ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2019 Dec 30; 7(24):4420-4426.
https://doi.org/10.3889/oamjms.2019.874
eISSN: 1857-9655
Basic and Clinical Medical Researches in Vietnam

Neuromuscular Blockade Agents Reversal with Sugammadex Compared to Neostigmine in the Living Kidney Donors

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Citation: Quang TL, Thu HNT, Quoc KN, Thu HN, Van DP, Tien NLB, Thanh VV, Nga VT, Toi CD. Neuromuscular Blockade Agents-- Reversal with Sugammadex Compared to Neostigmine in the Living Kidney Donors. Open Access Maced J Med Sci. 2019 Dec 30; 7(24):4420-4426. https://doi.org/10.3889/oamjms.2019.874

Keywords: muscle relaxants; living kidney donors; sugammadex

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Received: 10-Nov-2019; **Revised:** 16-Nov-2019; **Accepted:** 17-Nov-2019; **Online first:** 20-Dec-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKROUND: The reversation of NMBA (neuromuscular blocking agents) prevents numerous postoperative complications, increases quality of recovery and decreases the time, expenditure spending in hospital. The choice of medicine used to reverse NMBA depends considered as a key fators to gain the best outcome and to avoid the side effects.

AIM: To evaluate the postoperative effect on muscle relaxation reversal and side effects of sugammadex 2 mg/kg versus the combination of neostigmine and atropine sulfate in the living kidney donors.

METHODS: A randomised controlled trial on 70 patients undergoing living kidney donation surgery were allocated to 2 groups. Patients in group I (SUGA) were reversed with sugammadex 2 mg/kg and in group II (NEO/ATR) with the combination of neostigmine and atropine sulfat.

RESULTS: With 35 patients in each group, the study results showed that after 3 mintutes of reversal patients reaching TOF value ≥ 0.9 in group SUGA is 91.4%, after 5 minutes 100% of patients in group SUGA reached TOF value ≥ 0.9 . In group NEO/ATR after 3 minutes 28.6% patients reached TOF ≥ 0.9 and 40% patients reached TOF≥ 0.9 after 5 minutes. The difference in percentage of patients reaching TOF ≥ 0.9 after 3 minutes, 5 minutes of reversal between two groups is significant ($p<0.05$). After 10 minutes, 100% patients in both group got TOF ≥ 0.9. Time to exutubation of group SUGA was 249.43 ± 81.75 seconds and it was 456.29 ± 146.45 seconds in group NEO/ATR. Nausea, bradycardia, and increased phlegm production in group NEO/ATR was 22.9%; 28.5%; 25.7% respectively; while those side effects were not met in group SUGA, the difference was significant ($p<0.05$).

CONCLUSION: The muscle relaxation reversal effect of sugammadex was faster than that of neostigmine, the duration TOF ≥ 0.9 and the time to extubation was significantly faster. Sugammadex did not cause hemodynamic changes before and after muscle relaxation reversal, neostigmine resulted in the bradycardia, increased phlegm secreting and other side effects. The renal function after 24 hours postoperatively of two groups was similar.

Introduction

Nowadays, living donor nephrectomy in Viet Nam is usually performed under laparascopic methods, due to numerous advantages for the donors such as reduced blood loss, decreased tissue trauma, lower analgesia requirement, faster resumption of food and drinks intake, shorter hospitalisation and better postoperative cosmetic appearance. However, increasing abdominal pressure due to pneunoperitonium can affect the kidney function by impairing renal perfusion flow and does not facilitate surgeon's procedure [1]. Therefore, profound neuromuscular blockade plays essential role in limitting the increase in abdominal pressure and facilitating surgical field for kidney removal. Postoperative residual curarization is a common complication after surgery that impacts the patient's safety. Postoperative residual curarization reduces ventilation response to hypoxia; induces laryngeal muscle and esophageal sphincter dysfunction which causes reflux, choking lungs; thus increasing risk of postoperative respiratory complications. Therefore, finding a safe way to reverse muscles relaxation is fundamental to achieving successful outcomes of

