Comparison of postoperative coagulation profiles and outcome for sugammadex versus pyridostigmine in 992 living donors after living-donor hepatectomy

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Abstract
Donor safety is the major concern in living donor liver transplantation, although hepatic resection may be associated with postoperative coagulopathy. Recently, the use of sugammadex has been gradually increased, but sugammadex is known to prolong prothrombin time (PT) and activated partial thromboplastin time (aPTT). We compared the postoperative coagulation profiles and outcomes of sugammadex versus pyridostigmine group in donors receiving living donor hepatectomy.

Consecutive donor hepatectomy performed between September 2013 and August 2016 was retrospectively analyzed. For reversal of rocuronium-induced neuromuscular blockade, donors received sugammadex 4 mg/kg or pyridostigmine 0.25 mg/kg. The primary endpoints were laboratory findings (PT, aPTT, hemoglobin, platelet count) and clinically evaluated postoperative bleeding (relaparotomy for bleeding, cumulative volume collected in drains). Secondary outcomes were anesthesia time, postoperative hospital day.

Of 992 donors, 383 treated with sugammadex and 609 treated with pyridostigmine for the reversal of neuromuscular blockade. There were no significant differences between both groups for drop in hemoglobin and platelet, prolongation in PT, aPTT, and the amount of 24-h drain volume. Bleeding events within 24 h were reported in 2 (0.3%) for pyridostigmine group and 0 (0%) for sugammadex group (P = 0.262). Anesthesia time was significantly longer in pyridostigmine group than that in sugammadex group (438.8 ± 71.4 vs. 421.3 ± 62.3, P < 0.001). Postoperative hospital stay was significantly longer in pyridostigmine group than that in sugammadex group (P = 0.002).

Sugammadex 4 mg/kg was not associated with increased bleeding tendency, but associated with reduced anesthesia time and hospital stay. Therefore, sugammadex may be safely used and will decrease morbidity in donor undergoing living-donor hepatectomy.

Abbreviations: aPTT = activated partial thromboplastin time, NMB = neuromuscular blockade, PT = prothrombin time.

Keywords: coagulation abnormality, living liver donor, postoperative bleeding, sugammadex

1. Introduction
Donor safety is the major concern in living donor liver transplantation\textsuperscript{[1]} Maximal care should be taken not to cause any postoperative complications, because living liver donors are healthy individuals. However, donor hepatectomy is frequently associated with postoperative coagulation abnormality as they undergo major hepatectomy in which more than half of the liver volume is usually resected\textsuperscript{[2–4]}. Although the clinical significance of posthepatectomy coagulation abnormality is still less clear, there are concerns that it may lead to complications such as postoperative intra-abdominal bleeding or relaparotomy\textsuperscript{[2]}

Sugammadex (Bridion; MSD, Oss, The Netherlands) is a selective relaxant-binding agent which may replace the conventional reversal agents of neuromuscular blockade (NMB). During last decade, the use of sugammadex has been rapidly increased, as it has been shown to improve surgical conditions\textsuperscript{[5,6]} and postoperative outcomes\textsuperscript{[7,8]} with its ability to reverse even profound NMB effectively\textsuperscript{[9]}. Nevertheless, several reports advocated that sugammadex may be associated with longer clotting time and higher amount of postoperative bleeding\textsuperscript{[10–12]}. Nonetheless, no safety or clinical effect data have been published thus far on sugammadex in living liver donors, although these coagulation abnormalities have the potential to increase the risk of postoperative bleeding. In this...
study, we compared the postoperative coagulation profiles and outcomes of sugammadex versus pyridostigmine in donors receiving living donor hepatectomy.

2. Methods

Our institutional review board approved this retrospective observational study (No. 2015-1171). We reviewed clinical data of the 992 consecutive donors who underwent donor hepatectomy for living donor liver transplantation between September 2013 and August 2016. We collected patient’s baseline characteristics, intraoperative variables, and postoperative variables using our institutions record system (Asan Medical Center Information System Electronic Medical Records). Baseline characteristics included age, sex, and body mass index. Both preoperative and immediate postoperative laboratory variables were collected, which included hemoglobin, platelet, PT, aPTT, total bilirubin, albumin, and creatinine. Intraoperative variables were graft volume, volume of infused fluids, urine output, and operation time. Amount of bleeding in the surgical drains during 24 h after surgery was collected. Postoperative hospital day, admission to the intensive care unit, and need of relaparotomy for bleeding control were noted.

