

The Effect of Rocuronium Dosage on Intubation Conditions in Liver Transplant Recipients

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ABSTRACT

Introduction: Neuromuscular blockers (NMB) play an important role in improving conditions in orthotopic liver transplantation (OLT). Depending on clinical conditions, diseases, and pharmacological interactions, the effective NMB dose for complete NMB varies. Our study investigated the effects of rocuronium used during rapid sequence intubation. The effects of this drug on onset of action and intubation conditions were studied in a control group and in an OLT patient group.

Methods: The study is prospective, involving 90 patients over the age of 18. The 45 patients scheduled to undergo OLT were assigned to Group 1, while the 45 patients without liver dysfunction scheduled to undergo a 4-6-hour surgery under general anesthesia were assigned to Group 2. Groups were dosed with 1.2 mg/kg rocuronium based on ideal body weight, and the effect on the time to reach a train-of-four (TOF) value of zero (TOF 0), time to intubation scores, and hemodynamic parameters was evaluated.

Results: The demographic data across the groups were comparable. No significant differences were observed between the groups concerning TOF 0 time ($p=0.806$), intubation times ($p=0.987$), and intubation scores ($p=0.898$). However, when evaluating OLT patients individually, a statistically significant correlation was found between TOF 0 time and Child score ($p=0.029$, $p<0.05$).

Conclusion: In patients with end-stage liver disease undergoing OLT, administering rocuronium at a dosage of 1.2 mg/kg based on ideal body weight, during rapid sequence intubation results in sufficient intubation conditions. Furthermore, there were no delays noted in the onset of rocuronium's action.

Keywords: Orthotopic liver transplantation, neuromuscular block, rocuronium, rapid serial intubation, ideal body weight

Introduction

Orthotopic liver transplantation (OLT) is the definitive treatment modality for end-stage liver disease, regardless of its origin. Neuromuscular block (NMB) provides better surgical conditions in all laparotomy and laparoscopic operations including OLT (1). Succinylcholine and rocuronium are preferred as neuromuscular muscle relaxant agents for rapid sequence induction. There are conditions that limit the use of succinylcholine, one of which is hyperkalaemia (2). The ability of sugammadex to rapidly reverse the activity of rocuronium has led it to be preferred as an alternative agent to succinylcholine (3,4). The pharmacokinetics and pharmacodynamics of rocuronium bromide may change in patients with hepatic dysfunction, which may result in a longer elimination half-life and unpredictable onset of action. The literature contains studies related to the duration of action of rocuronium in

patients undergoing OLT, but few studies address the onset of action of rocuronium and its effect on intubation conditions (5,6).

In our literature review, the duration of action of NMBs in OLT patients was evaluated, but studies of the onset of effect of rocuronium dose and intubation conditions are limited. In our study, we aimed to evaluate the effects of NMB on onset of action and intubation conditions by administering rocuronium according to the ideal body weight in patients undergoing OLT and those with normal liver function tests.

Methods

This study employs a prospective observational design and is conducted in accordance with the Helsinki-2013 Declaration. Ethical approval was obtained from the Malatya Clinical Research Ethics Committee (protocol number: 2022/61, date: 29.06.2022).



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To determine the required sample size, a power analysis was conducted, indicating that a minimum of 41 patients from each group, totaling 82 patients, should be included to identify a significant difference, with a type 1 error rate (alpha) of 0.05, a statistical power (beta) of 0.8, and an effect size of 0.10.

In this prospective observational study, two groups were defined: patients scheduled for liver transplantation (Group 1) and patients without liver dysfunction undergoing abdominal surgery lasting 4-6 hours (Group 2). Although the study employed a prospective observational design, a block and stratified randomization approach was applied to ensure balance between the groups and to minimize selection bias.

