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ORIGINAL ARTICLE

Sugammadex antagonism of rocuronium-induced neuromuscular blockade in patients with liver cirrhosis undergoing liver resection: a randomized controlled study

Mohamed ABDULATIF [1] *, Maha LOTFY [2], Mahmoud MOUSA [2], Mohamed H. AFIFI [3], Khaled YASSEN [2]

[1]Department of Anesthesiology, Faculty of Medicine, Cairo University, Cairo, Egypt; [2]National Liver Institute, Menoufiya University, Menoufiya, Egypt; [3]Faculty of Medicine, Menoufiya University, Menoufiya, Egypt

*Corresponding author: Mohamed Abdulatif, 1 Al-Saray Street, Al-Manial, Cairo, Postal Code 11559, Egypt.
E-mail: mohamedabdulatif53@gmail.com

ABSTRACT

BACKGROUND: This randomized controlled study compared the recovery times of sugammadex and neostigmine as antagonists of moderate rocuronium-induced neuromuscular block in patients with liver cirrhosis and controls undergoing liver resection.

METHODS: The study enrolled 27 adult patients with Child class "A" liver cirrhosis and 28 patients with normal liver functions. Normal patients and patients with liver cirrhosis were randomized according to the type of antagonist (sugammadex 2 mg/kg or neostigmine 50 μg/kg). The primary outcome was the time from antagonist administration to a train-of-four (TOF) ratio of 0.9 using mechanosensor neuromuscular transmission module. The durations of the intubating and top-up doses of rocuronium, the length of stay in the post-anesthesia care unit (PACU), and the incidence of postoperative re-curarization were recorded.

RESULTS: The durations of the intubating and top-up doses of rocuronium were prolonged in patients with liver cirrhosis than controls. The times to a TOF ratio of 0.9 were 3.1 (1.0) and 2.6 (1.0) min after sugammadex administration in patients with liver cirrhosis and controls, respectively, P=1.00. The corresponding times after neostigmine administration were longer than sugammadex 14.5 (3.6) and 15.7 (3.6) min, respectively, P<0.001. The duration of PACU stay was shorter with the use of sugammadex compared to neostigmine. We did not encounter postoperative re-curarization after sugammadex or neostigmine.

CONCLUSIONS: Sugammadex rapidly antagonize moderate residual rocuronium-induced neuromuscular block in patients with Child class "A" liver cirrhosis undergoing liver resection. Sugammadex antagonism is associated with 80% reduction in the time to adequate neuromuscular recovery compared to neostigmine.

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KEY WORDS: Neuromuscular blocking agents - Rocuronium - Sugammadex - Complications - Liver cirrhosis.

Liver resection is a major operation that might affect perioperative liver functions.[1] These effects are more obvious in patients with liver cirrhosis.[2] Liver cirrhosis is a progressive disease characterized by loss of functional hepatocytes that might substantially affect drug pharmacokinetics.[3]

Rocuronium is an intermediate acting non-depolarizing neuromuscular blocker that is mostly eliminated by liver uptake and biliary excretion.[4]

Its onset time and duration are prolonged in patients with liver cirrhosis due to an increased volume of distribution[5] and increased elimination half-life.[6-8]

Sugammadex is a selective binding agent that forms stable complexes in a 1:1 ratio with rocuronium.[9] Sugammadex-rocuronium complex is eliminated by the kidney.[10] The use of sugammadex in different patient populations including end-stage renal failure[11] is associated with rapid recovery of neuromuscular functions. To date, there are no published randomized controlled trials comparing the pharmacodynamic profiles of sugammadex and neostigmine in patients with liver dysfunction undergoing liver surgery. This randomized controlled study was designed to compare the neuromuscular recovery times with the use of sugammadex and neostigmine as antagonists of moderate rocuronium-induced neuromuscular block in patients with child "A" liver cirrhosis and patients with normal liver functions undergoing liver resection. We hypothesized that the use of sugammadex will be associated with a shorter adequate neuromuscular recovery time compared to neostigmine.

