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Diaphragm ultrasound to evaluate the antagonistic effect of sugammadex on rocuronium after liver surgery in patients with different liver Child-Pugh grades: study protocol for a prospective, double-blind, non-randomised controlled trial

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ABSTRACT

Introduction The use of muscle relaxants is an indispensable in the general anaesthesia but is prone to accidents, which are often related to residual muscle relaxant. Therefore, how to timely and effectively eliminate the residual effect of muscle relaxants after surgery has become an urgent clinical problem. Rocuronium is a non-depolarising muscle relaxant that is primarily metabolised by the liver. Patients with liver dysfunction can affect the metabolic process of rocuronium, thereby delaying the recovery of muscle relaxation. Sugammadex (SUG) is a novel-specific antagonist of aminosteroidal muscle relaxants, which can effectively antagonise muscle relaxants at different depths. However, whether liver dysfunction affects the antagonistic effect of SUG against rocuronium has not been reported. Therefore, we hypothesise that with the increase of patients' liver Child-Pugh grade, the recovery time of rocuronium antagonised by the same dose of SUG after surgery will be prolonged, and the incidence of muscle relaxation residual will be increased in the short term.

Methods and analysis This study is a prospective, double-blind, low-intervention, non-randomised controlled clinical trial involving 99 patients with American Society of Anesthesiologists (ASA) I–III, body mass index 18.5–24.9 kg/m^2, who will undergo laparoscopic radical resection of liver cancer under general anaesthesia in the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Ultrasonography will be applied to monitor the change rate of diaphragm thickness at different time after extubation to evaluate the occurrence of residual muscle relaxant, which indirectly reflects the dose–effect relationship of SUG antagonising against rocuronium in patients with different liver Child-Pugh grades preoperatively.

Ethics and dissemination The protocol was reviewed and approved by the Medical Ethics Committee of Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology (UHCT21012). The findings will be disseminated to the public through peer-reviewed scientific journals.

Trial registration number NCT05028088.

Strengths and limitations of this study

- This study is the first to evaluate the effect of Child-Pugh grades of liver function on the dose–effect relationship of sugammadex (SUG) antagonising rocuronium.
- This study provides a non-invasive and painless method for monitoring residual muscle relaxation in patients undergoing extubation after surgery.
- The limitation of this study is that we only pay attention to the effect of different Child-Pugh grades of liver function on the dose–effect relationship of SUG antagonising rocuronium, and we did not try to further explore the precise dose of SUG antagonising rocuronium in patients with different liver function Child grades.
- The limitation of this study is that it is a single-centre clinical study, and the results obtained seem to have certain limitations, and the large-sample, multicentre clinical controlled studies will obviously be necessary to verify the conclusions in the future.

INTRODUCTION

Background

Muscle relaxation is one of the three major elements of general anaesthesia (sedation, analgesia and muscle relaxation),[1] which plays an important role in providing muscle relaxation conditions for tracheal intubation, eliminating man-machine confrontation during mechanical ventilation and meeting the needs of muscle relaxation in various

surgical and diagnostic operations. In recent years, with the increasing availability of general anaesthesia, the application of muscle relaxants has increased significantly. However, the use of muscle relaxants is one of the most accident-prone elements of general anaesthesia,[2] and the residual muscle relaxant is the most common cause of anaesthesia accidents caused by muscle relaxants.[3 4] Postoperative muscle relaxation often brings many harms to patients,[5 6] such as: respiratory muscle weakness leads to insufficient alveolar ventilation, which leads to hypoxaemia and hypercapnia; throat muscle weakness leads to upper respiratory tract obstruction and increases the risk of reflux aspiration; coughing weakness leads to the inability to effectively discharge airway secretions and causes postoperative pulmonary complications; in addition, residual muscle relaxation often makes patients feel fatigue, 'feeling of death' and diplopia during recovery from anaesthesia, and even endangering the life of the patient in severe cases. A recent survey on postoperative muscle relaxation and acute respiratory events involving a large sample indicated that the incidence of postoperative muscle relaxation was 9%–56.5% without the use of muscle relaxation antagonists.[7] Therefore, how to effectively eliminate the residual muscle relaxation in patients after surgery has become a clinical problem and research hotspot that anaesthesiologists urgently need to solve.

The monitoring of muscle relaxants and the rational use of muscle relaxant antagonists are the two areas that anaesthesiologists need to pay most attention to when dealing with the problem of residual muscle relaxant.

