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Cerebral Oxygenation and Metabolism after Reversal of Rocuronium: Comparison between Sugammadex versus Neostigmine

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ABSTRACT

Background: Recovery from neuroanesthesia requires stable hemodynamics and optimal cerebral oxygenation.

Objective: The purpose of this study was to compare the effect of low dose sugammadex with neostigmine on recovery and cerebral hemodynamic profile after supratentorial tumor resection.

Patients and Methods: In this double-blind randomized study, forty patients were allocated according to the reversal used after supratentorial tumor surgery into, sugammadex 2 $mg \cdot kg^{-1}$ (group S) or neostigmine 0.05 $mg \cdot kg^{-1}$ + atropine 0.02 $mg \cdot kg^{-1}$ (group N). Duration from reversal to train of four 0.9 was a primary outcome. Arterial and jugular bulb blood samples obtained after induction, before closure of dura, before reversal, ten minutes after reversal then one hourly for 3 hours postoperative for the calculation of arterial-jugular oxygen content difference "CaO_2-jO_2," cerebral oxygen extraction "CEO_2", jugular venous oxygen saturation ($SjvO_2$), estimated cerebral metabolic rate "$eCMRO_2$," and cerebral blood flow equivalent "CBFe," as secondary outcomes.

Results: We demonstrated that recovery time (duration from reversal to train of four 0.9) was significantly shorter with sugammadex (P=0.001). Sugammadex recorded significant increased CEO_2 and CaO_2-jO_2 at 10 minutes after reversal, at 1 hour (hr), 2 hr and 3 hr postoperatively. Sugammadex resulted in significant decreased $SjvO_2$ and CBFe at 10 minutes after reversal, at 1 hr, 2 hr and 3 hr postoperatively without significant effect on $eCMRO_2$.

Conclusion: Low dose sugammadex (2 $mg.kg^{-1}$) provided rapid and effective reversal of rocuronium NMB superior to neostigmine with improved cerebral hemodynamic profile after supratentorial tumor surgery.

Key words: Cerebral hemodynamic, Neostigmine, Sugammadex, Supratentorial tumor.

INTRODUCTION

Among the requirements of the modern anesthesia practice, is the use of neuromuscular blocking agents, which provide good surgical conditions especially in patients subjected to neurosurgical procedures. Reversal agents like neostigmine are frequently used to hasten the restoration of neuromuscular function. However, this drug neither provides predictable nor a sufficient rapid recovery of neuromuscular function[(1,2)], and might cause many adverse effects in relation reduced activity of cholinesterase enzyme[(3)].

Sugammadex (Bridion®); a ɤ-cyclodextrin derivative is a new reversing agent used to reverse the neuromuscular blockade (NMB) produced by rocuronium or vecuronium. Unlike neostigmine, sugammadex reverses deep NMB and could be administered to reverse NMB immediately without waiting for partial recovery. It does not affect cholinesterase activity and thus there is no need for anticholinergic agents (like atropine), which should be used with neostigmine[(4,5)]. Early recovery is targeted in neurosurgery specially those undergoing brain tumor resection for achieving early neurologic assessment and therefore for accelerating the diagnosis and management of serious complication[(6)].

Aims during emergence from neurosurgical anesthesia are to maintenance the stability of blood pressure and intracranial pressure, thus normal cerebral perfusion pressure (CPP) with adequate oxygenation, normal arterial carbon dioxide tension ($PaCO_2$), as well as normal temperature. Elevated blood pressure, cough, and asynchrony with mechanical ventilator enhance the risk of postoperative hematoma and edema. Residual curarization is particularly risky for patients with cranial pathologies in which level of consciousness and protective reflexes can be compromised due to the underlying disease or the neurosurgical intervention[(7)].

To our knowledge, rather than recovery profile, there is a little number of studies available in the literatures comparing cerebral hemodynamics and oxygenation effects of low dose sugammadex with neostigmine in neurosurgical patients. So, the current comparative, randomized and double blind study was conducted to investigate short term effect of low dose sugammadex versus neostigmine on recovery and cerebral hemodynamic profile after reversing the rocuronium neuromuscular blockade in patients undergone supratentorial tumor excision.

PATIENTS AND METHODS

Forty consecutive patients aged 21-60 years of both sexes, admitted to the Neurosurgery Department for elective surgical removal of supratentorial brain neoplasms were included in this study. The patient flow is depicted in Fig. 1.

Ethical consent:

The study was approved by the medical local Ethics Committee in Mansoura University Hospital/Egypt (MD /16.07.22 July 2016) and was registered in Clinical trial registration:

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NCT02944175 (ClinicalTrials.gov). Patients were interviewed and written informed consents were obtained from the patients to be a part of our research. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All cases admitted between April 2016 and May 2018 who were qualified for elective resection of supratentorial brain tumors at Department of Anesthesia and Surgical Intensive Care were eligible to be included in the study. Inclusion criteria included: American Society of Anesthesiologists physical status I and II, both sexes, supratentorial brain tumor surgery with Glasgow coma scale (GCS) of 13-15 and willingness to participate.

Patients were excluded in cases of associated severe decompensated illnesses (heart, respiratory, liver or kidney diseases), morbid obesity, documented hypersensitivity to one of the used drugs, surgery in sitting or prone position and patients with altered level of consciousness and associated pregnancy.

All cases underwent surgical resection of the tumor via one neurosurgeon.

Earlier studies regarding the effectiveness of sugammadex in reversing rocuronium-induced blockade were based on recovery of train of four (TOF). Sugammadex effectively reversed deep NMB in 2-3 minutes through giving it until TOF ratio is 90% [8-10]. Therefore, 19 cases in either group were needed to determine at least ≥ 5 minutes difference between groups regarding such variable and to be capable of rejection of null hypothesis, which the population means in each group, are equal with probability (power) 0.85. The Type I error probability related to such test of null hypothesis (α) was 0.05. Therefore, a total of 40 cases were included in the current work.