Materials and methods

Patient enrollment started after approval of the study protocol by the Institutional Review Board of the National Liver Institute, Menoufiya University (Protocol number: 0982014, Date of approval: November 1st, 2014). The study was registered in the ClinicalTrials.gov identifier number: NCT02414880. The study was conducted in the Anesthesiology Department, National Liver Institute. A written informed consent was taken from each patient. The study included adult patients aged 18 to 60 years undergoing liver resection. The study population was stratified to patients with normal liver functions and patients with liver cirrhosis. Subsequent randomization of each category to neostigmine and sugammadex groups was carried out using an online randomization program (http://www.randomizer.org). Random allocation numbers were concealed in opaque closed envelops.

Patients fulfilling the inclusion criteria underwent clinical evaluation including preoperative laboratory assessment of liver and renal functions the day before surgery. Other diagnostic or laboratory workup was requested by the attending anesthesiologist and the surgeon according to the patient clinical condition and the proposed surgical intervention. Two of the study groups included patients with liver cirrhosis complicating chronic hepatitis C viral infection and categorized as Child-Turcotte-Pugh class "A." The other two groups served as controls and included patients with normal preoperative liver functions. We excluded patients with co-existing neuromuscular disease, body mass index more than 35 kg/m^2, with renal impairment, receiving medications known to affect neuromuscular transmission, allergic to any of the study medications, or having major intraoperative blood loss.

Basic intraoperative monitoring included: electrocardiography, pulse oximetry, end-tidal CO_2, invasive arterial blood pressure, central venous pressure, esophageal temperature, fraction inspired oxygen, expired end-tidal sevoflurane concentrations, and urine output. Depth of anesthesia was monitored using Entropy module (General Electric, Boston, MA, USA).

General anesthesia was induced by propofol 1.5-2 mg/kg and fentanyl 2 μg/kg. Rocuronium 0.6 mg/kg (Esmeron, Organon, USA) was used to facilitate endotracheal intubation after achieving complete suppression of the *adductor pollicis* muscle response to train-of-four (TOF) supramaximal ulnar nerve stimulation. Anesthesia was maintained with a mixture of air, oxygen and the end-tidal sevoflurane concentration was adjusted to keep Entropy reading between 40 and 60. Fentanyl 1 μg/kg/h was infused for supplementary intra-operative analgesia. Muscle relaxation was maintained by additional top-up doses of rocuronium 0.15 mg/kg administered after detection of the first response to TOF stimulation (T1). Lung ventilation parameters were adjusted to maintain normocapnia.

Intraoperative normothermia was maintained using warm intravenous fluids and a forced air warm blanket (Model 750-Bair Hugger Temperature Management Unit, SMA MISR, Arizant Healthcare Inc, Eden Prairie, MI, USA). Intraoperative fluid, and blood replacement therapy were guided by the continuous monitoring of

the central venous pressure and were titrated to maintain hemodynamic stability and a hemoglobin level of 10 g/dL.

The neuromuscular function was monitored according to the good clinical research practice (GCRP) guidelines for pharmacodynamic neuromuscular studies[12] using piezoelectric kinemyography neuromuscular transmission module (General Electric AISYS Anaesthesia machine, Boston, MA, USA). Two pre-gelled surface electrodes were placed 2-3 cm apart over the ulnar nerve at the wrist. The piezo-electric transducer was appropriately placed between the thumb and index fingers. After induction of anesthesia, a 5 second 50 Hz tetanic ulnar nerve stimulation was performed to reduce the time required for twitch stabilization. This was followed by 2-5 minutes of TOF stimulation at 2 Hz, repeated every 15 s, until stabilization of the evoked adductor pollicis twitch response. A thermistor was used to monitor and ensure a temperature of 30-32 °C at the skin overlying the *adductor pollicis* muscle.