Acetylcholinesterase (AChE) inhibitors, such as neostigmine, are commonly used in clinical diagnosis and treatment as muscle relaxant antagonists.[8] However, the application of AChE inhibitors still has some disadvantages, such as increased glandular secretion, sinus bradycardia and insufficient muscle relaxation antagonism. Sugammadex (SUG) is a novel-specific antagonist for aminosteroid muscle relaxants, with high affinity and high selectivity, and it parcels amino non-steroidal muscle relaxants and forms a stable chelate. Along the concentration difference, the muscle relaxants located at the neuromuscular junction are transported to the plasma and then excreted through the kidneys, rapidly reducing the concentration of muscle relaxants in the blood and tissues.[9] There have been a large number of research data on the mechanism of action, pharmacokinetic characteristics, drug interactions, as well as safety and effectiveness of SUG, and its clinical application scope is still expanding. However, for special patients and under special circumstances, the clinical application needs to be further explored and improved.

Cirrhosis induced by chronic viral hepatitis is considered to be the main cause of primary liver cancer. China is a country with a high incidence of liver cancer, according to the data released by WHO in 2014, there are about 74 million cases of hepatitis B virus carriers in China, including 28 million hepatitis B patients, and about 260 000 patients die of liver cirrhosis and liver cancer caused by hepatitis B every year.[10 11] The gradual evolution of hepatitis, cirrhosis and liver cancer is regarded to be the main process of liver cancer, in which surgery is the first choice for radical treatment of liver cancer, and patients are often accompanied by liver function abnormalities of varying degrees.

Rocuronium is a non-depolarising muscle relaxant commonly applied in clinical anaesthesia, which mainly acts on the neuromuscular junction and blocks skeletal muscle N-type choline receptor to relax muscles. It has the advantages of fast onset, medium duration and less accumulation in the body, and is widely used in clinical practice.[12] Rocuronium is mainly absorbed by the liver and excreted by the hepatobiliary tract. Liver dysfunction is able to influence the metabolic process of rocuronium, then affecting muscle relaxation recovery.[13] van Miert *et al*[14] found that there was no significant difference in the onset time and maximum degree of neuromuscular block after rocuronium treatment in patients with mild or moderate cirrhosis compared with healthy adult control group, but the recovery time of neuromuscular block was significantly prolonged. Magorian *et al*[15] indicated that although liver function damage did not change the plasma clearance rate of rocuronium, it increased its distribution volume in the body, leading to a longer elimination half-life of rocuronium. Parasa *et al*[16] pointed out that Child-Pugh grade C patients with severe liver cirrhosis significantly prolonged the onset time of rocuronium. In conclusion, rocuronium acting time and duration were significantly prolonged in patients with liver dysfunction due to increased volume of distribution in vivo and prolonged elimination half-life.[17]

SUG is a highly effective and specific antagonist of rocuronium,[18] and whether liver dysfunction affects its antagonistic effect on rocuronium is unclear, especially for Child-Pugh grade C patients. Therefore, we hypothesised that with the increase of liver Child-Pugh grade, the recovery time of postoperative muscle relaxation was significantly prolonged and the incidence of muscle relaxation residual in a short period was significantly increased in patients who received the same dose of SUG antagonism rocuronium after liver surgery.

At present, the degree of muscle relaxation is mainly measured by muscle relaxation monitor in clinic, in which the train of four (TOF) ratio <0.9 is the diagnostic criteria for postoperative residual muscle relaxation.[19] However, the application of muscle relaxation monitors is often difficult to be performed routinely due to complex operation, tedious man–machine connection, easy interference of external factors on the interface, and more importantly, the detection of muscle relaxation in awake patients is likely to trigger unpleasant feelings. Cappellini *et al*[20 21] creatively applied diaphragmatic ultrasound in the assessment of muscle relaxation residual in awake patients, in which the rate of change of diaphragmatic thickness (the difference between end-of-inspiratory and end-of-expiratory diaphragm thickness divided by end-of-expiratory diaphragm thickness) was lower than 0.36 to be diagnosed as muscle relaxation residual.