surgery. Neostigmine is a common neuromuscular blockade reversal agent; with anticholinesterase mechanism which allows acetylcholine to build up at the neuromuscular junction and subsequently results in competitively inhibiting non-depolarizing blocking drugs at the nicotinic receptor of motor nerve terminals. On the other hand, this drug simultaneously acts on muscarinic receptor that leads to several side effects, so neostigmine is frequently used with anticholinergic drugs such as atropine. The dose of neostigmine should be adjusted according to TOF count, and postoperative residual curarization may still exist after neostigmin administration [2], [3]. If neostigmine is used when TOF < 0.9, it may also increase the residual neuromuscular blockade [4], [5], [6]. Sugammadex, a cyclodextrin, is thought to be an antagonist - a selective relaxant-binding agent (SRBA), which reverses the aminosteroid group like rocuronium through an encapsulating mechanism to form a rigid sugammadex-rocuronium complex and then excreted in urine. Sugammadex has some advantages such as allowing reversal of profound blockade, rapid onset as well as no muscarinic side effects and no atropine combination requirement [7], [8], [9]. Dose of sugammadex and neostigmin chosen for reversal are based on TOF value [10]. In the world, there are several studies demonstrating the safety and efficacy of sugammadex and comparing the neuromuscular blockade reversal effect of sugammadex versus that of neostigmine.

An analyzed randomized controlled trial on the reversal function of sugammadex and neostigmine conducted by M.Carron et al in 2016 shows that in comparison to neostigmine, sugammadex reverses the neuromuscular block faster ($p < 0.0001$), has a stronger relation to TOF during extubation period, and decreases risk of recurarization after endotracheal tube withdrawing (OR = 0.05, CI 95%: 0.01 – 0.43; $p = 0.0068$). Sugammasex also has a significant relation to reduction of all complications ($p < 0.00016$) [1].

In Vietnam, there have been rare studies comparing the reversal effectiveness and side effects between sugammadex and the combination of neostigmine and atropine, especially on patients experiencing living donor nephrectomy. For that reason, we conducted this study to evaluate the differences in efficacy, undesirable effects between sugammadex 2 mg/kg and the combination of neostigmine and atropine at different doses and atropine sulfate in the living kidney donors.

Materials and Methods

Criteria for selection

- Age 18-60 years old, ASA I - III.
- Laparocopic donor nephrectomy.
- General anesthesia.
- Normal results of complete blood count, physiochemical tests, echocardiogram.
- Surgery duration > 60 minutes.

Criteria for exclusion

- Patient's disagreement to participate in study.
- Patients did not meet selection requirement.
- Patients who have renal or hepatic dysfunction.
- Patients having history of malignant hyperthermia or neuromuscual diseases.
- Patients with difficult airway.
- Prolonged diabetes patients with complication, neurological complication.
- Patients with BMI < 17 kg/m^2 or > 30 kg/m^2.
- Patients taking medications interacting with neuromuscular relaxants such as anticonvulsants, magnesium, and some antibiotics.
- Patients having allergy to opioid, NMBA, anesthetics.

Patients rejected from study

- Patients had allergy to medications, or anaphylaxis shock to anesthetics.
- Patients with surgical complications.
- Patients had postoperative severe condition which required treatment in ICU and mechanical ventilation > 24h.

Study methods

This study was a single blinded randomized controlled trial. Patients were allocated to 2 groups:

- Group I (SUGA) : Sugammadex 2 mg/kg were used to reverse NMBA.
- Group II (NEO/ATR): Different doses of neostigmine combined with atropine sulfate were used

The study was perfomed at Center of Anestheisa and Surgical intensive care, Viet Duc hospital from March to September of 2018. Convenience sampling with 35 patients in each group, and patients were ramdomly assigned into group SUGA or NEO/ ATR by ballot when they were in operation center.

Research process

Preparing patients included: Anesthesia examination, explaining to patients about anesthesia

method and research. After ASA standard monitoring was applied, induction was carried out with fentanyl 1.5 mcg/kg, propofol 2 mg/kg, rocoronium 0.6 mg/kg, then an endotracheal tube was intubated when the TOF was 0. Anesthesia was maintained by sevoflurane at the MAC of 1-1.5 and intraoperative TOF was observed, additional dose of rocuronium (0.15 mg/kg) was utilised when TOF count reached 2 out of 4. TOF value after surgery was recorded right after operation. The patients were reversed neuromuscular blockade when TOF count > 0: Group SUGA (n = 35) was reversed with sugammadex 2 mg/kg, group NEO/ATR (n = 35) was reversed with neostigmine at different doses based on TOF Scan which were 60; 50; 40; 30 mcg/kg to TOF value of 1;2;3;4 respectively [10] and neostigmine was combined with atropine at ratio of 3:1. The TOF values were recorded at the time of blockade reversal, after reversal every minute until 20 minutes and then at 30 minutes and 60 minutes. Endotracheal tube extubation was performed when patients met criteria of full awareness; heart rate < 100 bpm; systolic blood pressure > 90mmHg; respiratory rate 10-12 rates/min; SpO2 > 95%; body temperature >35.5^{0}C; TOF ratio ≥ 0.9 [11].