At the end of surgery and when two responses of the adductor pollicis muscle to TOF stimulation were detected (T2), patients with liver cirrhosis and controls were randomly allocated to receive sugammadex (Bridion, Organon, Netherlands) 2 mg/kg or neostigmine 50 μg/kg combined with atropine 20 μg/kg. All patients continued to receive 0.6% end-tidal sevoflurane concentration to prevent inadvertent hand movement until adequate recovery of neuromuscular transmission (TOF ratio of 0.9 and 1.0). Neuromuscular transmission monitoring continued for 15 minutes after achieving a TOF ratio of 1.0 to rule out recurarization. After extubation, patients were transferred to the postanesthesia care unit (PACU) on oxygen mask and discharged to the surgical intensive care unit after achieving a modified Aldrete score of 10 or more.[13]

The primary outcome measure of the study was the time from the administration of sugammadex or neostigmine to the recovery of a TOF ratio of 0.9. The secondary outcome measures included: 1) the duration of the initial intubating dose of rocuronium (the time interval in minutes from the administration of the intubating dose to the recovery of the first twitch in the TOF response (T1); 2) the duration of top-up doses of rocuronium (the time interval in minutes from the administration of each top-up dose to the recovery of the first twitch in the TOF response (T1); 3) the total intraoperative dose of rocuronium (the sum of the intubating dose and subsequent top-up doses); 4) the time from the start of antagonist administration to a TOF ratio of 1.0; 5) the duration of surgery (time between skin incision and closure); 6) the duration of anesthesia (time between induction of anesthesia and extubation); 7) the duration of stay in PACU (the time interval from admission to PACU until the patient discharge to the surgical intensive care unit), 8) the incidence of postoperative recurarization (recurrence of neuromuscular block was defined as a decrease in the TOF ratio to <0.9 after full recovery had been documented).

Sample size and power of the study

The primary outcome of the study was the time from the administration of sugammadex or neostigmine to the recovery of a TOF ratio of 0.9. Previous studies indicated that when sugammadex and neostigmine were used to antagonize moderate rocuronium-induced block (T2), the times to achieve a TOF ratio of 0.9 were 2.3 (1.0)[14] and 6.9 (3.5) minutes,[15, 16] respectively. Using this substantiated assumption of the expected effect size and variance, power analysis was performed using two-tailed analysis of variance for independent samples (Omnibus Test). At a power of 0.95 and an alpha error of 0.05, we calculated that a minimum sample size of 12 patients will be required for each of the four study groups. This was increased to 15 patients to compensate for possible dropouts.[17] The Power Analysis and Sample Size software (PASS 13 software; NCSS, LLC, Kaysville, UT, USA) was used for sample size calculation.

To date, no controlled randomized studies evaluated the pharmacodynamic profile of sugammadex in patients with hepatic impairment. However, a population pharmacokinetic-pharmacodynamic interaction model of sugammadex has been developed by Merck Sharp and Dohme (MSD) pharmaceutical company and was used to simulate the reversal of rocuronium-induced neuromuscular block in patients with hepatic impairment. The model predicts that the recovery

time will be prolonged by 2.55 min in hepatic impairment following sugammadex 2 mg/kg given at the reappearance of T2. Data on file with MSD.[18] Using this pharmacokinetic simulation assumption, our study including 12 patients in each group is powered to detect the difference in the response to sugammadex in normal patients and patients with liver cirrhosis.

Statistical analysis

Continuous data are presented as means (SD). Categorical data are presented as frequencies and percentages. Comparisons of continuous variables among the four study groups were done using two-way analysis of variance (ANOVA). This parametric analysis assessed the type of antagonist, the liver status (cirrhotic *versus* normal), and the interaction of the two factors (antagonist and liver status). The durations of the first and last top-up doses of rocuronium in different study groups were analyzed using two-way ANOVA mixed model (within-between study groups) with repeated measure. Post-hoc Tuckey test was used for pairwise multiple comparisons.[19] χ^2 Test was used for comparing categorical data. Fisher's Exact Test was used when the expected frequency was less than 5. All statistical analyses were two-tailed and a P value of less than 0.05 was considered statistically significant. All statistical analyses were done using the Statistical Package for the Social Science (SPSS Inc., Chicago, IL, USA).