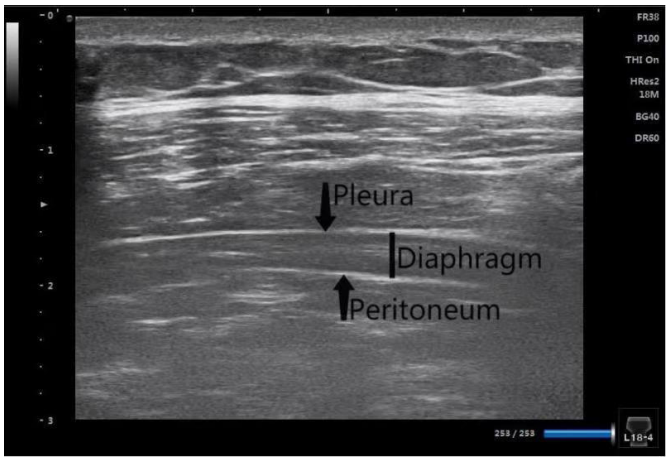

Figure 1 Images of the diaphragm ultrasound. THI, Tissue Harmonic Imaging.

Diaphragm is the most important respiratory muscle, which is responsible for 60%–80% of the whole respiratory muscle action. As early as 1985, ultrasonography was used to evaluate the function of the diaphragm, reflecting the systolic function of the diaphragm by measuring the thickness change of the fixed area.[22] Diaphragm thickness refers to the distance between the pleura and peritoneum of the diaphragm at the junction of the thorax, which can be measured by B-mode ultrasound. A 13 MHz linear array ultrasonic probe vertically places in the 8–10 ribs between anterior axillary line and midaxillary line. At a distance of 1.5–3 cm from the skin, we are able to observe two parallel layers with strong echo, the pleura and the peritoneum. Of note, the pleura is closer to the skin, while the peritoneum is farther away from the skin, and the area between them with a lower echo is the diaphragm (as show in figure 1). Images of the diaphragm should be taken at the end of expirations and inspirations, and under these two breathing conditions, the thickness of the diaphragm can be measured. Then based on that, the rate of change in the thickness of the diaphragm can be calculated.[23 24] Regarding the normal value of the diaphragm thickness in healthy adults, there are related literature reports: the functional residual air position is (1.7±0.2) mm during spontaneous breathing, while at the maximum inspiratory position is (4.5±0.9) mm.[25] Our study intends to use diaphragmatic ultrasound to assess residual muscle relaxation.

Making use of our existing clinical basis and equipment, this study intends to verify our hypothesis that the more severe the abnormal liver function of the subjects, the longer the recovery time of postoperative muscle relaxants, the higher the incidence of residual muscle relaxants in the short term.

METHODS AND ANALYSIS

Study design

This study is a prospective, double-blind, low-intervention, non-randomised controlled clinical trial, carried out in the Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, and is expected to be conducted from 15 February 2021 to 31 December 2022. The design of this study protocol has referred to the Standard Protocol Items: Recommendations for Interventional Trials 2013 guideline,[26] please see online supplemental material 1.

Study population

Inclusion criteria

1. Age between 18 and 65 years old.
2. Patients scheduled for laparoscopic radical resection of liver cancer under general anaesthesia.
3. Patients ASA classification I–III.
4. Body mass index 18.5–24.9 kg/m$^{2.}$
5. Able to give informed consent.
6. The surgical position is suitable for BIS monitoring and muscle relaxation monitoring.

Exclusion criteria

1. Patients with allergic to rocuronium and SUG.
2. Patients with central and peripheral nervous system diseases, such as polio, Parkinson's disease, peripheral neuropathy, etc.
3. Patients with neuromuscular system diseases, such as multiple sclerosis, myasthenia gravis, atrophic myotonia, etc.
4. Patients with diaphragm dysfunction, pneumothorax, pleural effusion, mediastinal pneumatosis.
5. Pregnant women or nursing mothers.

Grouping and blind method

This study is a non-randomised controlled study: the designated research coordinator, who does not participate in the follow-up study, will check the electronic medical record system and divide the patients into three groups (child A group, child B group and child C group) according to the results of preoperative liver function tests and Child-Pugh grades standards. Meanwhile, the patients will be numbered, which will be used by the researchers in turn.

Blinding the researchers: a designated study coordinator who is responsible for the preservation and preparation of drugs and information coordination among researchers. Assign a nurse to administer the drugs and record the participants' basic information. Another researcher is follow-up person in charge of patient follow-up, as well as records data from diaphragm ultrasound monitoring. Above-mentioned research workers will not know each other's records during the whole study.

Blinding the patients: all patients are treated with a uniform appearance syringe and microsyringe pump during the operation, and the same ultrasound machine will be used for diaphragm ultrasound monitoring in the study.