Induction of anesthesia was performed using 4 to 5 mg/kg thiopental sodium, 1 to 2 μg/kg fentanyl, and 0.6 mg/kg rocuronium. Intraoperative anesthetic management was followed our institutional protocol for donor hepatectomy, which has been previously described in detail. Before graft harvest, 5000 IU of intravenous heparin was administered and reversed with 50 mg of protamine immediately after graft harvest. At the end of the surgery, either one of the reversal agents (sugammadex or pyridostigmine) was administered after confirmation of over 2 twitch responses on the train-of-4 stimulation. Sugammadex was given in dose of 4 mg/kg, and pyridostigmine was given in dose of 0.25 mg/kg with glycopyrrolate 0.01 mg/kg. In cases when adequate reversal (train-of-4 ratio > 0.9) was not achieved with pyridostigmine within 10 min, additional dose of sugammadex 4 mg/kg was administered. All patients were extubated after reaching train-of-4 ratio 0.9.

Surgical management also followed our institution’s standardized protocol. Briefly, through J-shaped incision, cholecystectomy was performed. After identification of bile duct anatomy, hepatic parenchymal dissection was performed using cavitron ultrasonic suction aspirator (CUSA Excel, Valleylab Inc, Boulder, CO). Various types of grafts were harvested including (extended) right, right posterior, left, left plus caudate, and (extended) left lateral lobes. Argon beam coagulator and fibrin sealants were used for hemostasis.

The primary outcome was changes of immediate postoperative PT and other laboratory variables compared with preoperative value. Secondary outcomes included amount of drain during first 24 h after surgery, need of relaparotomy for postoperative bleeding, admission to intensive care unit, and length of hospital stay. Variables are expressed as numbers and percentages, means ± standard deviation, or median with the interquartile range as appropriate. Between group comparison were performed using the chi-squared test or Fisher exact test for categorical variables, and the Student t test or Mann–Whitney U test for continuous variables as appropriate.

3. Results

Of 992 donors, 332 treated with sugammadex and 660 treated with pyridostigmine for the first trial of reversal of NMB. Of 660 donors with pyridostigmine, 51 (7.7%) failed to extubate at first attempt because of residual NMB, thus sugammadex was subsequently administered. Therefore, 383 were classified as sugammadex group and 609 were classified as pyridostigmine group. Table 1 demonstrated patient characteristics and preoperative laboratory data.

After the completion of donor hepatectomy, immediate postoperative PT was significantly increased in pyridostigmine (0.99 ± 0.05 to 1.20 ± 0.09, P < .0001) and sugammadex group (1.01 ± 0.05 to 1.22 ± 0.08, P < .0001) (Fig. 1). There were no significant differences between both groups for PT prolongation (0.20 ± 0.07 vs. 0.21 ± 0.07, P = .344). Table 2 demonstrated intraoperative and postoperative variables. Amount of drain during first 24 h after surgery was similar between the 2 groups (151.3 ± 101.6 vs. 169.2 ± 103.9, P = .107). Relaparotomy for bleeding control within 24 h was reported in 2 (0.3%) for pyridostigmine group and 0 (0%) for sugammadex group (P = .262).

Anesthesia time was significantly longer in pyridostigmine group than that in sugammadex group (438.8 ± 71.4 vs. 421.3 ± 81.0 h, P = .001).

![Figure 1. Changes in prothrombin time (INR) at baseline (blue spots) and immediately after the hepatectomy (red spots) in pyridostigmine and sugammadex groups.](image-url)

![Table 1. Patient characteristics and preoperative laboratory data.](table-url)
In fact, presumed anticoagulant effect of sugammadex, of PT and aPTT by 10% to 20% in preclinical in vivo and in vitro information stated that sugammadex could result in prolongation residual NMB or respiratory complication in any patients. causes for admission to intensive care unit were not related to pyridostigmine group (0.8%) admitted to intensive care unit. The P
than that in sugammadex group (11.7 ± 1.9, P<.001). When excluding patients who received both pyridostigmine and sugammadex due to residual NMB, time from the end of surgery to end of anesthesia was significantly longer in pyridostigmine group than sugammadex group (12 [8–16] min vs. 10.5 [7–15] min, P=.008). Postoperative hospital stay was significantly longer in pyridostigmine group than that in sugammadex group (11.7 ± 4.0 vs. 11.0 ± 1.9, P=.002). Three in sugammadex group (0.8%) and 5 patients in pyridostigmine group (0.8%) admitted to intensive care unit. The causes for admission to intensive care unit were not related to residual NMB or respiratory complication in any patients.