An anesthetist was un-blinded to sugammadex and he had the ability of adjusting the anesthesia and NMB in the treatment group, and evaluate sugammadex's effects on patient's flow through the operating room. The safety and TOF-Watch® SX assessors were blinded to the treatment group, did not observe preparation of trial drugs and did not share in randomization, preparation of study drugs, or permitted to be present in operating room during operation.

The day prior to operation, after having written consents, all patients were evaluated for detailed medical history and examination including manifestations of high intraocular pressure (IOP), type and site of the tumors. ECG and investigations for complete blood picture, blood sugar level, liver functions, serum creatinine, prothrombin time, activity and INR. Patients were fasted for 8 hours.

The day of surgery in the recovery room, a cannula (18 G) was secured into a peripheral vein (usually an antecubital vein). Patient received i.v. midazolam 0.05 mg/kg plus 1.5-2 $\mu g.kg^{-1}$fentanyl 10 min before induction. Preanesthetic monitoring for basal reading included HR, pulse oximetry and non-invasive blood pressure. NMB monitoring (Train-of-Four (TOF) Watch SX monitor; (Organon, Dublin, Ireland) also was available. According to closed envelope randomization, patients were classified into 2 equal groups according to the drug used for reversal of the neuromuscular blockade, sugammadex group (GS) (20 patients) and neostigmine group (GN) (20 patients). Patient flow chart is shown in figure (1), which discusses the consort diagram for patient recruitment in the trial. Induction of anesthesia was started with pre-oxygenation with 100% O_2 for 3-5 min, sleep inducing dose of propofol (1-2 $mg.kg^{-1}$) then endotracheal intubation using proper sized cuffed armored ETT was facilitated by rocuronium bromide (Esmeron 0.6 mg/kg i.v.), to produce muscle relaxation and patients underwent intubation when TOF=0 was attained. Anesthesia was maintained by isoflurane 1%, O_2: Air (1:1) and fentanyl in repeated doses (20 μg) when needed with subsequent doses of rocuronium 0.15 $mg.kg^{-1}$ every 20 minutes to maintain sufficient muscle relaxation guided by TOF monitoring. Patients were connected to mechanical ventilator with tidal volume and respiratory rate underwent adjustment to keep $ETCO_2$ around 30 mmHg and SpO_2 more than 95%. Mannitol (20%) 1 $gm.kg^{-1}$was given 20 minutes before opening the dura via central line.

Patient was infused warm saline 0.9% to maintain central venous pressure (CVP) ~5 mmHg. On surgical bleeding requiring transfusion, blood transfusion was performed to maintain hemoglobin (Hb)≥10 gm/ dl or hematocrit (Hct) ~30%. Immediately after induction of anesthesia, arterial cannula (20 G) was secured into radial artery of undominant hand following carrying out Modified Allen's test with local infiltration of 0.5 ml xylocaine 2%. A single lumen central venous catheter (18 G) (Amecath, France) was also secured into right subclavian vein; confirmation of its accurate position was established by chest X-Ray. Then, the right internal jugular vein underwent retrograde cannulation and the position of catheter tip was confirmed by X-Ray (C-arm) (Jugular bulb catheterization). In this retrograde technique, patients were supine with the head in a neutral position.

The right internal jugular vein underwent cannulation in cephalad direction by Seldinger technique, at the level of the cricoid cartilage. The catheter was forwarded through the introducer to jugular bulb, the level of mastoid process. Once the catheter was inserted, it was important to ensure its accurate position to reduce contamination from extra cerebral blood[11]. It was also important to sit catheter as close to jugular bulb roof as possible. Even a 2-cm difference could result in 10% contamination. This rises exponentially as the tip is withdrawn further. The position of catheter tip was confirmed by performing a lateral or an anteroposterior (AP) X-ray on the neck. In lateral radiograph, catheter tip should be cranial to the

disc between C1/C2 and as close to skull base as possible. In AP film, tip should be above the line extending from atlanto-occipital joint space and below inferior orbital margin. Besides, tip must lie above the line connecting the tips of mastoid processes.

At the end of operation, when 2 responses were attained on TOF stimulation, the studied drugs were administered intravenously. Sugammadex 2 mg/kg (Bridion® 200 mg/2 ml) in GS or neostigmine 0.05 mg/kg plus atropine 0.02 mg/kg in GN, both were diluted to a total volume of 10 ml saline. When TOF ≥ 90%, patients were extubated.

Pulse, blood pressure (BP), arterial oxygen saturation (SaO_2), end tidal carbone dioxide ($ETCO_2$) and CVP were monitored immediately after induction (basal) thereafter every half an hour up to the end of operation then, immediate before giving the reversal and 10 minutes after administration of the reversal and hourly till 6^{th} hour, and at 9^{th}, 12^{th} and 24^{th} hour postoperatively.

Simultaneous radial artery and jugular bulb blood samples were withdrawn for laboratory tests including arterial and jugular blood gases, Hb and Hct level were taken at induction of anesthesia with stable hemodynamic parameters, after finishing surgical manipulation of the brain and just before closure of the dura, before reversal of residual neuromuscular blocking, ten minutes after reversal then one hourly for 3 hours postoperatively.

The time period between sugammadex or neostigmine intake and recovery of TOF ratios to 90 percent following NMB produced by rocuronium was recorded (The primary study endpoint).

Estimated parameters were:

- Estimated Cerebral Metabolic Rate for O_2 ($eCMRO_2$)[12] as follow: $eCMRO_2$= arterial jugular oxygen content difference x arterial carbon dioxide tension/100
- Cerebral Extraction Ratio of Oxygen (CEO_2) [13]: CEO2 = SpO_2- jugular venous oxygen saturation
- Cerebral Blood Flow equivalent (CBFe) [14]: CBFe= 1/ (arterial O_2 content - jugular venous O_2 content)
- Arterial-jugular O_2 Content Difference (CaO_2-jO_2):
  CaO_2- jO_2 = CaO_2- $CjvO_2$
  CaO_2 = (SaO_2xHbx 1:34) +0:003 x PaO_2
  $CjvO_2$= ($SjvO_2$xHbx 1:34) + 0:003 x $PjvO_2$

Where CaO_2 is arterial oxygen content; $CjvO_2$ is jugular venous oxygen content; and $SjvO_2$ is jugular venous oxygen saturation.