Randomization was performed using computer-generated random sequences with a 1:1 allocation ratio. To reduce predictability, permuted variable block sizes (4, 6, and 8) were used. To maintain clinical balance between groups, stratified randomization was performed according to the following variables:

Child-Pugh class: A/B vs. C

Body mass index (BMI) category: <25 kg/m², 25-30 kg/m², and >30 kg/m²

Mallampati score: I-II vs. III-IV

Allocation concealment was maintained using a centralized electronic randomization system; if this was unavailable, sequentially numbered, opaque, sealed envelopes were used. Group assignments were concealed from the clinicians administering the study interventions and from the outcome assessors.

After obtaining written informed consent from all participants, randomization was completed, and a total of 90 patients were included in the study, with 45 patients in each group.

Patients with confirmed renal dysfunction, those diagnosed with neuromuscular diseases, and individuals with a history of malignant hyperthermia were excluded from the study. Additionally, patients with a BMI exceeding 35 kg/m², as well as pregnant or breastfeeding women, were not included. Those who chose not to participate and 16 patients who underwent surgery in emergency situations were omitted from the analysis. In our study, patients who were excluded due to emergency surgery were not included in the analysis because of missing demographic and clinical data. All patients received information regarding the study's details and provided written informed consent. Ultimately, a total of 90 patients were enrolled in the study, with 45 patients in each group (Figure 1).

Demographic information for the patients, such as age, gender, and height, was carefully documented. Body weight, ideal body weight, and BMI were measured using bioelectrical impedance analysis with the Tanita BC-418 MA device (Tokyo, Japan). Significant medical scores, including the American Society of Anesthesiologists (ASA) score and Mallampati score, were recorded alongside preoperative laboratory values, which included creatinine (mg/dL), albumin (mg/dL), platelet count, international normalized ratio (INR), and total bilirubin (mg/dL). Furthermore, the Child-Turcotte-Pugh (CHILD) and Model for End-Stage Liver Disease (MELD) scores were calculated and documented.

The presence and severity of encephalopathy were also evaluated and noted (7).

Anaesthesia Management

Patients were taken to the operating room without premedication. Routine non-invasive blood pressure, pulse, oxygen saturation (SpO₂) and electrocardiography monitoring were performed. In addition, Bispectral index (BIS) (Masimo SET® Rainbow, Masimocorp. Irvine, CA) was monitored to measure the depth of anesthesia and NMB was monitored with train-of-four (TOF) TOF-Watch SX (Organon/Ireland, a division of MSD Swords, Dublin, Ireland).

Our study was conducted in a single-blind design. Due to its prospective observational nature, it was not feasible to achieve complete blinding of the operators. Nevertheless, the assessment of intubation scores was performed by an independent and experienced anesthesiologist who was blinded to the group allocation, thereby minimizing potential bias in the subjective measurements. Furthermore, it was clearly stated in the study that the observer assessing the intubation scores was blinded; the operators were not involved in data analysis; and all measurements were carried out according to a standardized protocol.

Patients were preoxygenated with 100% oxygen through a face mask for 3 minutes. Anesthesia induction was facilitated by the intravenous (IV) administration of thiopental at a dose of 3-5 mg/kg, along with 1 mg/kg of lidocaine and 1-2 µg/kg of fentanyl. After achieving an appropriate depth of anesthesia, indicated by a BIS value between 40-60, rocuronium bromide (CURON 50 mg/5 mL, Gensenta İlaç Sanayi ve Ticaret A.Ş.) was administered IV at a dose of 1.2 mg/kg based on the ideal body weight. Following anesthesia induction, neuromuscular function was monitored using a TOF-Watch SX device equipped with an acceleromyography transducer, which was placed on the distal phalanx of the thumb. The ulnar nerve was stimulated at the wrist, and repeated TOF assessments were conducted at 15-second intervals.

The time taken for the TOF value to reach zero was recorded as time to TOF zero. Female patients were intubated using endotracheal tubes with an internal diameter of 7-7.5 mm, whereas male patients were intubated with tubes ranging from 8-8.5 mm; all procedures were conducted by an experienced anesthesiologist. Proper placement of the endotracheal tube was confirmed through auscultation and monitoring of end-tidal carbon dioxide (ETCO₂) levels. Intubation times and conditions were evaluated using the Helbo-Hansen Raalo and Trap-Anderson scoring system (8). For patients who required additional rocuronium, a supplementary dose of 0.1 mg/kg was given, and these doses were carefully documented.