### 4. Discussion

Compared with pyridostigmine, use of 4 mg/kg of sugammadex in living liver donor did not affect PT prolongation, amount of blood drain volume, and incidence relaparotomy for bleeding control within 24 h after donor heparectomy. Anesthesia time and postoperative hospital stay were significantly shorter in sugammadex group than those in pyridostigmine care group. These results suggest sugammadex can be safely used in donor heparectomy despite transient coagulation abnormalities are frequently seen in living liver donors.

When sugammadex was first introduced, supplemented information stated that sugammadex could result in prolongation of PT and aPTT by 10% to 20% in preclinical in vivo and in vitro studies.[13] In fact, presumed anticoagulant effect of sugammadex, at least in part, was the reason for the US Food and Drug Administration not to approve sugammadex in 2008.[14] Clinical trials in healthy subjects showed transient aPTT and PTT prolongations after 4 and 16 mg/kg of sugammadex.[12,16]

Following clinical studies in surgical patients also reported the similar coagulation abnormalities.[10,11] Thus, according to the current drug supplementation, additional caution should be exercised when used in high-dose or in patients with high risk of bleeding.[17] Not only sugammadex may cause coagulation abnormality, but liver resection also causes PT prolongation because of consumptive or dilutional coagulopathy after hepatic resection. We hypothesized that even minor PT prolongation may be harmful to donors because the concurrence of 2 situations can aggravate coagulation abnormality in donors at a high risk of postoperative bleeding. As the donor safety should be of utmost priority, even a theoretical bleeding risk needs to be clarified. Our results demonstrate that treatment with 4 mg/kg of sugammadex was not associated with an increased bleeding risk in living liver donor as compared with pyridostigmine. This finding was robust insofar as it was observed across laboratory findings and various clinical endpoints of postoperative bleeding and blood loss. The average prolongation of PT (INR) was 0.21 for sugammadex versus 0.20 for the pyridostigmine group, showing that treatment with sugammadex did not result in a larger increase in PT compared with pyridostigmine.

Most of data on the effect of sugammadex on coagulation are limited to few plasmatic coagulation assay and platelet function testing, limiting the understanding this drug.[10,12,16,18] These studies suggested that effect of sugammadex on PT and aPTT was not related to platelet function or factor Xa activity.[16,18] According to a recent study by Dirkmann et al, its anticoagulant effect is rather seems to be an in vitro artifact caused by phospholipid-binding effect.[15] However, there are still

### Table 2

**Perioperative variables and postoperative outcomes.**

|                          | Pyridostigmine (n=609) | Sugammadex (n=383) | P   |
|--------------------------|------------------------|--------------------|-----|
|                          |                        |                    |     |
| **Intraoperative variables** |                        |                    |     |
| Graft volume, mL         | 683.4 ± 202.1          | 675.8 ± 185.7      | .706|
| Donor liver lobe type, right/left | 505/101               | 323/60             | .560|
| Crystalloid, mL          | 2662.2 ± 791.3         | 2627.9 ± 560.4     | .005|
| Colloid, mL              | 213.3 ± 81.2           | 206.9 ± 42.8       | .436|
| Urine output, mL         | 721.5 ± 371.1          | 652.3 ± 308.2      | .061|
| **Postoperative laboratory data** |                        |                    |     |
| Hemoglobin, mg/dL        | 12.8 ± 1.4             | 12.6 ± 1.4         | .168|
| Platelet, ×10^9/μL       | 198 ± 46               | 206 ± 47           | .006|
| PT, INR                  | 1.20 ± 0.09            | 1.22 ± 0.08        | <.001|
| Prolongation of PT, INR  | 0.20 ± 0.07            | 0.21 ± 0.07        | .344|
| aPTT, s                  | 27.1 ± 5.6             | 26.9 ± 4.1         | .679|
| Prolongation of aPTT, s  | 1.0 ± 5.3              | 1.4 ± 4.2          | .236|
| Total bilirubin, mg/dL   | 2.0 ± 0.6              | 1.9 ± 0.7          | .820|
| **Outcome variables**    |                        |                    |     |
| Relaparotomy for postoperative bleeding | 2 (0.3%) | 0 (0%) | .262|
| Drain volume during first 24h, mL | 151.3 ± 101.6 | 169.2 ± 103.9 | .107|
| Total anesthetic time     | 438 ± 71.4             | 421.3 ± 62.3       | <.001|
| Time from the end of surgery to end of anesthesia | 12 (8–16) | 11 (8–15) | .050|
| Hospital stay, d         | 11.7 ± 4.0             | 11.0 ± 1.9         | .002|
| Postoperative ICU admission | 5 (0.8%)               | 3 (0.8%)           | .948|
| Relaparotomy for postoperative bleeding | 2 (0.3%) | 0 (0%) | .262|

Values are expressed as mean ± standard deviation, median (interquartile range), or number (%).

