG and depth of anaesthesia

**Conflict of Interest**

none

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## Summary

**Background:** In adults anaesthetised with propofol, muscle relaxants may decrease the Bispectral Index (BIS). The aim of this prospective randomized trial was to detect the influence of a muscle relaxant bolus on the BIS and the Cerebral State Index (CSI) in children under propofol anaesthesia.

**Methods:** Forty paediatric patients, age  $6.6 \pm 3.3$  years, weight  $24 \pm 9$  kg, scheduled for surgical procedures requiring general anaesthesia were enrolled. Two minutes after i.v. injection of  $0.3 \text{ mcg kg}^{-1}$  of sufentanil general anaesthesia was induced by an initial bolus of  $3 \text{ mg kg}^{-1}$  of propofol, followed by a continuous infusion titrated to achieve a stable BIS value of  $50 \pm 5$ . Patients received either mivacurium  $0.25 \text{ mg kg}^{-1}$  (Group Miva) or NaCl 0.9%  $0.12 \text{ ml kg}^{-1}$  (Group Con). Mean BIS and CSI values per minute were compared between (Miva vs. Con) and within groups (Baseline vs. 5 min. after study drug administration).

**Results:** The observed changes in BIS and CSI values before and after administration of study drugs revealed no differences between the study groups. Mean baseline BIS- and CSI-values were lower than 5 minutes after study drug administration. There were no intergroup differences with respect to BIS and CSI values at any time point.

**Conclusions:** These data suggest that in paediatric patients anaesthetised with propofol, administration of mivacurium has no impact on BIS-, and CSI- values.

## Keywords:

electroencephalogram; bispectral index; cerebral state index; children; propofol; neuromuscular block

## Introduction

For the adult patient population there are conflicting data in the literature as to whether or not frontal electromyogram activity (EMG) affects the reliability of the BIS as a measure of depth of hypnosis (DH). On the other hand it is nowadays widely accepted that high frontal EMG activity might falsely elevate electroencephalogram (EEG) based indices of the depth of hypnosis (DoH) in anaesthetised subjects, whereas absence of EMG activity in awake subjects might result in a falsely low DH-index (1).

Already in 1946 Gray and Halton (2) suggested some kind of synergism between curare and barbiturates and an even more pronounced synergism between this combination and the inhalational anaesthetics ether and cyclopropane. In a recent editorial Bonhomme and Hans (3) gave an overview of the theories that have been published about how neuromuscular blocking agents (NMBA) may affect both the hypnotic and the antinociceptive component of anaesthesia. The de-afferentation theory suggests that prolonged sensory deprivation results in a decrease in power together with a shift of the power-spectrum towards lower frequencies in the human EEG (4). However, with respect to NMBA it is noteworthy to stress that muscle relaxation does not produce total sensory deprivation (3). Schwartz et al. (5) demonstrated that pancuronium increases the duration of isoelectricity during isoflurane EEG burst suppression in dogs and suggested that the effect of isoflurane on the brain is enhanced by nondepolarizing NMBA. Lanier et al. (6) suggested that in lightly anaesthetised dogs muscle afferent receptors mediate effects of active muscle movement in response to painful stimulation on the brain in terms of EEG activation, cerebral vasodilatation and increased cerebral blood flow. Pancuronium induced paralysis abolished movement and the afferent response, resulting in attenuated responses of EEG, cerebral blood flow and cerebral vascular resistance following painful stimulation. Messner et al. (7) reported a significant decrease in Bispectral Index (BIS) values in two fully awake volunteers after succinylcholine administration.

Like the BIS™-monitor (Aspect Medical Systems, Natick, U.S.A.), the Cerebral State Monitor

1  
2 (CSM™, Danmeter A/S, Odense, Denmark) performs a computerised analysis of the EEG. CSM  
3  
4 EEG processing results in an index indicating the hypnotic component of anaesthesia, the  
5  
6 Cerebral State Index (CSI). Until now there are, to our best knowledge, no published data  
7  
8 available with respect to the possible effects of neuromuscular block (NMB) on the accuracy of  
9  
10 CSI calculation (3).  
11  
12

13  
14 In this prospective randomised trial we tested the hypothesis that mivacurium induced NMB in  
15  
16 children anaesthetised with propofol results in a lower level of consciousness as detected by the  
17  
18 BIS and the CSI, thus a decrease of both indices.  
19  
20