Analyzing data

The research data was analyzed and processed by SPSS 20.0 software. Quantitative variables were described in average and standard deviations. Qualitative variables were described in percentage (%). Chi square, T-test with 95% confidence, the difference was statistically significant when p <0.05.

Results

Common features of study groups

Of 70 patients assessed for eligibility, 35 patients were randomly allocated to two groups. There are no significant differences in baseline characteristics between 2 groups such as gender, age, BMI, hemoglobin concentration or serum electrolyte (Table 1).

Table 1: Patients demographic

Features	Group SUGA (n = 35)	Group NEO/ATR (n = 35)	P
Gender (male/female)	28/7	25/10	
Age (yrs): X ± SD	33 ± 7.37	31.83 ± 7.70	
BMI (kg/m²): X ± SD	21.86 ± 3.39	20.77 ± 2.32	
Hemoglobin: X ± SD	147.09 ± 9.81	147.17 ± 9.82	
Serum sodium (mmol/l): X ± SD	136.8 ± 1.98	136.66 ± 2.04	> 0.05
Serum potassium (mmol/l): X ± SD	3.88 ± 0.33	3.82 ± 0.30	
Serum calcium (mmol/l): X ± SD	2.30 ± 0.12	2.27 ± 0.11	
Serum creatinine (mmol/l): X ± SD	80.69 ± 14.20	81.66 ± 13.28	
Serum albumin (mmol/l): X ± SD	45.49 ± 2.67	44.58 ±2.58	
Blood loss (ml): X ± SD	114.29 ± 53.64	118.57 ± 40.38	

In our study, the rate of right kidney collection in group I was 60% and group II was 71.4%, there was no significant difference in the two groups (p> 0.05). The average anesthesia time of group I was 178.43 ± 36.54 minutes and group II was 171.43 ± 25.71 minutes, this time of the two groups did not differ significantly (p > 0.05). The average amount of blood loss between the two groups was not statistically significant with p > 0.05.

Anesthesia time and medication used in surgery

The total amount of propofol, fentanyl and sevoflurane used to induce and maintain anesthesia in the two groups were matching. The average rocuronium used in group I, II are the same which are 76.15 ± 17.78 mg and 71.20 ± 11.53 respectively. There was no difference in the total amount of rocuronium used as well as the quantity of rocuronium in the last 45 minutes of the operation and the repeated dose of rocuronium of the two groups (p> 0.05) (Table 2).

Table 2: Characteristics of drugs used in surgery

Group / Index	Group I (n = 35)	Group II (n = 35)	P
Fentanyl (mg)	0.21 ± 0.05	0.9 ± 0.04	
Propofol (mg)	125.71 ± 24.53	117.74 ± 18.43	
Sevoflurane (ml)	29.69 ± 6.69	28.14 ± 6.95	> 0.05
Rocuronium (mg)	76.15 ± 17.78	71.20 ± 11.53	
Rocuronium used in the last 45 min (mg)	9.0 ± 2.56	8.17 ± 2.68	
Times of repeating rocuronium	3.14 ± 0.73	3.17 ± 0.66	

Postoperative indexes

Patients were monitored at the end of surgery the temperature; MAC (Minimum aveolar concentration) and Et Sevoflurane (expiratory sevoflurane concentration). The temperature at the end of surgery in group SUGA was 36.42 ± 0.37^{0}C which is 36.41 ± 0.37^{0}C in group NEO/ATR. MAC got to 0.44 ± 0.07 and 0.43 ± 0.06 in group SUGA and NEO/ATR. The expiratoty Sevoflurane concentration of group SUGA is 0.5 ± 0.06 comparing to 0.47 ± 0.07 in group NEO/ATR. All showed no differences with p value > 0.05

Rate of TOF ≥ 0.7 and ≥ 0.9 after reversal of NMBAs over time

After 2 minutes of reversal: 94.3% of patients in group SUGA achieved TOF ≥ 0.7, while only 31.4% of patients achieved TOF ≥ 0.7 in group NEO/ATR, the variance was statistically substantial with p <0.05. After 4 minutes of reversal: 100% patients of group SUGA achieved TOF ≥ 0.7, which statistically significantly distinguished from 65.7% in group NEO/ATR with p < 0.05. After 7 minutes of reversal: 100% of patients in both study groups achieved TOF ≥ 0.9 (Figure 1).