Interventions

Main instruments: Drager Fabius anaesthesia machine, Intellivue MX600 monitor, TOF-Watch SX muscle relaxation monitor, Philips IU22 Colour Doppler Ultrasound Diagnostic Instrument.

Dlaphragm ultrasound scan: Prior to anaesthesia induction, patients will lie on the bed in a semi-recumbent (45°) position. A skilled ultrasound operator will use the Philips IU22 Colour Doppler Ultrasound Diagnostic Instrument to identify and locate the diaphragm through the hyperechoic pleura and peritoneum.

Anaesthesia method: After the patient entered the operating room, the peripheral vein access of the forearm will be opened, and the non-invasive blood pressure, ECG, saturation of pulse oxygen and Bispectral Index (BIS) are routinely monitored. During anaesthesia induction, propofol 2.5 mg/kg and sufentanil 5 µg/kg will be injected intravenously. When the BIS value drops below 60, the muscle relaxation monitor will be calibrated. After T1 and TOF are stable, rocuronium will be injected intravenously at 0.6 mg/kg. By the time T1=0, endotracheal intubation will be given, and the ventilator parameters will need to be adjusted to volume control ventilation (tidal volume 8–10 mL/kg, respiratory rate (RR) 12–18 times/min and fractional inspired oxygen 60%). During the maintenance stage of anaesthesia, the pneumoperitoneum pressure will be at a low level of 8–10 mm Hg, propofol target controlled infusion (TCI) will be applied to maintain the plasma concentration of 2.5–5.5 µg/mL, remifentanil TCI will be used to keep the plasma concentration of 0.5–5 ng/mL and rocuronium will be continuously pumped intravenously with 0.3–0.6 mg/kg/hour for deep muscle relaxations, with the the post-tetanic twitch count value of 1–2.

Muscle relaxation monitoring: Our study will use TOF-Watch SX muscle relaxation monitor to monitor the depth of muscle relaxation in general anaesthesia patients. We will standardise the electrode position of the muscle relaxation monitor. The distal electrode is placed at the intersection of the radial edge of the flexor carpi ulnaris muscle and the proximal edge of the wrist curve, while the proximal electrode can be placed 2–3 cm away from the distal electrode. The electrodes are placed on both sides of the predicted position of the ulnar nerve, which can reduce the influence caused by errors in judging the position of the nerve.

Measurement of diaphragmatic thickness: When B-mode ultrasound will be used to measure the thickness of the diaphragm, a 5–12 MHz linear array ultrasound probe will be put in the left midaxillary line between the 8 and 10 costals, where is called the diaphragmatic zone of apposition (ZAP). In the breathing exercise, the diaphragm is relatively fixed at ZAP, and the breathing action has little influence on the movement of the diaphragm at ZAP, the diaphragm only shows systolic and diastolic changes. Therefore, the measurement of the diaphragm thickness at ZAP can truly reflect the overall thickness change of the diaphragm during the respiratory cycle. Each value will be measured three times in three consecutive breathing cycles, and the average of the three measurements will be taken. The values of diaphragmatic thickness at the end of inspirations (DTEI) and diaphragmatic thickness at the end of expirations (DTEE) will be recorded, respectively, then the change rate of diaphragmatic thickness fraction (DTF%)=(DTEI − DTEE)/DTEE ×100% will be calculated. In addition, Diaphragmatic baseline recovery fraction (△DF) = (preanaesthetic DTEI − postoperative DTEI)/preanaesthetic DTEI ×100% also will be calculated. Ultrasound measurement will be performed by two doctors who are experienced in critical ultrasound. The measurement results will be kept confidential to the investigator, who will then analyse the ultrasound data.