### 21 22 23 **Materials and methods**

24  
25 After approval of the institutional ethics committee of the Erasmus University Medical Center  
26  
27 Rotterdam, The Netherlands, and written informed consent was obtained from the patients'  
28  
29 parents or caregivers, 40 children, aged between 2 and 12 years, ASA physical status I or II,  
30  
31 scheduled for elective minor paediatric or urological surgery were studied. Patients were primarily  
32  
33 excluded from the study if they suffered from significant cardiovascular, respiratory or  
34  
35 neurological disease or if they were taking chronic medication known to affect the central nervous  
36  
37 system.  
38  
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40  
41 All patients had a standardised anaesthetic. Induction of general anaesthesia was performed as  
42  
43 follows: After establishment of intravenous access, intravenous sufentanil  $0.3 \mu\text{g kg}^{-1}$  was  
44  
45 administered. Two minutes later propofol  $3 \text{ mg kg}^{-1}$  was injected, if necessary followed by  
46  
47 subsequent doses of  $0.5 \text{ mg kg}^{-1}$  until loss of responsiveness (LOR). LOR was defined as the  
48  
49 moment of loss of eyelash reflex combined with the absence of response to verbal or mild tactile  
50  
51 stimulation. At that moment patients were considered to be unconscious. Then a continuous  
52  
53 propofol infusion was started, initially at a rate of  $10 \text{ mg kg}^{-1} \text{ h}^{-1}$ . Immediately after LOR both BIS  
54  
55 and CSI monitoring were established. The continuous propofol infusion was then titrated to  
56  
57 achieve a stable BIS value of  $50 \pm 5$  for at least 60 seconds. Then, patients were prospectively  
58  
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60

1  
2 randomized to receive in a double blinded fashion either mivacurium  $0.25 \text{ mg kg}^{-1}$  (Group Miva),  
3  
4 or an equal volume of NaCl 0.9% (0.125 ml/kg) (Group Con). The syringes were labelled as  
5  
6 “study medication”. Patients were randomised by the sealed envelope method.  
7

8  
9 Initially patients were either breathing spontaneously via a face mask or received manually  
10  
11 assisted ventilation in order to maintain an end-tidal carbon dioxide tension of 35–45 mmHg.  
12

13  
14 With the onset of NMB following mivacurium administration patients were completely ventilated.  
15

16  
17 During the whole study period (1 min. before administration of study drugs and 5 min. thereafter)  
18  
19 the patients remained untouched except of face mask ventilation, furthermore care was taken to  
20  
21 minimize the sound level of the anaesthesia induction room to a minimum.  
22

23  
24 Five minutes after study drug administration the registration of BIS, and CSI data was stopped.  
25

26  
27 After a deblinding procedure patients who had been randomised to the Control group were  
28  
29 allowed to receive mivacurium and the conduct of anaesthesia was further unrestricted at the  
30  
31 discretion of the anaesthesiologist in charge. Assessment of NMB was performed by Train-of-  
32  
33 Four (TOF) stimulation of the ulnar nerve 5 minutes after study drug administration. During the  
34  
35 study period no TOF stimulations were applied in order to avoid unnecessary artefact  
36  
37 contamination of the EEG readings.  
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41

### 42 **Cerebral State Index (CSI) monitoring**

43  
44 After the skin was prepared with alcohol and abraded with gauze, three silver-silver chloride  
45  
46 electrodes (Medicotest A/S, Olstykke, Denmark) were positioned at the mid forehead (+), left  
47  
48 forehead (reference) and left cheekbone (-). Electrode placement and skin preparation were  
49  
50 performed until the electrodes' impedance was less than 1000 Ohms. The algorithm that  
51  
52 calculates the CSI is based on several sub parameters within the 6-42.5 Hz frequency band of the  
53  
54 EEG and on burst suppression. The CSI is a dimensionless scale, ranging from 100 (fully awake)  
55  
56 to 0 (very deep hypnosis). CSI values between 40 and 60 can be considered as the range for  
57  
58 surgical anaesthesia (1). Besides the CSI, the Cerebral State Monitor also gives information about  
59  
60

1 facial EMG activity. Unfortunately there is no information available to the public about the EEG  
2  
3 frequency range, which is being used by the Cerebral State Monitor to measure and quantify  
4  
5 EMG activity (dB).  
6  
7  
8  
9