Other parameters to be recorded were operation duration, urinary output, amount of blood loss, and blood transfusion and the total dose of neuromuscular blockade used.

Postoperatively, all cases were monitored in neurosurgical ICU for 24 hours for follow up. Any intra-operative or postoperative major events were reported. The level of sedation for all patients was evaluated using Ramsay sedation scale[15] every 5 min post-extubation till shifting to ICU (Table 1).

Table (1): Ramsay sedation scale[15]

Patient awake, anxious, agitated or restless	1
Patient awake, cooperative, orientated and tranquil	2
Patient drowsy with response to commands	3
Patient asleep, brisk response to glabella tap or loud auditory stimulus	4
Patient asleep, sluggish response to stimulus	5
No response to firm nail-bed pressure or other noxious stimuli	6

Data analysis

Data underwent analysis by Statistical Package for the Social Sciences for windows, version 21. Initially, the normality of data was tested by Kolmogorov Smirnov test. Numbers, percent or ratio represented qualitative data. Relationship between qualitative variables was examined by Chi-square test. Continuous variables were represented as means± SDs (standard deviations). Both groups underwent comparison using unpaired Student-t test and Mann-Whitney test for parametric and non-parametric data, respectively. Results were considered statistically significant when P value< 0.05.

RESULTS

From April 2016 to May 2018, 60 patients were included (Fig. 1). Of the 60 study subjects enrolled, 20 were excluded after randomization: eight were not meeting inclusion criteria and 12 patients were not willing to participate.

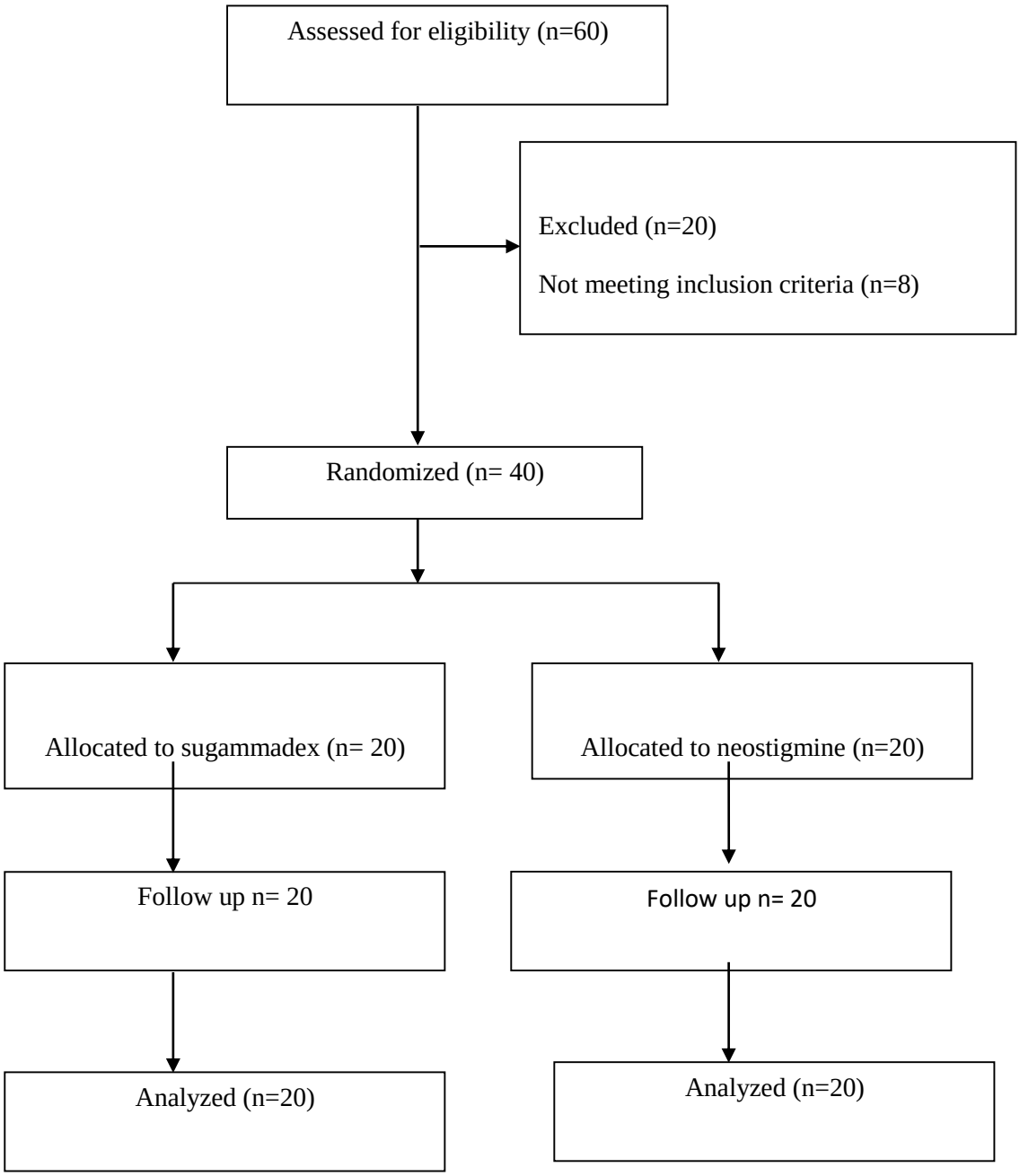

Figure (1): Consort diagram for patient recruitment in the trial

No participants were lost to follow-up. Data from 40 participants were analyzed. Baseline demographic data are listed in table 2. Regarding age, gender, body mass index, ASA physical condition of patients, preoperative GCS, pathology and side of the tumor were presented with no statistically significant difference between both groups (Table 2).