Patients undergoing OLT underwent left radial artery cannulation for continuous blood pressure monitoring and blood sampling after intubation. Right jugular vein catheterization was also performed for central venous pressure measurement and vasopressor therapy. Body temperature of all patients was monitored by nasopharyngeal probe insertion and body temperature was not lowered below 37 °C by covering with a thermal blanket and warming all infusion fluids (Hot Line® SIMS Medical System Inc, Rocklan, MA, USA; Fluido® Pressure Chamber, TSCI, Amersfoort, Netherlands).

Anesthesia maintenance was achieved using a combination of 2% sevoflurane and rocuronium administered at a continuous rate of 0.1 mg/kg/hour, alongside intermittent bolus doses of fentanyl, in an oxygen-air mixture. Patients were placed on mechanical ventilation to maintain ETCO₂ levels within the target range of 30 to 40 mmHg. To assess hemodynamic parameters, heart rate (HR), mean arterial pressure, systolic arterial pressure, diastolic arterial pressure, and SpO₂ levels were measured at multiple time intervals: before anesthesia, following induction, after intubation, and subsequently at 1, 5, 15, and 30 minutes after intubation.

In Group 1 patients who underwent OLT, the amount of ascites (mL) drained during surgery was recorded, and the study was terminated.

Statistical Analysis

IBM SPSS Statistics 22 program was used for statistical analysis while evaluating the findings obtained in the study. The parameters' compliance with a normal distribution was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency,) Student's t-test was used for comparisons of normally distributed parameters between two groups, and Mann Whitney U test was used for comparisons between two groups of parameters that were not normally distributed. The chi-square test, Fisher's exact chi-square

test, Fisher Freeman Halton exact chi-square test, and continuity (Yates) correction were used to compare qualitative data. Pearson correlation analysis was used to examine the relationships between parameters that conform to a normal distribution, and Spearman's rho correlation analysis was used to examine the relationships between parameters that do not conform to a normal distribution. Significance was evaluated at the $p < 0.05$ level.

Results

Among the 90 patients involved in the study, 44 (48.9%) were female and 46 (51.1%) were male. The average age of the patients was 50.12 ± 12.10 years. There were no significant differences between the groups regarding demographic factors such as age, gender, height, weight, ideal weight, average BMI, and Mallampati scores ($p > 0.05$) (Table 1).

There were no statistically significant differences between the groups regarding rocuronium administration, duration until the TOF reached 0, and intubation times ($p > 0.05$). Notably, only one patient (2.2%) in Group 1 required an additional dose, while none in Group 2 did ($p > 0.05$). Additionally, there was no statistically significant difference in intubation scores between the groups ($p > 0.05$), with excellent intubation scores reported in 71.1% of Group 1 and 73.3% of Group 2 (Table 2).

Table 1. Evaluation of demographic data [mean $\pm$ SD or number (%)]

		Group 1 (n=45)	Group 2 (n=45)	p value
Age (years)		51.62 $\pm$ 13.1	48.62 $\pm$ 10.96	¹ 0.242
Height (cm)		165.2 $\pm$ 9.29	165.47 $\pm$ 9.17	¹ 0.891
Total weight (kg)		73.87 $\pm$ 11.81	72.87 $\pm$ 11.65	¹ 0.687
Ideal weight (kg)		59.87 $\pm$ 10.21	59.11 $\pm$ 9.97	¹ 0.723
BMI		27.07 $\pm$ 4.55	26.82 $\pm$ 3.73	¹ 0.781
Gender (%)	Female	19 (42.2%)	25 (55.6%)	² 0.292
	Male	26 (57.8%)	20 (44.4%)	
Mallampati	I	11 (24.4%)	28 (62.2%)	³ 0.001*
	II	24 (53.3%)	15 (33.3%)	
	III	10 (22.2%)	2 (4.4%)	