### 10 11 **Bispectral Index (BIS) monitoring**

12 For BIS registration a paediatric four-sensor BIS™ probe (BIS™ Paediatric Sensor; Aspect  
13  
14 Medical Systems International BV, De Meern, The Netherlands) was attached to the patient's  
15  
16 forehead according to the instructions of the manufacturer. A BIS<sub>XP</sub>™ monitor was used. On the  
17  
18 BIS<sub>XP</sub>™ monitor EMG activity is being displayed as the power in the 70-110 Hz frequency range  
19  
20 of the EEG in dB-units (8).  
21  
22  
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27

28 All EEG data, incl. EMG in dB, were collected at 5-sec intervals using Rugloop™ (Demed,  
29  
30 Temse, Belgium), synchronized with Labgrab™ (Demed), and stored on a personal computer for  
31  
32 subsequent analysis.  
33  
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36

### 37 **Statistics:**

38  
39 Individual mean BIS and CSI values of two periods of 60 seconds were calculated for the  
40  
41 occasions "Baseline" (after stable BIS values of  $50 \pm 5$  for at least 1 min, prior to study drug  
42  
43 administration) and 5 min. after study drug administration. Mean values per patient were  
44  
45 subsequently used for statistical analysis. Datasets were furthermore tested for normality by the  
46  
47 Kolmogorov-Smirnov test. Intergroup comparison of the change in BIS and CSI values was  
48  
49 performed by the Mann-Whitney Rank Sum Test. Intragroup comparison of mean BIS and CSI  
50  
51 (baseline versus 5 min. after drug administration) was performed by paired t-test.  
52  
53  
54  
55

56 In order to reach a power of 0.9 and an alpha level of 0.05 a total of 36 patients would be required  
57  
58 to detect a 10 percent difference in BIS values between both study groups. In order to compete for  
59  
60 possible drop outs 20 patients per group were included.

1  
2 Statistical analysis was performed using SigmaStat, version 3.5 (Systat Software Inc., San Jose,  
3 CA, USA). For power analysis G\*Power, version 3.0.10 was used (9). P values of <0.05 were  
4 considered statistically significant. Variables are presented as mean±sd unless otherwise stated.  
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6  
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## 10 11 **Results**

12 Forty patients were enrolled between March and November 2008. Due to synchronisation  
13 problems, EEG data acquisition failed in one patient of the control group. Per protocol analysis  
14 was performed using the data obtained from 39 patients. Study groups did not differ with respect  
15 to age (group Miva 85±49 months, group Con 73±28 months) and body weight (group Miva  
16 24.9±11.3 kg, group Con 22.5±5.8 kg). Propofol consumption was also comparable between  
17 groups (Group Miva 10.0±0.6 mg kg<sup>-1</sup> h<sup>-1</sup>, Group Con 10.0±0.2 mg kg<sup>-1</sup> h<sup>-1</sup>; n.s.).  
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28 Pooled mean values per patient of BIS and CSI (baseline and 5 minutes after study drug  
29 administration) together with the results of intragroup comparison of the change in BIS and CSI  
30 are presented in table 1. Both BIS and CSI values were higher 5 min. after study drug as  
31 compared to baseline in all participants of the study. With respect to the change in BIS and CSI  
32 (baseline vs. +5 min.) no differences were found between groups Miva and Con (see table 2).  
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40 The absence of all four twitch responses to TOF stimulation of the ulnar nerve in all patients of  
41 group M confirmed complete NMB, whereas TOF stimulation evoked four twitches in all patients  
42 allocated to group C. The BIS<sub>XP</sub> monitor recorded a constant level of EMG activity throughout the  
43 study period irrespective of study drug administration (Group Miva 32±1 dB, Group Con 32±1,  
44 n.s.). No EMG activity was recorded by the CSM throughout the whole study period. No side  
45 effects or adverse events were recorded in any patient.  
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## 56 **Discussion**

57 In the present paediatric study mivacurium induced NMB had no effect on both the BIS and the  
58 CSI in paediatric patients anaesthetised with propofol. To our best knowledge until now there are  
59  
60

1  
2 no other studies published which addressed this issue in the paediatric surgical population. To  
3  
4 compare our results with other published data we mainly have to refer to papers dealing with the  
5  
6 use of the BIS in adult patients.  
7