Table (2): Demographic data of the studied groups (Age, Sex, BMI, ASA, preoperative GCS, Pathology and side of the lesion. Data are expressed in mean ± (SD) and numbers (%)

	GS (n=20)	GN (n=20)	P
Age (years)	42.55 ± 11.48	48.55 ± 9.34	0.078
Sex			
Male	12 (60%)	14 (70%)	0.507
Female	8 (40%)	6 (30%)	
BMI (kg/m^2)	25.95 ± 2.09	24.53 ± 3.00	0.089
ASA			
I	12 (60%)	10 (50%)	0.525
II	8 (40%)	10 (50%)	
Preop. GCS	14.45 ± 0.83	14.5 ± 0.76	0.843
Pathology			
Meningioma	9 (45%)	10 (50%)	0.752
Glioma	11 (55%)	10 (50%)	
Side of lesion			
Right	7 (35%)	10 (50%)	0.589
Left	10 (50%)	7 (35%)	

GS: Sugammadex group (n=20), GN: Neostigmine group (n=20). BMI: Body Mass Index. ASA: American Society of Anesthesiologists. GSC: Glasgow coma scale.

No statistically significant difference existed between both groups regarding intraoperative data including operation's duration, urinary output, amount of blood loss, blood transfusion and dose of rocuronium (Table 3).

Table (3): Intraoperative data of the studied groups: Data are expressed in mean± SD

	GS (n=20)	GN (n=20)	P-value
Duration of surgery (hour)	4.45 ± 0 .89	4.70 ± 0.73	0.337
UOP (ml)	1715.00 ± 489.12	1620.00 ± 658.23	0.607
Blood loss (ml)	835.00 ± 478.24	915.0 ± 402.98	0.571
Volume of blood transfusion (ml)	1000.00 ± 353.55	833.33 ± 443.81	0.366
Dose of rocuronium (mg/kg)	154.25 ± 30.23	150.00 ± 38.90	0.702

GS: Sugammadex group (n=20), GN: Neostigmine group (n=20). UOP: urine output

Recovery data (duration from reversal to train of four 90%, Ramsay sedation scores) were significantly of lower values in GS compared to GN postoperatively (Table 4).

Table (4): Recovery data: data are expressed in mean ±SD

	GS (n=20)	GN (n=20)	P value
Mean time (minutes) for recovery of the TOF ratio to 90%	3.95 ± 2.88	11.00 ± 2.96	0.001*
10 min	3.50 ± 0.51	4.45 ± 0.51	0.001*
15 min	2.85 ± 0.59	3.95 ± 0.39	0.001*
20 min	2.25 ± 0.64	3.20 ± 0.52	0.001*

- GS: Sugammadex group (n=20), GN: Neostigmine group (n=20). * Significant difference when comparing both groups.

Pulse, mean arterial blood pressure (MAP) did not show statistically significant difference immediate before reversal administration. However, they were significantly lower in GS compared to GN 10 minutes following reversal administration and in the first and second hours postoperatively while no significant difference existed between the two groups from the third hour onward throughout the remaining study periods (Figures 2, 3). Arterial oxygen saturation showed no statistically significant difference before reversal administration. However, it was significantly higher in GS compared to GN 10 min after administration of the reversal and in the first and second hours postoperatively while there was no significant difference between the two groups from the third hour onward (Figure 4). Central venous pressure (CVP) did not show statistically significant difference between both groups throughout the study (Figure 5).

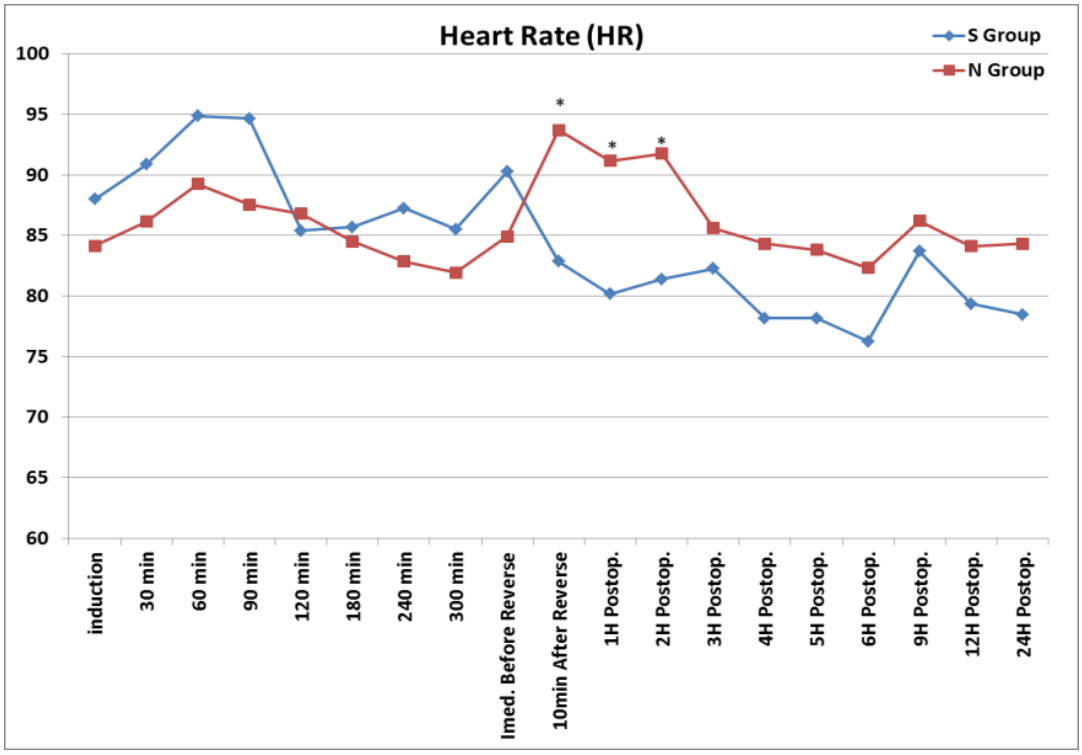

Figure (2): Intraoperative and postoperative heart rate changes (beat/minute) in the studied groups.
- S Group: Sugammadex (n=20), N Group: Neostigmine (n=20)
* Significant difference when comparing both groups.