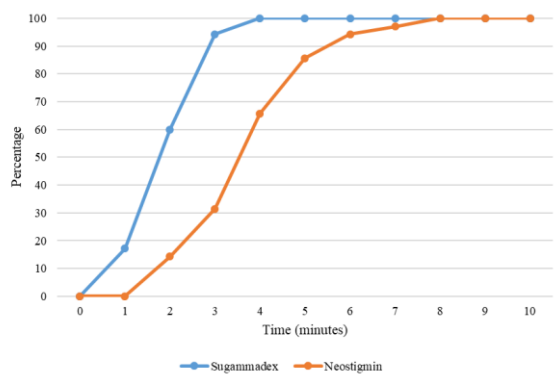

Figure 1: The ratio reaches TOF 0.7 after reversal of NMBAs over time

After 3 minutes of reversal: group SUGA had 91.4% patients achieving TOF ≥ 0.9, contrasting with only 28.6% patients in group NEO/ATR and the difference was also statistically significant with p <0.05 . After 5 minutes of reversal: 100% patients in group I gained TOF ≥ 0.9, whereas in group II only 40% of patients obtained TOF ≥ 0.9 and the mismatch was also substantial with p <0.05. After 10 minutes of reversal: 100% patients in the two study groups acquired TOF ≥ 0.9 (Figure 2).

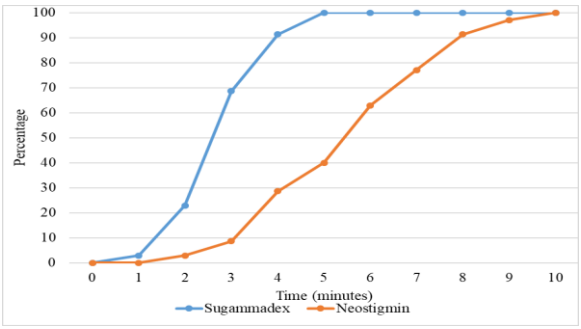

Figure 2: The ratio reaches TOF ≥ 0.9 after reversal of NMBAs over time

Time to TOF ≥ 0.7; ≥ 0.9 and time to extubation

Time from starting reversing neuromuscular block to reach TOF ≥ 0.7 and TOF ≥ 0.9 in group I is faster signigicantly than the one in group II with p <0.05 (Table 3).

Table 3: Time to TOF ≥ 0.7; ≥ 0.9 and time to extubation

Group Time (second)	Group I (n = 35)	Group II (n = 35)	p
Time to TOF ≥ 0.7			
$\bar{X}$ ± SD	107.57 ± 54.87	215.57 ± 81.76	<0.05
Min – Max	30-300	75-435	
Time to TOF ≥ 0.9			
$\bar{X}$ ± SD	155.29 ± 62.51	313.29 ± 105.77	<0.05
Min – Max	45-360	120-570	
Time to extubation after NMBAs reveral	249.43 ± 81.75	456.29 ± 146.45	<0.05

Side effects of NMBAs reversal

Sugammadex did not cause changes in the heart rate and blood pressure as well as other side effects, while heart rate was recorded to decrease in the neostigmine and atropine group. There were 2.9% patients experiencing xerostomia, 2.9% patients undergoing headaches in sugammadex group. In group used combination of neostigmine and atropine: 28.5% patients had bradycardia; 25.7% increased phlegm production; 11.4% suffered xerostomia; 11.4% had headaches; 22.9% represented nausea. Among them, bradycardia, increased secretion of mucus, and nausea were statistically significantly different from group S with p <0.05. All patients in both groups had neither arrhythmias nor bronchospasm. 28.5% patients with bradycardia were sinus one (Table 4).