Results

Fifty-five patients completed the study. Twenty-eight patients were living related donors with preoperative normal liver functions undergoing liver resection for liver transplantation and 27 patients with liver cirrhosis undergoing liver resection for neoplastic lesions complicating chronic hepatitis C viral infection. Five patients were excluded (Figure 1). Patients with liver cirrhosis were older than controls. The surgical and anesthesia durations were prolonged in patients with normal liver than in patients with liver cirrhosis (Table I, II).

The durations of the intubating and top-up doses of rocuronium were prolonged in patients

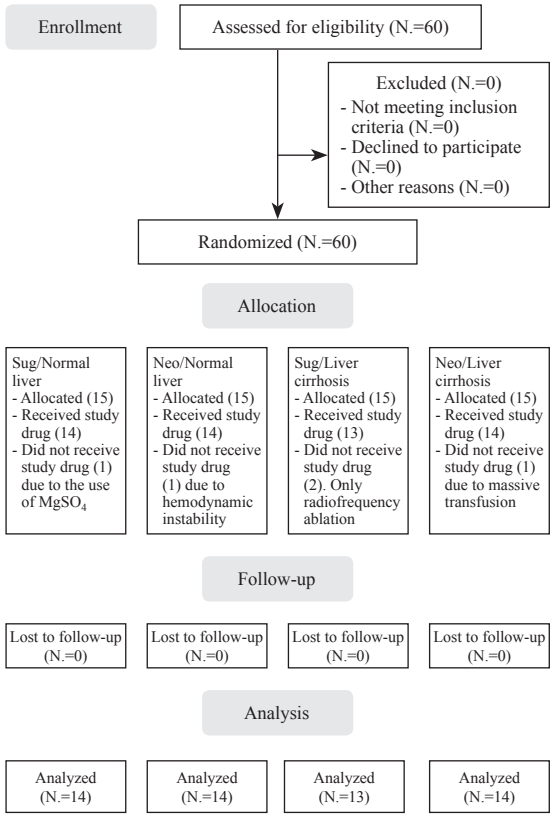

Figure 1.—CONSORT flow diagram showing allocation of patients at different stages of the study.
Sug: sugammadex; Neo: neostigmine; $MgSO_4$: magnesium sulphate.

with liver cirrhosis than controls. Furthermore, there was progressive increase in the duration of top-up doses of rocuronium in the four study groups (Table III). The total intraoperative rocuronium requirements were lower in patients with liver cirrhosis than controls (Table III). The times to a TOF ratio of 0.9 and 1.0 after neostigmine administration were longer than sugammadex. However; there was not statistically significant difference between normal patients and patients with liver cirrhosis after the administration of sugammadex or neostigmine (Table III, Figure 2). The duration of PACU stay was shorter with the use of sugammadex compared to neostigmine (Table III). We did not encounter postoperative re-curarization after sugammadex or neostigmine administration. All patients survived and discharged home within 4-10 days.