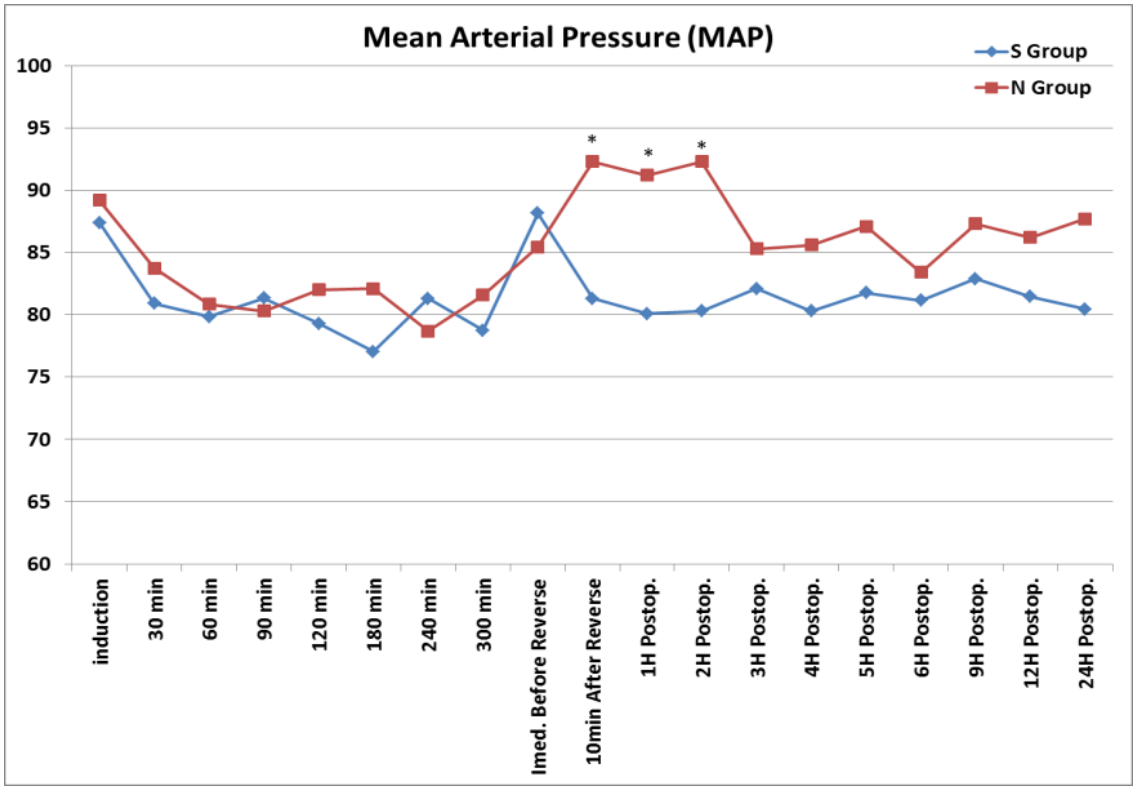

Figure (3): Intraoperative and postoperative non-invasive mean arterial blood pressure (MAP) (mmHg) in the studied groups
- S Group: Sugammadex (n=20), N Group: Neostigmine (n=20).
* Significant difference when comparing both groups.