Table 4: Side effects

Group Side effect	Group I n (%)	Group II n (%)	P
Nausea	1(2.9)	8(22.9)	<0.05
Bradycardia	0	10(28.5)	<0.05
Increased phlegm production	0	9(25.7)	<0.05
Xerostomia	1(2.9)	4(11.4)	>0.05
Headache	1(2.9)	4(11.4)	>0.05

Discussion

The patients in the two study groups did not differ in terms of common characteristics: patient age, height, weight, BMI classification. As far as surgical type, perioperative used drugs, postoperative parameters, arterial blood gas of the two groups were concerned, there were not significant difference.

In the regard of the effect of neuromuscular blockade reversal agent, the results of the study showed that the group of patients receiving dose of 2 mg/kg sugamadex had a significantly faster recovery time of TOF compared with the patients receiving the combination of neostigmine and atropine at the ratio 3:1. The dose of sugammadex or neostigmine was adjusted according to TOF count value mearsured right after operation. In the study, time to start reversing neuromuscular blockade was when there was at least one twitch of TOF [12]. Acorrding to Hristovska's study, time to get TOF 0.9 when reversed by sugammadex is significantly faster than that by neostigmine at every different dose in patients who were maintained by either intravenous anesthetics or volatile agents during anesthesia [13]. After 3 minutes of sugammadex injection, 91.4% patients achieved TOF ≥ 0.9, whereas only 28.6% of patients obtained TOF ≥ 0.9 after 4 minutes of neostigmine injection, this difference was statistically significant with p <0.05. After 5 minutes of reversal, 100% patients of group I achieved TOF ≥ 0.9, while the figure for group 2 was 40%.

Neostigmine is a neuromuscular blockade

reversal agent that has been used for a long time and is clinically popular. The drug causes inactivation of acetyl cholinesterase through the irreversible carbamylation process. Neostigmine cannot resolve the muscle relaxant when the neuromuscular blockade is deep. Neostigmine's neuromuscular blockade reversal effect usually initiates in about 1-2 minutes and reaches maximum within 6-10 minutes, so it takes about 10 minutes for neostigmine to fully perform [14],[15]. In our study, the group treated with neostigmine combined with atropine had an average recovery time of TOF ≥ 0.7 was 215.57 ± 81.76 seconds, the slowest recovery time of TOF ≥ 0.7 was 435 seconds; the average recovery time of TOF ≥ 0.9 was 313.29 ± 105.77 seconds, the latest was after 570 seconds. In this group, the number of patients who received neostigmine when there was 1-2-3-4 stimulating response (TOF 1/4) was 4-13-7-11 respectively. In our study, the time to achieve TOF ≥ 0.9 was shorter than that of Manfred, Blobner [16], and Tiffany Woo [17], Cheong Ho [18]; in the study of Blobner and plus, the average recovery time of TOF ≥ 0.7 is 7.2 minutes, recovery of TOF ≥ 0.9 is 18.6 minutes. This difference may be due to the fact that Blobner and Woo administered reversal agent at the time of TOF =2/4, while we injected reversal agent at times of different TOF values. In our study, patients who recieved neuromuscular blockade reversal at the time of TOF=2/4 had average recovery time of TOF ≥ 0.7 and TOF ≥ 0.9 was 238.85 ± 80.89 seconds and 339.23 ± 115.80 seconds respectively. This result is longer than that of Wu Xinmin [19], this difference can be attributed to the fact that we used sevofluran for anaesthesia maintenance. Sevofluran has been shown to slow neostigmine's muscle relaxant recovery [20].

Sugammadex was approved for use in Europe in 2008 by the European, Pharmaceutical Authorities. In 2015, sugammadex was accepted by the American Pharmaceutical Society, and now it has been used in 70 countries [21]. With the mechanism of direct action through rapid chemical interaction, sugammadex forms a stable complex with non-depolarizing muscle relaxants. Sugammadex 16 mg/kg can be used in case of rescue when intubation is not possible after 1.2 mg/kg rocuronium injected, TOF achieved the value of ≥ 0.9 after 2 - 3 minutes [22]. In our study, we used dose of 2mg/kg sugammadex for all TOF count values. The results showed that after sugammadex injection, average time of TOF achieved ≥ 0.7 was 107.57 ± 54.87 seconds; and TOF ≥ 0.9 was 155.29 ± 62.51 seconds. The fastest time to recover TOF ≥ 0.7 was 0.30; and the fastest time to reach TOF ≥ 0.9 was 45 seconds. In this group, the number of patients receiving neuromuscular blockade reversal agent at the moment of TOF count = 1-2-3-4 stimulus response was 15-14-5-1 respectively. In patients who were reversed at TOF score of 2 stimuli, the average recovery time of TOF ≥ 0.7 and TOF ≥ 0.9 was 84.64 ± 24.67 seconds and 136.43 ± 32.10 seconds, correspondingly. Our results was similar to other studies, which showed that sugammadex can quickly dissolves rocuronium molecule: the average time of TOF ≥ 0.9 was 155.29 seconds; after 3 minutes, 91.4% patients recovered TOF ≥ 0.9; after 5 minutes, 100% patients recover TOF ≥ 0.9.