TABLE I.—*Patients characteristics. Values are mean (SD) or number.*

Variable	Group 1 Sugammadex normal liver (N.=14)	Group 2 Neostigmine normal liver (N.=14)	Group 3 Sugammadex liver cirrhosis (N.=13)	Group 4 Neostigmine liver cirrhosis (N.=14)
Age (years)	34.1 (12.1)	33.4 (12.9)	60.2 (5.3)*	58.0 (5.5)*
Weight (kg)	77.6 (7.3)	72.9 (6.8)	79.5 (10.8)	78.9 (7.1)
Gender (M/F)	8/6	11/3	9/4	10/4
ASA (I,II, III)	12/2/0	13/1	0/3/10	0/4/10
Liver resection				
Right lobe resection	12	11	2	2
Left lobe resection	2	3	7	8
Non-anatomical resection	0	0	4	4
Duration of surgery (min)	345.9 (84.8)	381.5 (105.1)	291.3 (82.6)*	269.4 (77.2)*
Duration of Anesthesia (min)	402.4 (89.4)	450.4 (104.3)	340.8 (82.6)*	329.1 (79.5)*

*Significant difference between normal patients and patients with liver cirrhosis.
ASA: American Society of Anesthesiologist physical status.

TABLE II.—*Preoperative liver and renal function tests. Values are mean (SD).*

Variable	Group 1 Sugammadex normal liver (N.=14)	Group 2 Neostigmine normal liver (N.=14)	Group 3 Sugammadex liver cirrhosis (N.=13)	Group 4 Neostigmine liver cirrhosis (N.=14)	P value
Total bilirubin (mg/dL)	0.73 (0.5)	0.64 (0.2)	0.86 (0.2)	1.34 (2.1)	0.33
Direct bilirubin (mg/dL)	0.25 (0.3)	0.19 (0.1)	0.29 (0.1)	0.77 (1.8)	0.34
Total serum proteins (g/dL)	7.6 (0.6)	7.8 (0.5)	6.7 (0.9)*	6.9 (0.6)*	<0.001
Serum albumin (g/dL)	4.1 (0.4)	4.3 (0.5)	3.6 (0.5)*	3.6 (0.5)*	0.001
AST (unit/L)	25.5 (12)	19.5 (4.8)	69.6 (35.1)*	67.2 (32.4)*	<0.001
ALT (unit/L)	24.5 (11)	19.1 (6.8)	60.3 (31.3)*	65.3 (19.4)*	<0.001
ALP (unit/L)	70.0 (18.5)	60.3 (13.7)	82.7 (17.8)*	89.9 (41.2)*	0.017
GGT (unit/L)	33.7 (22.6)	26.5 (10.5)	63.2 (35.0)*	122.1 (163.7)*	0.019
Serum urea (mg/dL)	23.8 (6.8)	24.9 (6.1)	29.3 (9.3)	26.5 (5.4)	0.21
Serum creatinine (mg/dL)	0.75 (0.1)	0.64 (0.2)	0.68 (0.2)	0.73 (0.2)	0.39

*Significant difference between normal patients and patients with liver cirrhosis; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase.

TABLE III.—*Neuromuscular data and post-anesthesia care unit duration of stay. Values are mean (SD).*

Variable	Group 1 Sugammadex normal liver (N.=14)	Group 2 Neostigmine normal liver (N.=14)	Group 3 Sugammadex liver cirrhosis (N.=13)	Group 4 Neostigmine liver cirrhosis (N.=14)
Duration of intubating dose of rocuronium (min)	36.0 (5.9)	35.9 (4.7)	42.8 (4.5)*	41.5 (5.7)*
Duration of the first top-up dose of rocuronium (min)	15.4 (4.3)	16.4 (4.4)	28.2 (4.9)*	33.8 (15.0)*
Duration of the last top-up dose of rocuronium (min)	34.1 (4.0)‡	40.2 (7.2)‡	47.5 (5.9)*‡	50.0 (8.9)*‡
Total dose of rocuronium (mg)	179.3 (26.8)	172.9 (43.1)	133.0 (33.0)*	125.4 (17.7)*
Time to train of ratio recovery to 0.9 (min)	2.6 (1.0)†	15.7 (3.6)	3.1 (1.0) †	14.5 (3.6)
Time to train of ratio recovery to 1.0 (min)	3.54 (1.1)†	18.6 (4.3)	4.4 (1.3)†	17.1 (3.2)
Duration of stay in PACU (min)	22.8 (2.4)†	43.2 (5.0)	23.0 (2.3)†	43.9 (7.4)

*Significant difference between normal patients and patients with liver cirrhosis (P<0.001); †significant difference between sugammadex and neostigmine (P<0.001); ‡significant difference between the first and last top-up doses of rocuronium (P<0.001).