8  
9 Rigouzzo et al. (10) presented in abstract form paediatric data on the effects of [atracurium](#)  
10  
11 induced NMB on the BIS in children anaesthetised with propofol and sevoflurane. The authors  
12  
13 applied [Target Controlled Infusion \(TCI\)](#) technique and observed a significant decrease of BIS  
14  
15 values after injection of [atracurium](#) in children with low propofol plasma concentrations (2 and 3  
16  
17  $\mu\text{g ml}^{-1}$ ), whereas there was no effect of NMB with higher plasma concentrations (4-6  $\mu\text{g ml}^{-1}$ )  
18  
19 and in children anaesthetised with sevoflurane. [These data suggest a direct, dose dependent effect](#)  
20  
21 [of propofol on the EMG.](#)  
22  
23  
24  
25

26 The results of this study agree with data published by Greif et al. (11) who investigated the impact  
27  
28 of different stages of mivacurium induced neuromuscular block on the BIS and fronto-temporal  
29  
30 EMG activity in adult volunteers under propofol anaesthesia. In their study Greif et al. used a TCI  
31  
32 system to achieve a constant level of hypnotic depth. A propofol plasma concentration of  $3.8\pm 0.4$   
33  
34  $\mu\text{g ml}^{-1}$  resulted in a BIS level of  $39\pm 4$ . Compared to our paediatric study with an overall  
35  
36 baseline BIS value of  $48\pm 4$  this represents a considerably deeper level of hypnosis. Greif et al  
37  
38 furthermore measured a constant level of EMG activity of  $28\pm 1$  dB irrespective of the degree of  
39  
40 NMB. They hypothesised that the combination of a deep level of hypnosis and minimal EMG  
41  
42 background activity NMB had no further impact on both the BIS and the EMG. Any extrapolation  
43  
44 of the conclusions made by Greif et al. to the paediatric patients of our study is certainly  
45  
46 speculative to some degree. However, it cannot be ruled out that at a BIS level of  $48\pm 4$ , [indicative](#)  
47  
48 [of surgical anaesthesia](#) and an EMG activity of  $32\pm 1$  in children under propofol anaesthesia the  
49  
50 application of NMB has no impact on both EMG activity and hypnotic depth as measured by the  
51  
52 BIS.  
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58 In our study propofol was titrated using a conventional infusion pump to achieve a stable BIS of  
59  
60  $50\pm 5$  prior to the application of the study medication. Once having achieved the desired BIS level,

1 the propofol infusion rate remained unaltered until the end of the study period. It would  
2 undoubtedly have been desirable to apply TCI technology but unfortunately we had no devices  
3 available which incorporate paediatric pharmacokinetic models validated for use in small  
4 children. The design of this study renders thus the possibility that, due to redistribution, a constant  
5 infusion rate even over a period as short as 6 minutes, does not necessarily result in a stable DoH.  
6 That might explain the mild increase of BIS and CSI values in both study groups over time, even  
7 in the absence of physical or acoustic stimulation, indicating the likelihood of a decrease of  
8 hypnotic depth as a result of distribution of propofol among the compartments of the body, which  
9 leads to both a lower plasma- and effect-site drug concentration.  
10

11 In a recent study by Dahaba et al. (8) the administration of mivacurium 0.15 mg/kg to adult  
12 patients under deep propofol/remifentanyl anaesthesia resulted in a transient decline of BIS<sub>XP</sub>  
13 values from 41±3 to 35±3 (p = 0.003). TCI was applied to establish stable BIS of approximately  
14 40 which was deemed to reflect a state of deep surgical anaesthesia. Recordings of BIS values  
15 were started after verifying the absence of EMG activity.  
16

17 In the present study recordings of facial EMG via the BIS monitor revealed a constant activity of  
18 32dB in all patients throughout the study period, whereas the Cerebral State Monitor did not  
19 detect any EMG activity. TOF stimulation of the ulnar nerve confirmed complete NMB in all  
20 patients allocated to group Miva. However, that did not result in any changes of facial EMG  
21 activity, as measured by the BIS-monitor. The site of EMG-monitoring might contribute to this  
22 finding. Human skeletal muscles consist of two different types of fibres which can be classified  
23 on the basis of their metabolic and electrophysiological characteristics. Type I, or slow twitch  
24 muscle fibres are the predominant fibres in muscles with an almost exclusive postural function,  
25 whereas a high percentage of type II (fast twitch) fibres, can be found in muscles with usually  
26 phasic activity. For the adductor pollicis Johnson et al. (12) reported a percentage of type I fibres  
27 as high as 80%, whereas in the orbicularis oculi they found 85% of type II fibres. Secher et al.  
28 (13) suggested that tubocurarine affects human muscles in proportion to their type I muscle fibre  
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2 content. In their study the application of tubocurarine resulted in a significantly greater reduction  
3  
4 of muscle strength of the m. gastrocnemius (54% type I fibres) than in the m. soleus (71% type I  
5  
6 fibres). Not surprisingly there is thus significant evidence that upper face muscles are less  
7  
8 sensitive to non-depolarizing neuromuscular blockers than hand muscles, at least under  
9  
10 anaesthesia conditions (14-16).  
11  
12