¹: Student t-test, ²: Continuity (Yates) correction, ³: chi-square test, * $p < 0.05$, SD: Standard deviation, BMI: Body mass index

Table 2. Comparison of neuromuscular blocker use intubation score between groups [mean $\pm$ SD or number (%)]

		Group 1 (n=45)	Group 2 (n=45)	p value
Rocuronium dose (mg)		72.51 $\pm$ 13.12 (75)	72.0 $\pm$ 12.08 (70)	¹ 0.616
TOF 0 time (seconds)		117.44 $\pm$ 62.28 (109)	112.38 $\pm$ 51.22 (108)	¹ 0.806
Intubation time (seconds)		14.73 $\pm$ 7.76 (12)	14.89 $\pm$ 7.45 (13)	¹ 0.987
Additional dose	None	44 (97.8%)	45 (100%)	² 1.000
	Done	1 (2.2%)	0 (0%)	
Intubation score	Perfect	2 (71.1%)	33 (73.3%)	³ 0.898
	Good	10 (22.2%)	10 (22.2%)	
	Middle	3 (6.7%)	2 (4.4%)	

¹: Mann Whitney U test, ²: Fisher's exact test, ³: Fisher Freeman Halton exact test, SD: Standard deviation, TOF 0: Train-of-four value of zero

In the analysis of patients in Group 1, a statistically significant association was identified between the TOF 0 time and Child score ($p=0.029$) (Figure 2). However, no positive correlation was found between TOF 0 time and either ascites or MELD scores ($p>0.05$). Additionally, the evaluation of the relationship between intubation time, intubation scores, ascites, the Child-Pugh score, and MELD scores revealed no statistically significant findings ($p>0.05$) (Table 3).

Table 4 presents the results of the multivariable linear regression analysis assessing the factors influencing TOF 0 duration. In the full model, none of the predictors reached statistical significance ($p>0.05$). The intercept indicates the baseline predicted TOF 0 duration of approximately 195 seconds when all predictors are held at zero.

Although BMI showed a negative association with TOF 0 duration ($\beta=-2.66$ s per unit increase, $p=0.121$), this effect did not reach statistical significance in the full model. Other variables, including age, ASA class, Mallampati score, Child score, MELD score, albumin, INR, total bilirubin, and encephalopathy, also showed no significant independent effects.

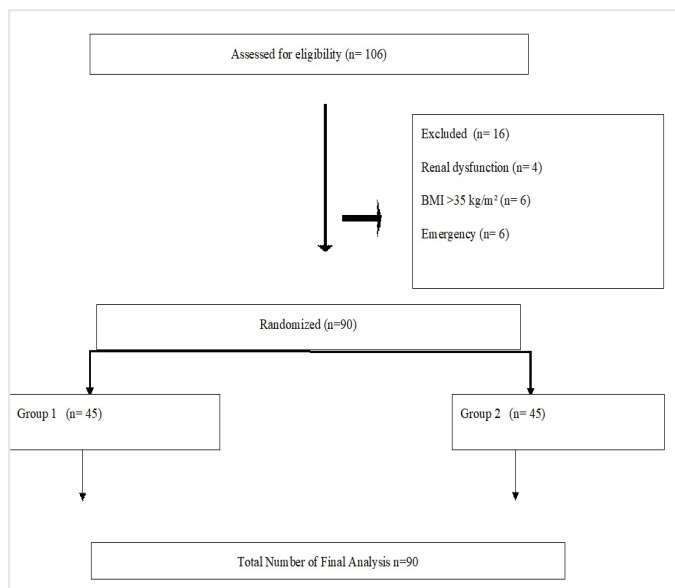


Figure 1. CONSORT flow diagram of this study
BMI: Body mass index

High collinearity was observed among liver-function-related variables (Child score, MELD score, and albumin), which may have reduced the precision of their individual estimates. The relatively low R^2 (0.115) suggests that most of the variability in TOF 0 duration remains unexplained, indicating the potential influence of additional clinical or perioperative factors not included in the current model.