Discussion

The present study demonstrated that the durations of action of the intubating and top-up doses of rocuronium were prolonged in older patients with liver cirrhosis, with no clear evidence if it was the first or the second factor, or both, to produce such an effect. Neuromuscular

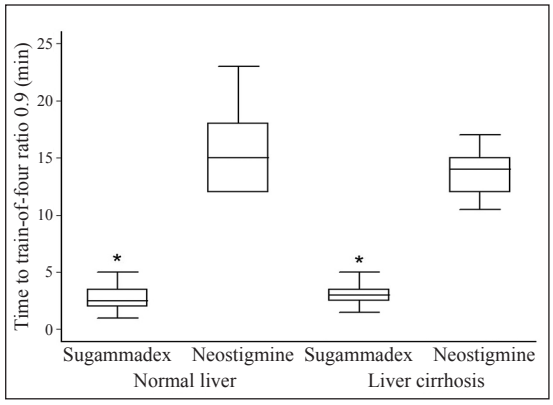

Figure 2.—Box and Whisker plot of the median and interquartile range of the duration to achieve a train-of-four ratio of 0.9 in the four study groups.
*Significant difference between sugammadex and neostigmine.

block induced by rocuronium was rapidly and effectively antagonized by the administration of sugammadex in patients with Child class "A" liver cirrhosis and in controls undergoing liver resection. Sugammadex antagonism of rocuronium-induced neuromuscular block was associated with almost 80% reduction in the time to adequate neuromuscular recovery compared to neostigmine.

The extended duration of rocuronium-induced block in patients with liver cirrhosis could be related to the delayed elimination.[6-8] Van-Miert *et al.*[6] evaluated the pharmacodynamic and pharmacokinetic profiles of rocuronium in patients with Child class "A" or "B" liver cirrhosis. The clinical recovery from rocuronium-induced neuromuscular block was significantly prolonged in patients with liver cirrhosis compared to controls. Furthermore, Servin *et al.*[7] reported significant prolongation of the duration of action with successive maintenance doses of rocuronium in patients with liver cirrhosis who received five or more to-up doses. Patients with liver cirrhosis included in the present study were older than patients with normal liver functions. This could be an additional contributing factor to the prolonged neuromuscular block observed in patients with liver cirrhosis. The plasma clearance and volume of distribution of rocuronium are reduced in elderly patients with consequent prolongation of the duration of neuromuscular block.[20, 21]

This is the first randomized controlled study comparing neuromuscular recovery times from rocuronium-induced neuromuscular block following sugammadex and neostigmine administration in patients with liver cirrhosis and normal patients undergoing liver resection surgery. The use of sugammadex in patients with liver dysfunction changes the hepatic elimination of rocuronium to a completely different (liver-independent) renal pathway.[22] In contrast to our study, Nonaka *et al.*[23] compared the pharmacodynamic profiles of rocuronium in normal patients undergoing non-hepatic surgery and in patients with normal preoperative liver functions undergoing liver resection. The duration from the administration of rocuronium to 25% recovery of the first twitch in the TOF response (T1) was longer in patients undergoing liver resection than patients undergoing non-hepatic surgery (88 [20] *vs.* 68 [16] minutes, P<0.01). However, there was no difference in the duration from sugammadex administration to the recovery of the TOF ratio to 0.9 between the two groups. These findings are generally in line with the results of the present study. In the observational study by Fujita *et al.*,[24] sugammadex was administered after recovery of the second twitch in the TOF response in patients with liver dysfunction. Adequate TOF ratio of 0.9 was achieved in two minutes. In our study the analogous recovery time was slightly longer (3.1 minutes). This might be explained by the longer operative time and the larger total dose of rocuronium.