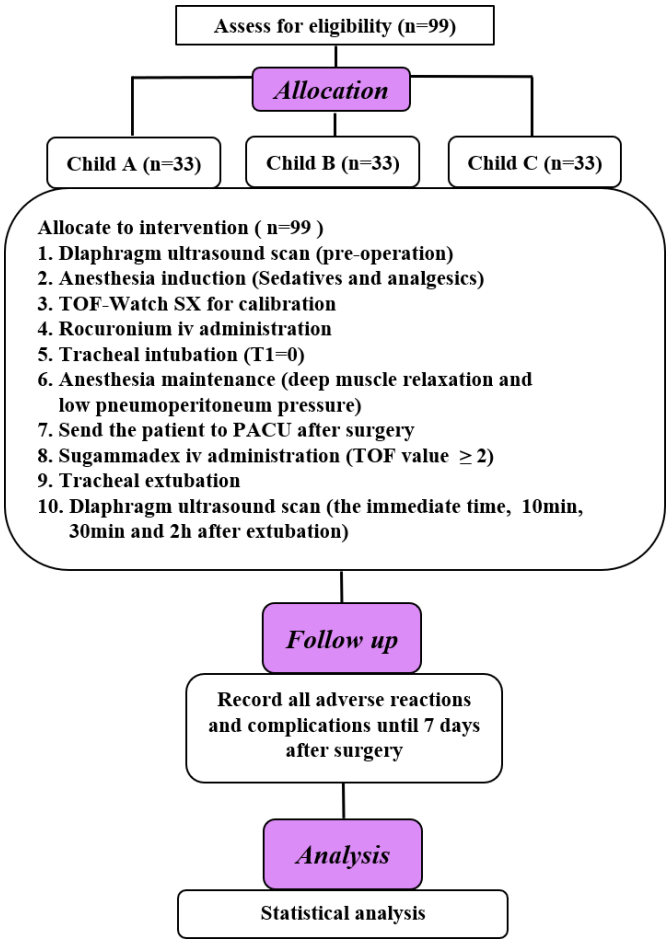

Figure 2 Study flow diagram. PACU, postanaesthesia care unit; TOF, train of four.

At the end of the operation, the infusion of anaesthetic drugs will be stopped, and the patients will be transferred into the postanaesthesia care unit (PACU) with endotracheal catheters and continued monitoring. When the TOF value was ≥2, patients in each group will be given SUG (2 mg/kg), respectively. When the patient's consciousness and spontaneous breathing are restored, he can open his eyes according to the doctor's instructions, shake hands firmly, and at the same time, he can complete the movement of raising his head continuously for more than 5 s to remove the tracheal tube. The researchers will record the recovery conditions of diaphragmatic function monitored by bedside ultrasound at the immediate time, 10 min, 30 min and 2 hours after extubation (figure 2).

Outcome measurements

The main observation indicators included the incidence of residual muscle relaxation at different time points after the operation and the baseline recovery rate of the diaphragm (immediately after extubation, 10 min, 30 min and 2 hours). The secondary observation indicators include muscle relaxation onset time (administration of rocuronium to tracheal intubation), intraoperative rocuronium dosage, muscle relaxation recovery time (administration of SUG to tracheal extubation), adverse reactions after SUG medication, PACU monitoring time and the incidence of postoperative pulmonary complications within 7 days (figure 3).

Statistical analyses and sample size calculation

SPSS V.26.0 software will be used for statistical analysis. In the statistical data, the counting data are expressed by the rate, while the measurement data are expressed by the mean±SD. If the variance of the measurement data is uniform, the measured values of each observation index

Primary outcome					
		Extubation	10min	30min	2h
TEI					
TEE					
△DF					
DTF					
Muscle relaxation onset time		Muscle relaxation recovery time			
PACU Monitoring time		Intraoperative rocuronium bromide dosage			
Adverse reactions after SUG medication		Postoperative pulmonary complications			
DTF=[(TEI-TEE)/TEE] x 100%					
△DF = (preanaesthetic DTEI − postoperative DTEI)/preanaesthetic DTEI ×100%					
Data related to surgery and anesthesia					
Operation time(min)		Anesthesia time(min)			
Propofol dosage(mg)		Sufentanil dosage(ug)			
Remifentanil dosage(mg)		SUG dosage(mg)			
Vital signs after the administration of SUG					
	SUG iv administration	5min	10min	30min	
SpO_2					
Systolic pressure					
Diastolic pressure					
Mean arterial pressure					
Heart rate					
Ramsay sedation score after surgery					
		Ramsay score			
0.5h after tracheal extubation					
1h after tracheal extubation					
2h after tracheal extubation					

SUG: Sugammadex
TEI: Thickness at the end of inspirations
TEE: Thickness at the end of expirations
DTF: Diaphragmatic thickness fraction
△DF: Diaphragmatic baseline recovery fraction
PACU: Post-Anesthesia Care Unit

Figure 3 Study data acquisition table. ΔDF, diaphragmatic baseline recovery fraction; DTF, diaphragmatic thickness fraction; PACU, post-anesthesia care unit; SUG, Sugammandex; TEE, thickness at the end of expirations; TEI, thickness at the end of inspirations.

among the groups are compared by analysis of variance, otherwise, the rank sum test is used. SNK-Q test was used for pairwise comparison of the measured values within the group. Count data comparison adopts row-list χ^2 test or the Fisher's exact test, as appropriate. For all comparisons, the $p<0.05$ is considered statistically significant.