13  
14 Given the algorithms implemented in the BIS-monitor and the CSM, EMG contamination of the  
15  
16 EEG signal renders the possibility to interfere with the calculation of both the BIS and the CSI.  
17  
18 EMG frequencies overlap the 30-47 Hz range of the EEG (1), from which the 'beta-ratio' of the  
19  
20 BIS algorithm is calculated. Thus, theoretically, elimination of EMG activity by NMB should lead  
21  
22 to another beta-ratio, resulting in an altered BIS value. In the present study, mivacurium induced  
23  
24 NMB had no impact on facial EMG activity as measured by the BIS-monitor. That might explain,  
25  
26 why the BIS remained unchanged despite complete NMB, as confirmed by TOF stimulation of  
27  
28 the ulnar nerve.  
29  
30

31  
32 Vasella et al. (17) applied atracurium  $0.4 \text{ mg kg}^{-1}$  to adult patients anaesthetised with  
33  
34 propofol/remifentanyl after establishing a stable BIS value of 55 using TCI. They reported that  
35  
36 NMB had no effect on the BIS. However, the application of neostigmine-glycopyrrolate led to a  
37  
38 significant increase BIS of  $7.1 \pm 7.5$ .  
39  
40

41  
42 As opposed to the BIS little is known about the Cerebral State Monitor. There are at least two  
43  
44 recent publications indicating that the CSI is capable to detect the graduated levels of propofol  
45  
46 anaesthesia both in adults and children. Adult data published by Weber-Jensen et al. (18) showed  
47  
48 a prediction probability (PK) value between the CSI and the Observer's Assessment of Alertness  
49  
50 and Sedation score of 0.92. For paediatric patients under various levels of propofol sedation  
51  
52 Disma et al. (19) reported a strong negative correlation ( $r = -0.823$ ;  $P < 0.0001$ ) between the CSI  
53  
54 and the University of Michigan Sedation Scale for children.  
55  
56

57  
58 The present study suggests that mivacurium induced neuromuscular block does not alter the level  
59  
60 of consciousness as measured by the CSI in children anaesthetised with propofol. This finding

1  
2 might be explained by the fact, that the CSM did not detect any EMG activity even prior to  
3  
4 mivacurium administration. This was possibly due to the rather narrow EEG band of 6-42.5 Hz  
5  
6 used by the CSM for calculation of the CSI. Unfortunately there is no specific information  
7  
8 available to the public about the frequency range of the CSM used for measurement of EMG  
9  
10 activity. Facial EMG activity peaks a approximately 70Hz, and may even reach 300Hz (1).  
11  
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13 Assuming that the CSM does not record any EEG/EMG activity outside the 6-42.5 Hz window  
14  
15 this might, at least partly, explain why there wasn't any detection of EMG activity at all.  
16  
17

18 The likelihood that mivacurium influences the BIS or the CSI appears to have very much to do  
19  
20 with the amount of the facial EMG signal. Our data suggest that, due to the known relative  
21  
22 insensitivity of the supraorbital muscles to NMBA (14-16), administration of mivacurium did not  
23  
24 result in any changes of the amount of EMG activity as measured by the BIS and the CSM. In  
25  
26 addition to that, propofol itself reduces EMG activity (10). Since in the children who participated  
27  
28 in our study propofol was titrated to achieve a rather deep level of hypnosis, it is, from a basic  
29  
30 science point of view, less likely that mivacurium induced NMB influenced facial EMG activity.  
31  
32

33 The results of this study should not be extrapolated to other combinations of anaesthetics, muscle  
34  
35 relaxants and monitors of hypnotic depth. Even with respect to other levels of hypnotic depth  
36  
37 using the same drug-monitor combination it remains speculative whether or not the impact of  
38  
39 neuromuscular block might the same as in this trial.  
40  
41  
42

43 In conclusion in this paediatric study mivacurium induced neuromuscular block did not alter the  
44  
45 level of consciousness as measured by either the Bispectral Index or the Cerebral State Index in  
46  
47 children anaesthetised with propofol.  
48  
49  
50