When examining hemodynamic parameters, Group 1 exhibited mean HRs that were significantly lower than those in Group 2 prior to anesthesia, and at the following time points: after intubation, and at 1, 5, 15, and 30 minutes following intubation ($p<0.05$) (Table 5).

Discussion

In our study, we compared patients with end-stage liver failure undergoing OLT, to those with normal liver function. We found that the duration of action of the NMB, as well as intubation times and conditions, was similar when administering rocuronium at a dose of 1.2 mg/kg based on ideal body weight. Our findings suggest that this dosage of rocuronium can effectively ensure adequate intubation conditions for patients undergoing OLT.

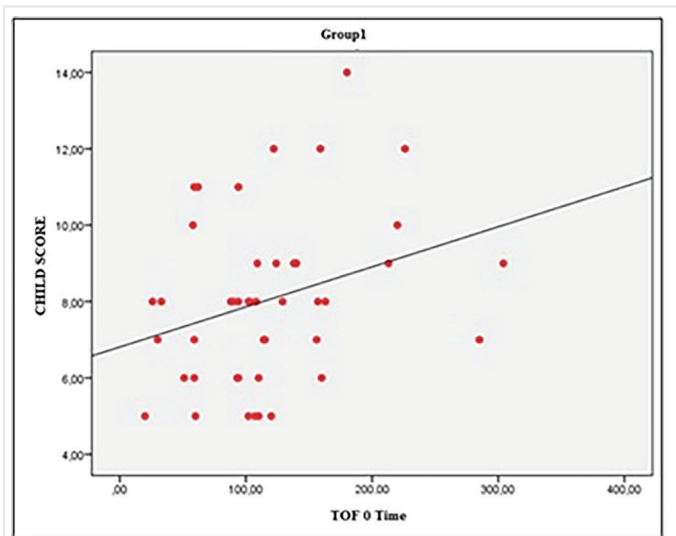


Figure 2. Relationship between Child score and TOF 0 time
TOF 0: Train-of-four value of zero

Table 3. Correlation of rocuronium. TOF 0 duration. Intubation duration and intubation score with a Spearman's rho correlation analysis
* $p<0.05$

Acid, Child and MELD score in Group 1

		Rocuronium dose	TOF 0 duration	Intubation duration	Intubation score
Acid	r	0.064	0.150	-0.012	-0.039
	p	0.674	0.325	0.938	0.800
Child score	r	0.273	0.326	-0.017	-0.029
	p	0.070	0.029*	0.912	0.851
MELD score	r	0.334	0.089	0.083	-0.014
	p	0.025*	0.560	0.588	0.927

Spearman's rho correlation analysis * $p<0.05$, TOF 0: Train-of-four value of zero, MELD: Model for End-Stage Liver Disease score

Table 4. Multivariable regression analysis for TOF 0 duration

Variable	Coefficient (β)	Std. error	t value	p value	95% CI lower	95% CI upper
Intercept	194.57	92.64	2.10	0.039	10.14	378.99
Age (years)	-0.08	0.59	-0.14	0.892	-1.24	1.08
Sex (male=1)	+16.42	12.81	+1.28	0.204	-9.08	41.92
BMI (kg/m ²)	-2.66	1.70	-1.57	0.121	-6.04	0.72
ASA class	-16.56	12.23	-1.35	0.180	-40.91	7.79
Mallampati	+4.60	9.82	+0.47	0.641	-14.96	24.15
Child score	+7.22	6.63	+1.09	0.280	-5.98	20.41
MELD score	-1.41	2.10	-0.67	0.504	-5.59	2.77
Albumin (g/dL)	-2.49	14.91	-0.17	0.868	-32.18	27.19
INR	+18.99	31.96	+0.59	0.554	-44.64	82.62
Total bilirubin	-0.24	2.90	-0.08	0.935	-6.02	5.54
Encephalopathy	-18.53	29.76	-0.62	0.535	-77.78	40.72

n=90, R²=0.115, Adjusted R²=-0.009, F-statistic=0.93 (p=0.521), TOF 0: Train-of-four value of zero, Std: Standard, CI: Confidence interval, BMI: Body mass index, ASA: American Society of Anesthesiologists, MELD: Model for End-Stage Liver Disease score, INR: International normalized ratio