In the regard of undesirable effects: The rate of patients with bradycardia, nausea, and increased secretion of group 2 was significantly higher than group I, this result is shown in Table 3.7. Group 2 had 10 patients with heart rate <50 beats/minute accounting for 28.5%, 9 patients had increased sputum secretion mounting to 25.7%, 4 patients with dry mouth and 4 patients with headache occupying 11.4% and 8 patients (22.9%) had nausea. On the contrary, Group I had only 1 patient with headache, 1 patient with nausea, 1 patient with xerostomia, each accounting for 2.9%. In our study, we did not see any patients with allergies, dizziness, hypotension ... after reversal. Nausea and vomiting are common concern after surgery. There are many factors that are thought to be related to postoperative vomiting and nausea such as laparoscopic surgery with pneumoperitoneum, usage of atropine for neuromuscular blockade reversal compared to patients without postoperative reversal (68% vs. 32%) [23]. In our study, we had 8 patients (22.9%) with nausea in group II, including 2 patients had severe nausea, this patient was given metoclopramide 10 mg intravenously, and responded well to treatment. In the group of using sugammadex for neuromuscular blockade reversal there was 1 patients (2.9%) who suffered from nausea and vomiting after surgery. Some other studies recorded the rate of postoperative nausea and vomiting in patients with neuromuscular blockade reversal by sugammadex: Blobner 4%, Tiffany Woo 7%, Yazar 5%; [16], [17], [22]. We did not document any patients with bronchospasm after extubation. But 25.7% patients in group II increased sputum production, whilst in group I there was no patient with this symtom. Emine Yazar noted that 2 patients (3.4%) had bronchospasm after neuromuscular blockade reversal with sugammadex, but the author did not describe these two cases [22]. 1 patient (2.9%) in group I and 4 patients (11.4%) in group II had headache after surgery, there was no difference between the two groups, p > 0.05. In Tiffany Woo's study, the headache rate of neuromuscular blockade reversal with sugammadex and neostigmine was 12% and 15% respectively [11]. The rate of dry mouth in group II was 11.4%; group I is 2.9%. Xerostomia in patients receiving neuromuscular blockade reversal with neostigmine are associated with the use of combined atropine. In addition, the evaluation of this symptom is also difficult, because the patient must fast to prepare for surgery, so the patient had a feeling of dry mouth before. In the Blobner study, the rate of dry mouth was 6% in both groups used neostigmine and sugammadex [16].

The objects of our study were patients who experienced laparoscopic nephrectomy, so it is necessary to monitor and evaluate plasma creatinine level before and after 24 hour of surgery which were shown to be not significantly different between the two groups.

In conclusion, Sugammadex has better neuromuscular block reversal effects than neostigmine. Recovery time reaching TOF ≥ 0.9 of group using sugammadex 2mg/kg is significantly faster than the one of group using neostigmine combined with atropine at the rate of 3:1 following TOF count. Sugammadex also reduces side effects induced by neuromuscular blockade reversal agents in living donor nephrectomy surgery.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study has been approved by Science and Medical Ethics Review Board of Viet Duc hospital and Committee of Science and Ethics of Hanoi Medical University.

Informed consent

The patient's family was fully explained about the research process and agreed to participate. Risk patients had been excluded to minimize the unwanted effects of monitoring methods. Information about medical records and images were kept confidentially. Informed consents were obtained from the patients included in the study.

Acknowledgement

We would like to send our sincere thanks to all patients and their families for their believes, consensus to participate in and help us complete this study. We are also grateful to all staffs from Center of anesthesia and surgical intensive care, Center of organ transplantation, Department of renal diseases and hemodialysis of Viet Duc Hospital for facilitating and supporting this study.

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