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57  
58  
59  
60

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**Table 1**

Intragroup comparison of EEG parameters BIS and CSI

Parameter	BIS		CSI	
	Miva	Control	Miva	Contra
Baseline	48.0 ± 4.8	48.7 ± 3.2	54.0 ± 7.7	54.8 ± 6.1
+ 5 min.	53.0 ± 6.6	52.0 ± 4.0	57.4 ± 7.1	56.8 ± 6.8
Diff. of means	-5.0 ± 7.1	-3.3 ± 4.5	-3.4 ± 5.3	-2.0 ± 2.5
95 % CI diff. of means	-8.7 - -1.3	-5.4 - -1.1	-5.9 - -1.0	-3.2 - -0.8
P value	0.01	0.005	0.009	0.002

Mean values ( $\pm$ sd) of Bispectral Index (BIS) and Cerebral State Index (CSI), at baseline and 5 minutes after study drug administration (+5 min.), together with the differences in means between baseline and +5 min., and 95 percent confidence interval for difference in means. P-values represent the results of a paired t-test.

**Table 2**

Intergroup comparison of differences in BIS and CSI values before and after administration of study drugs

	BIS	CSI
<b>Group Miva</b>		
$\tilde{x}$ (diff.)	2.8	4.3
IQR	0.8 – 11.1	0.5 – 6.4
<b>Group Control</b>		
$\tilde{x}$ (diff.)	1.9	2.5
IQR	0.2 – 5.8	0.2 – 4.0
P value	0.57 (n.s.)	0.29 (n.s.)

Median values ( $\tilde{x}$  diff.) and interquartile range (IQR) of differences in EEG parameters Bispectral Index (BIS) and Cerebral State Index (CSI) between baseline and 5 minutes after study drug administration (+5 min.). P values represent the results of a Mann-Whitney Rank Sum Test.



CONSORT Statement 2001 Checklist  
Items to include when reporting a randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	<u>How participants were allocated to interventions</u> (e.g., "random allocation", "randomized", or "randomly assigned").	1&2
INTRODUCTION Background	2	<u>Scientific background and explanation of rationale.</u>	3&4
METHODS Participants	3	<u>Eligibility criteria for participants</u> and the <u>settings and locations where the data were collected.</u>	4
Interventions	4	<u>Precise details of the interventions intended for each group and how and when they were actually administered.</u>	3-5
Objectives	5	<u>Specific objectives and hypotheses.</u>	4
Outcomes	6	<u>Clearly defined primary and secondary outcome measures</u> and, when applicable, any <u>methods used to enhance the quality of measurements</u> (e.g., multiple observations, training of assessors).	3
Sample size	7	<u>How sample size was determined</u> and, when applicable, <u>explanation of any interim analyses and stopping rules.</u>	6&7
Randomization -- Sequence generation	8	<u>Method used to generate the random allocation sequence, including details of any restrictions</u> (e.g., blocking, stratification)	5
Randomization -- Allocation concealment	9	<u>Method used to implement the random allocation sequence</u> (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	5
Randomization -- Implementation	10	<u>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</u>	5
Blinding (masking)	11	<u>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment.</u> If done, <u>how the success of blinding was evaluated.</u>	4&5
Statistical methods	12	<u>Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.</u>	6&7
RESULTS Participant flow	13	<u>Flow of participants through each stage</u> (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. <u>Describe protocol deviations from study as planned, together with reasons.</u>	7
Recruitment	14	<u>Dates defining the periods of recruitment and follow-up.</u>	6
Baseline data	15	<u>Baseline demographic and clinical characteristics of each group.</u>	7
Numbers analyzed	16	<u>Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat".</u> State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	7
Outcomes and estimation	17	<u>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision</u> (e.g., 95% confidence interval).	7, 14, 15
Ancillary analyses	18	<u>Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.</u>	n.a.
Adverse events	19	<u>All important adverse events or side effects in each intervention group.</u>	7
DISCUSSION Interpretation	20	<u>Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.</u>	7-12
Generalizability	21	<u>Generalizability (external validity) of the trial findings.</u>	7-12
Overall evidence	22	<u>General interpretation of the results in the context of current evidence.</u>	7-12

From Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357(9263):1191-1194.

The CONSORT Statement 2001 checklist is intended to be accompanied with the explanatory document that facilitates its use. For more information, visit [www.consort-statement.org](http://www.consort-statement.org).