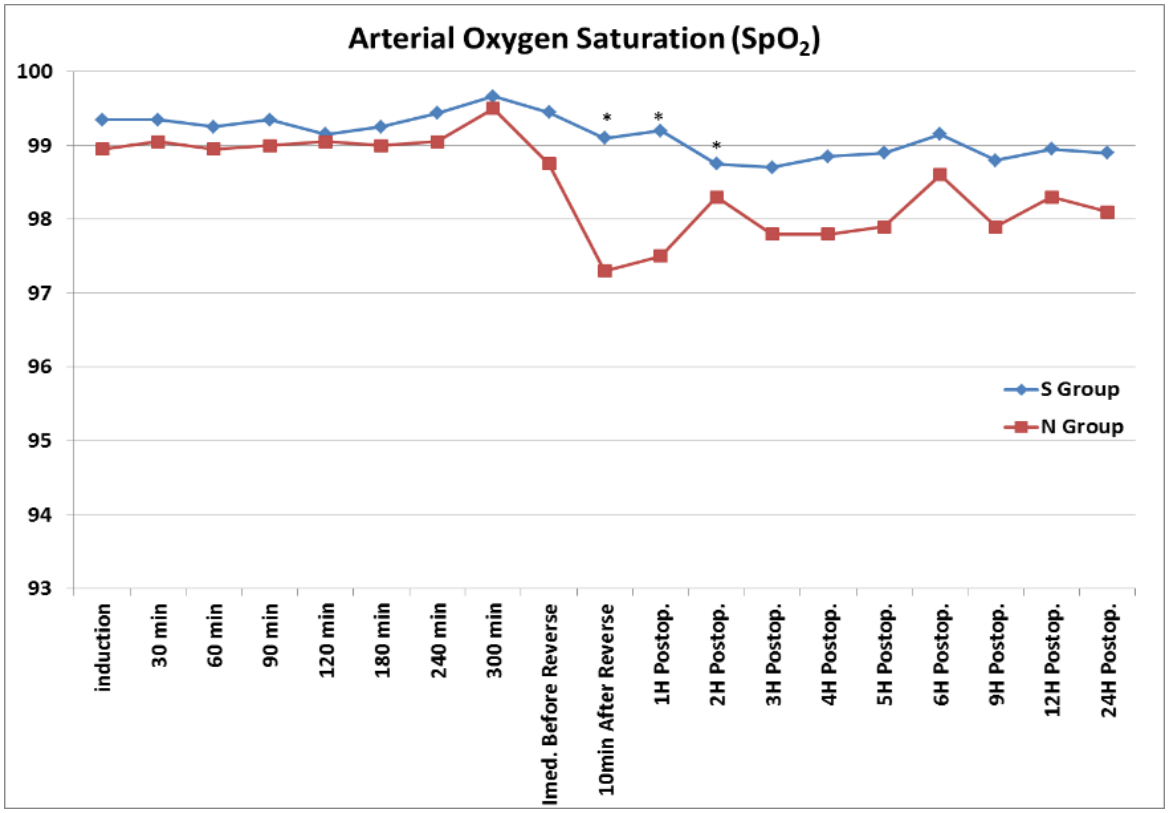

Figure (4): Intraoperative and postoperative arterial oxygen saturation (SpO_2) (%) in the studied groups
- S Group: Sugammadex (n=20), N Group: Neostigmine (n=20).
*Significant difference when comparing both groups.

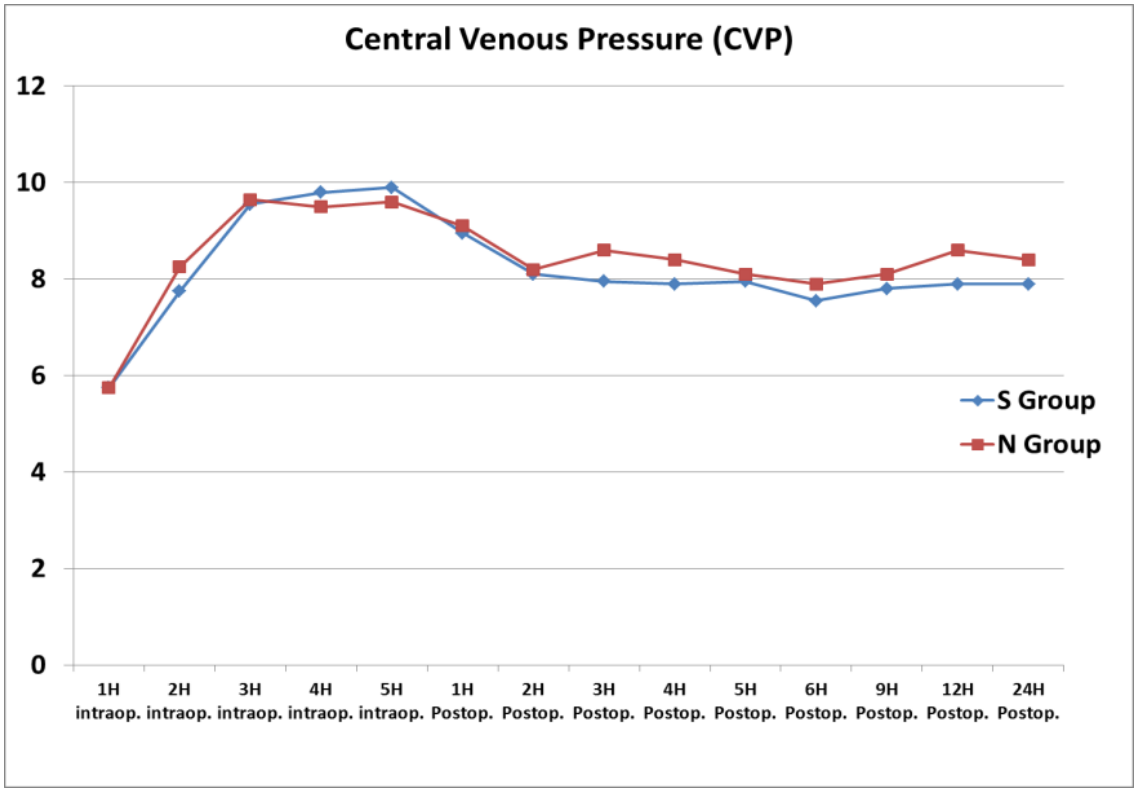

Figure (5): Intraoperative and postoperative central venous pressure (CVP) (mmHg) in studied group
- S Group: Sugammadex (n=20), N Group: Neostigmine (n=20).

Jugular venous oxygen saturation ($SjvO_2$) at induction, before closure of dura and immediate before reversal administration, revealed no significant difference between the two groups. However, SjvO2 was significantly lower in GS compared to GN 10 min after administration of reversal and for three hours postoperatively (Table 5).

Table (5): Jugular venous oxygen saturation ($SjvO_2$) (%) in the studied groups. Data are expressed in mean ±SD

	GS (n=20)	GN (n=20)	P
Induction	79.52 ± 12.54	79.71 ± 13.20	0.962
Before closure dura	78.04 ± 14.88	82.25 ± 8.35	0.278
Immediate before reversal	80.99 ± 13.34	80.59 ± 9.03	0.913
10 min after reversal	74.45 ± 9.57	82.95 ± 11.13	0.014*
Postoperative: 1H	67.39 ± 8.84	75.28 ± 12.66	0.029*
2H	61.99 ± 6.61	70.72 ± 15.16	0.026*
3H	57.26 ± 6.57	67.65 ± 16.69	0.016*

GS: Sugammadex group (n=20), GN: Neostigmine group (n=20).

- **$SjvO_2$**: Jugular venous oxygen saturation. * Significant difference when comparing both groups.

CaO_2-jO_2 at induction, before closure of dura and immediate before reversal administration did not show significant difference between the two groups.

However, CaO_2-jO_2 was significantly higher in GS compared to GN 10 minutes after administration of the reversal (P value 0.017) and for three hours postoperatively (P value 0.027 at 1 hr., 0.006 at 2 hr., 0.014 at 3 hr. respectively).

Cerebral Extraction Ratio of O_2 (CEO_2) at induction, before closure of dura and immediate before reversal administration showed no significant difference between both groups.