The main variable measured by outcome is the incidence of residual muscle relaxation after tracheal extubation for 10 min, and significant level α is equal to 0.05, a power of the test will be calculated with $1-\beta=0.80$. According to our preobservation results, 10 min after SUG antagonises rocuronium, the incidence of residual muscle relaxation under diaphragmatic ultrasound in patients with different liver Child-Pugh grades (Child A, Child B and Child C) before surgery is 4%, 16% and 40%, respectively. Cases will be allocated according to 1:1:1 into the three groups, considering that 10% of the samples probably fall off, and each group should contain 33 valid cases after calculation by the Power Analysis and Sample Size software, thus, a total of 99 cases will be included in this observation.

Patient and public involvement

Patients were not intrinsically involved in the design, recruitment or conduct of the study. Each patient will receive a 'Thank you letter' at the end of the study participation, and results of the study will be disseminated to patients after publication in peer-review journal.

DISCUSSION

Remaining muscle relaxation is a major safety risk after general anaesthesia, and its incidence is very high according to the existing research results. Adequate monitoring of muscle relaxation and timely use of muscle relaxation antagonists are of great significance to reduce the residual muscle relaxation incidence after general anaesthesia. However, various unfavourable factors limit the extensive application of muscle relaxation monitor. Without the guidance of the monitoring results of muscle relaxants, it is unreliable to rely solely on the subjective judgement of the anaesthesiologist for the residual muscle relaxants in patients after surgery, which leads to the failure of timely treatment of the residual muscle relaxants in many patients, and the consequences are serious. But it is encouraging that the prevalence of bedside ultrasound for us to non-invasively and timely assess of the function of diaphragm provides a possibility. The diaphragm is the most important respiratory muscle, and 60%–80% of the entire respiratory muscle function is completed by the diaphragm. As the technology of ultrasound monitoring of diaphragm function matures, it becomes possible to monitor the function of the diaphragm with bedside ultrasound and reflect the residual muscle relaxation.

As far as we know, diaphragmatic ultrasound has long been used in many clinical scenarios of diaphragmatic dysfunction.[27 28] Ultrasonographic assessment of the diaphragm is of little value if the operator is not trained adequately,[23] whereas the tool provides painless bedside assessment of the subject's major respiratory muscler when the operator is professionally trained and familiar with the procedure. Previous study has revealed that the reproducibility and repeatability of diaphragm ultrasonography are moderate.[20]

As a new specific antagonist of aminosteroidal muscle relaxants, SUG is favoured by anaesthesiologists since it can effectively antagonise muscle relaxants at different depths. SUG has a wide range of applications, but its efficacy in special patients needs to be further explored, such as patients with severe liver insufficiency. In this study, patients were divided into three groups according to the Child-Pugh grades of the liver before surgery. By evaluating the residual rate of postoperative muscle relaxation that SUG antagonises rocuronium, it reflects the dose-effect relationship in patients with different liver Child-Pugh grades. The above research provides a powerful theoretical basis for the rational application of muscle relaxant antagonists in patients with hepatic insufficiency in clinical anaesthesia.

In this study, ultrasound monitoring of the change rate of DTF was used as the diagnostic criteria for muscle relaxation residuals. It is of great significance for the use of ultrasound to monitor diaphragm function instead of using traditional invasive muscle relaxation monitors to assess residual muscle relaxation, and to promote the application in clinical practice. It is worth mentioning that the use of diaphragm ultrasound to assess the residual muscle relaxation after surgery, and then to intervene early, is of great significance for reducing the PACU monitoring time and the utilisation of medical resources, and at the same time ensuring the safety of patients after surgery.

ETHICS AND DISSEMINATION

This study protocol has been approved by the Medical Ethics Committee of Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology (UHCT21012). We will publish the results of this study in peer-reviewed journals and related websites.

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Contributors YL, SY, SS, YS, RC, CY, HX and XC contributed substantially to the study design. SS and YS drafted the manuscript. YL, SY, SS, RC, CY, HX and XC revised and approved the final version before submission. All authors read and approved the final manuscript.

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