Table 5. Evaluation of hemodynamic parameters [mean ± SD or number (%)]

		Group 1 (n=45)	Group 2 (n=45)	p value
Heart rate (beats/min)	Before anesthesia	78.56±13.77	86.76±16.4	0.012*
	Post induction	82.58±14.23	87.84±17.55	0.121
	After intubation	85.71±17.06	99.11±19.57	0.001*
	1. min	83.09±16.47	95.73±18.11	0.001*
	5. min	78.58±14.97	88.96±22.33	0.011*
	15. min	78.6±16.72	90.96±18.61	0.001*
	30. min	75.8±14.81	87.02±17.56	0.002*
SAP (mmHg)	Before anesthesia	137.4±28.06	140.07±24.47	0.632
	Post induction	113.36±21.86	115.71±27.55	0.654
	After intubation	122.56±25.47	146.84±29.79	0.000*
	1. min	115.09±23.52	124.42±31.46	0.115
	5. min	103.91±18.74	110.73±21.45	0.112
	15. min	98.8±21.63	107.76±18.73	0.039*
	30. min	98.71±20.21	112.4±17.03	0.001*
DAP (mmHg)	Before anesthesia	75.4±10.89	84.51±11.34	0.000*
	Post induction	66.24±15.75	76.73±13.02	0.001*
	After intubation	69.53±14.42	95.53±21.37	0.000*
	1. min	65.36±13.23	78.93±19.64	0.000*
	5. min	58.67±12.17	68.4±14.46	0.001*
	15. min	57.07±10.77	66.31±12.89	0.000*
	30. min	58.09±11.51	71.8±12.92	0.000*
MAP (mmHg)	Before anesthesia	97.73±17.92	106.24±17	0.023*
	Post induction	82.89±17.66	92.91±16.58	0.007*
	After intubation	88.87±17.55	115.44±23.78	0.000*
	1. min	84.33±17.09	96.53±24.49	0.007*
	5. min	76.16±14.67	85.76±14.66	0.003*
	15. min	74.4±13.38		0.005*
	30. min	75±13.36	87±13.39	0.000*

SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, Student t-test, *p<0.05, SD: Standard deviation, Min: Minute

Rapid serial intubation (RSII) for general anaesthesia is preferred in patients at high-risk of pulmonary aspiration. In OLT patients, there is a decrease in oncotic pressure due to a decrease in proteins, especially albumin, and ascites accumulation, which occurs in approximately 60% of cirrhotic patients. Since ascites increases intraabdominal pressure, RSII is recommended in these patients (9). The preferred NMBs in RSII are succinylcholine and rocuronium. Since succinylcholine has side effects leading to hyperkalaemia and rapid desaturation by increasing oxygen consumption and rocuronium has no contraindication, there is ongoing debate about the choice of agent for RSII (10). We do not prefer succinylcholine because of electrolyte disturbance, and potassium elevation that may develop preoperatively and in the intraoperative period in OLT patients.

Water-soluble drugs have limited distribution volumes that are not affected by fat depots. Therefore, under certain conditions, the administration of water-soluble drugs according to actual body weight may lead to an overdose. Overdose of hydrophilic NMBs, which are frequently used in anaesthesia practice, may result in prolonged recovery and postoperative respiratory complications. Since the distribution of hydrophilic drugs is limited to lean tissue, the dose to be administered should generally be based on ideal body weight or corrected body weight. Cirrhotic liver disease and renal insufficiency also result in an increased volume of distribution and lower plasma concentrations of hydrophilic drugs, leading to a situation where the initial dose is increased but lower maintenance doses are required. It is necessary to confirm adequate laryngeal muscle relaxation by neuromonitoring and to determine whether additional doses are needed. In our patients, we used TOF-Watch SX monitoring to evaluate the duration of action of NMBs by administering rocuronium according to ideal body weight.