However, CEO_2 was significantly higher in GS compared to GN 10 minutes after administration of reversal (P value 0.016) and for three hours postoperatively (P values 0.009 at 1 hr., 0.029 at 2 hr., 0.032 at 3 hr. respectively).

Cerebral blood flow equivalent (CBFe) at induction, before closure of the dura and immediate before reversal administration, showed no significant difference among both groups.

However, CBFe was significantly lower in GS compared to GN 10 min after administration of reversal (P value 0.012) and for three hours postoperatively (P values 0.032 at 1 hr., 0.007 at 2 hr., <0.001 at 3 hr. respectively). $eCMRO_2$ did not show any significant difference between the two groups throughout the study intervals (Table6).

Table 6: Arterial-jugular Oxygen Content Difference (CaO_2-jO_2, mL O2/100mL blood), Cerebral Oxygen Extraction (CEO_2, %), Cerebral Blood Flow Equivalent (CBFe, mL blood/mL O_2) and Estimated Cerebral Metabolic Rate for Oxygen ($eCMRO_2$, mL/100 g/min). Values are in mean± SD.

	CaO_2-jO_2		**CEO_2**		**CBFe**		**$eCMRO_2$**	
	GS	GN	GS	GN	GS	GN	GS	GN
Induction	**2.64 ± 1.64**	**2.42 ± 0.62**	**25.58 ± 18.47**	**19.63 ± 14.43**	**0.17 ± 0.07**	**0.17 ± 0.15**	**1.24 ± 0.75**	**1.13 ± 0.95**
Before closure dura	**2.09 ± 0.87**	**1.88 ± 1.35**	**23.34 ± 15.03**	**16.50 ± 10.45**	**0.17 ± 0.06**	**0.38 ± 0.87**	**1.32 ± 1.02**	**0.81 ± 0.46**
Immediate before reversal	**2.54 ± 2.87**	**1.97 ± 1.22**	**18.22 ± 11.89**	**13.72 ± 9.40**	**0.20 ± 0.19**	**0.22 ± 0.30**	**1.08 ± 0.97**	**0.74 ± 0.52**
10 min after reversal	**3.46 ± 2.17***	**2.07 ± 1.11**	**20.35 ±10.22***	**13.19 ± 7.55**	**0.16 ± 0.06***	**0.25 ± 0.14**	**1.37 ± 0.70**	**0.98 ± 0.60**
Postoperative :								
1H	**4.96 ± 2.00***	**3.71 ± 1.36**	**26.98 ± 7.50***	**19.61 ± 9.42**	**0.14 ± 0.04***	**0.18 ± 0.09**	**1.31 ± 0.75**	**1.14 ± 0.61**
2H	**5.48 ± 1.97***	**3.88 ± 1.46**	**29.54 ± 7.86***	**22.49 ± 11.48**	**0.14 ± 0.03***	**0.16 ± 0.03**	**1.42 ± 0.76**	**1.24 ± 0.63**
3H	**5.37 ± 2.13***	**3.88 ± 1.48**	**29.71 ± 9.37***	**22.01 ± 12.44**	**0.13 ± 0.03***	**0.18 ± 0.04**	**1.40 ± 0.73**	**1.18 ± 0.62**

- GS: Sugammadex group (n=20), GN: Neostigmine group (n=20). * Significant difference when comparing both groups.

DISCUSSION

The main benefits in neuroanaesthesia include: smooth and hemodynamically stable induction and surgical course, satisfactory operative field and quick emergence that allow early neurologic assessment together with maintenance of a good level of cerebral hemodynamics and oxygenation [(16)]. Recovery from supratentorial tumor surgeries requires a set of measures to offer brain protection aiming to decrease intracerebral pressure in order to improve normal brain cells metabolism, oxygenation and cerebral blood flow (CBF).

The current study was conducted to compare the effect of low dose sugammadex with neostigmine on the recovery and cerebral hemodynamic profile after supratentorial brain tumors resection.

Sugammadex is a selective relaxant binding medication completely encapsulates the molecule of steroidal neuromuscular blocking drugs and is excreted via the kidney unchanged[(17)]. Dose of sugammadex is dependent mainly on the dose of muscle relaxant used. The recommended doses are between 2 and 16 $mg.kg^{-1}$ body weight[(18)]. Studies have found the incidence of inadequate reversal with 0.5 mg.kg-1[(19)]. In this work, sugammadex was administered at a dose of 2 mg/kg based on phase II dose-finding trials[(20-21)] while the dosage of neostigmine and atropine were given according to the usual recommended dosages.

This clinical trial has demonstrated that sugammadex resulted in, stable systemic hemodynamics (HR and MAP) and arterial oxygen saturation as compared to neostigmine that demonstrated significant rise in HR and MAP 10 minutes after reversal, 1 hour and 2 hours postoperatively. Sugammadex resulted in significant decrease in both cerebral blood flow and jugular venous oxygen saturation and significant increase of cerebral O_2 extraction and arterio-jugular O_2 content difference at 10 minutes after reversal, 1, 2 and 3 hour postoperatively without significant effect on cerebral metabolism. Recovery time recorded by time of reversal administration till train of four (TOF) 0.9 and Ramsay sedation score were significantly shorter among sugammadex patients in comparison with neostigmine patients.

In the current study, patients reversed with sugammadex showed a maintained stability of MAP and pulse over the whole observation period during and following reversal while in neostigmine group, patients showed significant increase in MAP and pulse in the first ten minutes following reversal administration and 1 and 2 hours postoperatively and this is in accordance with the previous findings[(22)]. Following reversal using neostigmine plus atropine, a significant higher pulse and BP pressure values compared with sugammadex, which did not exceed the 20% beyond the baseline[(23)]. Muscarinic effects do not occur after sugammadex intake in its reaction with the rocuronium molecules with no effects on pseudocholinesterase or on muscarinic receptors[(24)]. These unwanted effects cause adverse effects when an anticholinesterase agent is concurrently administered with an anti-cholinergic agent and include tachycardia and/or arrhythmias[(25)]. Stable cardiovascular response at recovery time will have a special advantage particularly among neurosurgical subjects to keep normal cerebral blood flow and acceptable level of oxygenation.