We have chosen the time to achieve a TOF ratio of 0.9 as the primary outcome to allow for a meaningful comparison with previous relevant studies using the same end point for adequate neuromuscular recovery.[25, 26] We have also recorded the time to achieve a TOF ratio of 1.0 to minimize the possibility of subtle unrecognized residual curarization which might be associated with the use of piezoelectric transducers for neuromuscular monitoring.[27] We did not encounter recurarization with the use of sugammadex or neostigmine antagonism however, the use of sugammadex was associated with shorter duration of PACU stay. Brueckmann *et al.*[28] reported significant reduction in PACU stay with the use of sugammadex compared to neostigmine/glycopyrrolate in patients undergoing abdominal sur-

gery. The older age of patients with liver cirrhosis and the longer duration of anesthesia in patients with normal liver functions could be contributing factors for the extended PACU length of stay in the neostigmine groups.[29, 30]

The choice of cisatracurium might appear more appropriate for patients with liver dysfunction.[31] De Wolf *et al.*[32] reported minor differences in the pharmacokinetics and pharmacodynamics of a single dose of cisatracurium in liver transplant and control patients. It is to be noted however that cisatracurium had a relatively slow onset of action compared to rocuronium[33] and is associated with suboptimal intubating conditions with rapid sequence induction of anesthesia.[34] In normal patients, the time to achieve a TOF ratio of 0.9 is 4.7 times faster with rocuronium-sugammadex than with cisatracurium-neostigmine (geometric mean=1.9 *vs.* 9.0 min, P<0.0001).[35] Patients with significant liver dysfunction undergoing emergent liver transplant or urgent non-hepatic surgery will typically require rapid sequence induction of anesthesia.[36] In this clinical scenario, the use of rocuronium and sugammadex will have the potential dual benefit of rapid intubation and rapid adequate neuromuscular recovery without the possible gastrointestinal side effects of anticholinesterases.[37]

Limitations of the study

There are some limitations of this study. First, our findings are applicable only to patients with Child class "A" liver cirrhosis undergoing liver resection. The more severe forms of liver cirrhosis might be associated with more evident alterations in drug pharmacokinetics and pharmacodynamics.[3, 38] We have restricted our inclusion criteria to Child class "A" liver cirrhosis because hepatocellular carcinoma in patients with more advanced forms of liver cirrhosis (Child B or C) cannot be safely managed with major liver resection.[39] Second, we did not evaluate the pharmacokinetics of sugammadex in patients with liver cirrhosis. This is an important area for future research.

Conclusions

In conclusion sugammadex rapidly and effectively antagonizes moderate rocuronium-induced neuromuscular block in patients with Child class "A" liver cirrhosis undergoing liver resection. The duration of adequate neuromuscular recovery after sugammadex and neostigmine antagonism is comparable in patients with liver cirrhosis and controls.

What is known

• Rocuronium is mostly eliminated by liver uptake and biliary excretion. Its onset time and duration of action are prolonged in patients with liver cirrhosis due to an increased volume of distribution and increased elimination half-life.

• Sugammadex is a selective binding direct antagonist that forms stable complexes with rocuronium. Sugammadex-rocuronium complex is eliminated by the kidney. The use of sugammadex in patients with liver dysfunction changes the hepatic elimination of rocuronium to a liver-independent renal pathway.

What is new

• Sugammadex antagonism of rocuronium-induced neuromuscular blockade is associated with 80% reduction in the time to adequate neuromuscular recovery compared to neostigmine in patients with liver cirrhosis undergoing liver resection.

• The duration of PACU stay after liver resection is longer with the use of neostigmine. The older age of patients with liver cirrhosis and the longer duration of anesthesia in patients with normal liver function could contribute to the extended PACU length of stay.

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