Several studies have compared the onset of action of NMBs in liver diseases such as liver cirrhosis and hepatoma. Khalil et al. (11) investigated the 0.6 mg/kg rocuronium dose in patients who underwent surgery due to liver disease; they emphasized that the onset of action was prolonged by approximately 45%. Another study investigated the pharmacokinetic effects of 0.6 mg/kg rocuronium in liver disease using a control group. No relationship was found between the onset of action of rocuronium and liver disease (12). In our study, rocuronium onset of action and intubation scores were similar in patients with liver failure and those with normal liver function. The discrepancy observed in the literature review may be explained by changes in patient numbers and inappropriate use of neuromonitoring methods.

Sluga et al. (13) emphasised that they found the onset time for the effect of rocuronium to be 130 seconds, using propofol and 0.6 mg/kg rocuronium in rapid sequence intubation. In another study, optimal intubation conditions were achieved after 45-60 seconds at a rocuronium dose of 0.6 mg/kg (14). In our study, the time was 117.44 seconds on average in the patient group with liver failure and 112.38 seconds, in the patient group with normal liver function, and these times were statistically similar. However, the rocuronium dose used in our study was 1.2 mg/kg, which differs from doses reported in the

literature. We think that this difference may be due to the application of the rocuronium dose used in our study based on ideal body weight and the use of thiopental as an induction agent to provide haemodynamic stability, which differs from other studies. Similar studies on this subject are needed.

In our study, there was no significant correlation between TOF0 duration and MELD score, but there was a positive and moderate correlation (32.6%) which was statistically significant correlation between the Child score and another variable (unspecified). We think that the difference in these results is because the Child score includes subjective criteria such as encephalopathy, although it has been used as a reliable method for years in determining liver reserve (15).

Cardiomyopathy, diastolic dysfunction and coronary artery disease may accompany cirrhotic liver disease and blood pressure may be normal or low in these patients (16). The mechanism of systemic vasodilation in the pathogenesis of cirrhotic cardiomyopathy is still a matter of debate. However, it has been associated with various humoral mediators such as nitric oxide, adrenomedullin, natriuretic peptides, cytokines, hydrogen sulfide, endothelins, and endocannabinoids. Disruption of the balance in the release of these mediators causes vasodilatation. At the same time, bacterial endotoxins lead to peripheral vasodilatation by stimulating endogenous cannabinoid production (17,18). In our study, we think hypothesize that these reasons related to liver failure are responsible for the finding of a haemodynamically significant difference between the two groups.

Study Limitations

This study has a few limitations. First, it is a single-center study and may have a limited sample size. The generalizability of the results could be improved with a larger sample size. Additionally, OLT patients receive different drug treatments may influence the effects of rocuronium. This may make it difficult to interpret the results.

Conclusion

In patients with advanced liver failure scheduled for liver transplantation, administering rocuronium at a dose of 1.2 mg/kg based on ideal body weight appears to yield a similar onset of action to that seen in individuals with normal liver function, while also ensuring sufficient conditions for intubation. We propose that this rocuronium dosage can be safely utilized for anesthesia induction during OLT and rapid sequence intubation in this patient group. However, additional comprehensive studies are necessary to further validate our findings.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Malatya Clinical Research Ethics Committee (protocol number: 2022/61, date: 29.06.2022).

Informed Consent: All patients received information regarding the study's details and provided written informed consent.

Footnotes

Authorship Contributions: Surgical and Medical Practices - S.K.İ., D.D., Y.Z.Ç.; Concept - M.A.E., N.G., M.D., N.A.Y.; Design - S.K.İ., Y.Z.Ç., N.A.Y., M.A.E., M.D.; Data Collection or Processing - S.K.İ., O.O.Ö., Y.Z.Ç., M.D.; Analysis or Interpretation - D.D., N.A.Y., M.A.E., N.G.; Literature Search - D.D., N.G., O.O.Ö.; Writing - S.K.İ., D.D., O.O.Ö.

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