There was no significant change in arterial oxygen saturation (SpO_2) among sugammadex patients, while in neostigmine patients, SpO_2 was significantly lower at 10 min after reversal, 1 and 2 hours postoperatively. Despite this statistically significant decrease, the arterial oxygen saturation was still within the accepted physiological ranges. Low SpO_2 values are not infrequent in the postoperative period and are associated with many factors, such as residual effects of opioid drugs, operation type, patient's characteristics, co-morbid illness, usage of recruitment maneuvers, and the fractional inspired O_2 used during anesthesia and recovery[(26)].

In our study, the use of sugammadex (2 mg/kg) was associated with the reversal of NMB with TOF reaching 90 percent over 3.95 minutes (mean time value) compared to 11 minutes with neostigmine. It was proven that neostigmine is associated with slower recovery when reversing deep NMB[(27)]. Previous study proved that effective reversal dose of sugammadex for recovery of T2 after two hours of NMB induced via rocuronium 0.6 $mg.kg^{-1}$ appears to be 2–4 $mg.kg^{-1}$[(17)].

Our findings are consistent with a previous study that showed that sugammadex was associated with TOF reaching 90% in 5 minutes when utilized for reversal of moderate-profound NMB induced via rocuronium[(24)].

Such prompt eventless recovery seems to possess significant clinical implications while performing neurosurgical interventions, which necessitate maintaining profound neuromuscular blockade during the surgery succeeded by fast and smooth recovery; and hence allowing early neurologic assessment altogether with acceptable level of cerebral oxygenation and thus accelerate the diagnosis and dealing with serious events. Our findings are supported by the results of an earlier study, which revealed that sugammadex was associated with rapid and smooth recovery after NMB induced via rocuronium[(28)].

In this study, reversal of muscle relaxation was maintained with no evidence of recurarization in the two groups of patients throughout their stay in post-anesthesia neurosurgical care unit. This come in accordance with previous studies concluded that sugammadex was a very safe drug and showed minimal side effects even after administration of high i.v. dosage of 96 mg/kg to healthy subjects[(29)].

Jugular venous oxygen saturation $SjvO_2$ is a simple, cheap and reliable method for evaluation of CBF adequacy. $SjvO_2$ mirrors global cerebral perfusion and cerebral oxygen supply-demand balance. Jugular desaturation ($SjvO_2$ <50 %) suggest that CBF is not

sufficient for cerebral metabolism[30]. In the current study $SjvO_2$ demonstrated significant rise among neostigmine patients compared to sugammadex patients 10 minutes following reversal and for the three consecutive hours of readings. This means that sugammadex did not affect cerebral blood flow whereas in neostigmine group there was significant increase in cerebral blood flow, which might be secondary to the increased blood pressure in this group at the same time readings. Also sugammadex was accompanied with elevated cerebral extraction of oxygen due to maintained normal cerebral blood flow giving time enough to extract more oxygen than in neostigmine group that was accompanied with elevated cerebral blood flow. Also stable $eCMRO_2$ in sugammadex group preserved the balance between CBF and metabolic requirements of the brain. As long as Hb and SaO_2 remain constant, $SjvO_2$ indicates O_2 demand of the brain[31]. So, cerebral oxygen balance was preserved with sugammadex in comparison with neostigmine group.

Arterio-jugular oxygen content difference (CaO_2-jO_2) has an inverse association with cerebral blood flow and direct association with CMR in absence of ischemia, but when ischemia exists, such association cannot be predicted. Also, as $SjvO_2$, this content difference can be considered as an indicator of flow/metabolism balance. In the current study, the lower cerebral blood flow in sugammadex group than in neostigmine group gave enough time to the brain to extract more oxygen and so, CaO_2-jO_2 increased. Meanwhile, CBFe showed significant increase in the neostigmine group on the same events, of CaO_2-jO_2 decreases, so, the decrease of CaO_2-jO_2 in neostigmine group could be attributed to the increase in CBFe. This increase in CBFe in the neostigmine group could be explained with the increased mean arterial blood pressure that occurred at the same time of reading[32].

Cerebral oxygen extraction (CEO_2) and jugular venous oxygen saturation ($SjvO_2$) reveals CBF adequacy for cerebral metabolism. CEO2 demonstrated substantial rise among sugammadex patients compared to neostigmine patients started 10 minutes after reversal onward till three hours postoperatively indicating the accompanied decreased of CBF with sugammadex group.

Alterations in brain metabolism are lined to CBF alterations (Flow-metabolism coupling). This coupling is the metabolic explanation of cerebral autoregulation, which maintain a constant CBF during a wide range of cerebral perfusion pressure[33]. This coupling exists between the CBF and $CMRO_2$ under normal circumstances or even under some altered physiological conditions like fever and seizures, while it is disturbed under other pharmacological and pathological influences like brain tumors[34]. In the current work, no significant difference in $CMRO_2$ existed between sugammadex group and neostigmine group at all study intervals.

In fact, the deficiency of the clinical studies that discuss the effect of sugammadex on cerebral hemodynamics and oxygenation makes the clinical observations in the current study were the only source of explanations of various changes observed throughout this clinical trial.

This study was not free from limitations included, relatively small number of patients, and lacking of assessment of cognitive function regaining after surgery. Also less available facilities to follow recent methods for measurements of cerebral blood flow.

We think that, intra group statistics could be valuable to assess the different effect of each drug individually throughout its use. Future trials are essential to assess the cost-benefit relationship of sugammadex administration in routine clinical practice and to fulfill solutions for the earlier limitations.

CONCLUSION

Low dose sugammadex (2 $mg.kg^{-1}$) provided fast and effective reversal of NMB induced by rocuronium superior to neostigmine with stable cerebral hemodynamic profile after supratentorial tumor surgery. It is necessary to confirm such result by future studies involving larger patient populations and more focusing on dose related outcomes.

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