*Only including patients who received sugammadex as sole agent (n=281).*
controversy about the relation between sugammadex and postoperative bleeding especially in high-risk patients. Regarding its clinical implication, no study has demonstrated evidence of increased bleeding risk after sugammadex use except one study.[11] Even the author of this study commented that increased bleeding that they found may associate with other uncontrolled factors rather than sugammadex. In line with previous studies, our study demonstrated that the amount of drain volume was similar in both sugammadex and pyridostigmine groups. The incidence of relaparotomy for postoperative bleeding was not different between the 2 groups. Actually, there was no case of relaparotomy in sugammadex group.

The key secondary objectives of current study were to compare short-term outcome between 2 groups. Many previous studies demonstrated that sugammadex reverses NMB 3 to 8 times faster than conventional reversal agent does.[19,20] In addition, sugammadex could reduce the incidence of residual NMB, thus may result in reduced early postoperative pulmonary complications.[7,23] Postoperative residual muscle relaxation is associated with an increased risk of morbidity and mortality.[23] Furthermore, the subjectively felt degree of paralysis constitutes a substantial contributor to postoperative emotional stress, especially those with enormous psychological strain, who are frequently encountered among living liver donors.[24] These psychological burden may have a negative influence on outcome.[23] Our data implicated that sugammadex obviously has clinical benefit in living liver donors. In our study, sugammadex use was associated with shorter duration of surgery and hospital stay, despite that ICU administration was similar in both groups. In addition, 7.7% of donors who treated with pyridostigmine failed to extubate at first attempt because of residual NMB, thus sugammadex was subsequently administered. We speculate that such ability of sugammadex may help to enhance patient’s safety after donor hepatectomy.

We speculate that the shorter duration of anesthesia could be explained as one of the advantages of sugammadex. In a study regarding fast track bariatric surgery, anesthesia time of patients using sugammadex and neostigmine were 95 ± 21 and 47.9 ± 6.4 min, respectively (P < .001).[24] In another study, sugammadex group showed shorter duration of anesthetic recovery time when compared to the conventional reversal agent (24.1 [21.9–26.5] min vs. 19.9 [18.1–21.8] min, P = .020). Our result was in accordance with those previous studies. In our study, the time from the end of the procedure to discharge of operation room was shorter in sugammadex group, although it was not statistically significant (12 [8–16] min vs. 11 [8–15] min for pyridostigmine group and sugammadex group, P = .500). When excluding patients who received both pyridostigmine and sugammadex due to residual NMB, the time for sugammadex group was 10.5 (7–15) min (n = 281, P = .008 for vs. pyridostigmine group). We speculate that it partly explains the shorter duration of anesthesia in sugammadex group. Another reason might be that sugammadex may allow the practitioners to maintain deeper NMB until the end of the surgery, thus it might improve surgical condition especially during the time of wound closure. Previous studies demonstrated that profound NMB may facilitate the surgical procedure and could shorten the duration of the surgery.[7,12,23] As sugammadex enables rapid and reliable reversal of NMB, a better surgical condition could be provided until the very end of the surgery. Regarding the hospital stay, the difference between the 2 groups was small (11.7 ± 4.0 vs. 11.0 ± 4.9 for pyridostigmine and sugammadex groups, P = .002), thus it might not have clinical significance. Moreover, considering that length of hospital stay can be influenced by various factors, it is hard to define 1 specific reason for it.

There are several limitations in our study. First, retrospective design of study is clearly inferior to a prospective randomized trial. Consequently, although the large number of donors analyzed provides strong statistical power, our results should be viewed in the context of the retrospective study design. Second, patient selection was solely dependent on attending anesthesiologist’s decision, thus it might be relatively biased. Actually, sex in both groups was significantly different, although this may not affect the result of study. Lastly, in our result, sugammadex group showed similar prolongation in PT compared with pyridostigmine group, and anticoagulant effect on PT was relatively smaller compared with previous reports.[10–12] It is probably because of the time gap between sugammadex use and blood sampling. While the effect of sugammadex on coagulation is known to be limited and transient (<1 h),[20] it took relatively longer time from sugammadex administration to blood sampling in our study (median 149 min).

In conclusion, sugammadex was not associated with increased bleeding tendency in donors at a high risk of postoperative coagulopathy. Meanwhile, donors in sugammadex group were associated with reduced anesthesia time and hospital stay. Therefore, we believe that sugammadex can be safely used and will decrease morbidity in donor undergoing living-donor hepatectomy.

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