European Journal of Therapeutics

DOI: 10.5152/eurjther.2021.21003

Original Article

Effect of Sugammadex on Coagulation Parameters in Cesarean Section Patients a Prospective Controlled Observational Study

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ABSTRACT

Objective: To evaluate, for the first time in the literature, the effect of sugammadex in elective C/S patients in terms of hemostatic parameters and postoperative bleeding.

Methods: Seventy-six patients enrolled for this observational prospective controlled study. Patients were divided into two groups according to anesthetic reversal agent: sugammadex (group I) vs neostigmin (group II). Intraoperative and postoperative amount of bleeding were recorded. At the end of the surgery, after administration of reversal agent, and at postoperative 30th minute, 1st, and 2nd hours, activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR) values were recorded. Postoperative Hct, Hgb, and Plt values at 6th and 24th hours of reversal agent administration were also recorded.

Results: Alterations in aPTT, PT, and INR values were similar between the groups ($P = .986, .549, .05$, respectively).

Conclusion: Sugammadex at 2 mg kg^{-1} in cesarean section patients has a similar effect on coagulation parameters compared to neostigmin. Further studies are needed particularly in patients under thromboprophylaxis.

Keywords: Cesarean section, coagulation, sugammadex, aPTT, neostigmin, postpartum bleeding

INTRODUCTION

Maintenance of pregnancy and fetal well-being depends on several changes in hemostatic system. However, these changes in pregnancy may also cause an increase in maternal hematological complications during pregnancy, delivery, and postpartum period.[1-4] Hemostasis comprises very complex mechanisms with several alterations in both coagulation and fibrinolytic systems. In normal pregnancy concentration of coagulation factors, V, VII, IX, XII, fibrinogen, and von Willebrand factors show a significant increase.[5-8]

On the other hand, factor XI level, which is the one of the key factors for thrombin formation, decreases in pregnancy. Levels of coagulation inhibitors also show alterations during pregnancy. Protein C and antithrombin remain at the same levels, while protein C inhibitors and free and total protein S increase during pregnancy. Fibrinolytic system function is also inhibited during pregnancy and returns its normal activity just after the delivery.[5] As a result of all of these alterations, pregnancy becomes a hypercoagulable state. This hypercoagulable state is one of the preventive mechanism for postpartum hemorrhage after the delivery. Because we know that postpartum hemorrhage is still an important maternal mortality and morbidity reason in both vaginal and cesarean section (C/S) delivery, proper functioning of this system is very important.

Due to increasing trend of cesarean delivery in whole world, anesthetic management of C/S is more in sight of the researchers. Although regional anesthesia is more recommended by the guidelines for C/S, general anesthesia is still widely used around the world. Intubation of pregnant women is one of major challenges because of the higher incidence of difficult intubation compared to normal population.[9] Recently, a newly introduced sugammadex has being used for the reversal of nondepolarizing neuromuscular blocking agents (rocuronium and vecuronium) in C/S patients. Sugammadex shows its effect by encapsulation of vecuronium and rocuronium.[10-13] Compared to other acetylcholinesterase inhibitors (neostigmine, etc.), sugammadex has better recovery and less residual blocking effect.[14] Also, several studies have been showed its applicability in C/S patients.[15-19] On the other hand, studies have been reported the alterations in hemostatic parameters as an

How to cite: Destegül E, Destegül D, Kocaöz F. Effect of Sugammadex on Coagulation Parameters in Cesarean Section Patients a Prospective Controlled Observational Study. *Eur J Ther* 2021; 27(4): 293-298.

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Received: January 7, 2021 • **Accepted:** March 12, 2021

effect of sugammadex.[20-22] These studies especially underlined the prolongation in activated partial thromboplastin time (aPTT) and prothrombin time (PT). However, its clinical consequences, in the context of postoperative bleeding, in different surgical patients are still unknown.

In this study, we aimed to evaluate, for the first time in the literature, the effect of sugammadex in the elective CS patients in terms of hemostatic parameters and postoperative bleeding.

METHODS

This observational prospective study was conducted at a university hospital. After obtaining Ethical Committee approval was obtained in 2019 from Niğde Ömer Halisdemir University Medical Faculty Ethics Committee, informed consents were taken from all participants. A total of 76 patients scheduled for elective C/S were included in this study. All the patients were in the ASA I-II (American Society of Anesthesiologists). Patients with pre-eclampsia, intrauterin growth retardation (IUGR), pregestational or gestational diabetes mellitus, multiple gestation, macrosomic fetus, known hematologic disorders, abnormal blood tests result in platelet (Plt) count, activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR), and patients receiving anticoagulant/antiaggregant drugs were excluded from the study cohort. General anesthesia indications were maternal refusal of, or inability to cooperate with, neuraxial anesthesia.

Patients were divided into two groups: sugammadex (group I, n = 39) and neostigmine (group II, n = 37). Assignment of patients into groups was done by two anesthesiologists (D.D. and F.K.) preoperatively according to ASA guideline. All C/S operations were performed by same physician (E.D.).

In the operating room, all patients were monitorized for heart rate, pulse oximeter, end-tidal carbon dioxide level, noninvasive arterial pressure, and neuromuscular block monitoring (train of four (TOF) Watch SX monitor; Organon, Dublin, Ireland). Following the administration of 2-2.5 mg kg^{-1} propofol and 0.6 mg kg^{-1} rocuronium, intubation was performed. Maintenance of anesthetic status of patients was achieved with sevoflurane 2%, 2 L oxygen + 2 L dry air with 0.8 mL kg^{-1} tidal volume. To keep end-tidal volume CO_2 level at 30-35 mmHg, frequency of respiration was adjusted as 12 min^{-1}. Paracetamol (Parol flacon 10 mg mL^{-1}, Mefar Chemistry, İstanbul, Turkey) infusion 1 g/100 mL was applied to all patients after the removal of placenta. The modified Misgav-Ladach technique was used as C/S method in all patients. After the cord clamping, all patients received 20 U oxytocin infusion with 1,000 mL saline solution. Intraoperative blood loss was calculated by measurements of blood-soaked pads and amount of blood in aspiration tube. At the end of the surgery, group I patients were applied 2 mg kg^{-1} sugammadex (Bridion® 200 mg/2 mL, N.V. Organon Kloosterstraa 6, Holland), and group II patients were applied 0.05 mg kg^{-1} neostigmine and 0.02 mg kg^{-1} atropine. When TOF $\geq$ 0.9, patients were extubated and transferred to postoperative recovery room. After the operation, in the postoperative obstetric unit, blood samples were taken for coagulation parameters at 30th minute, 1st, and 2nd hours of following the administration of sugammadex or neostigmine. Whole blood counts samples were also taken from all patients at postoperative 6th and 24th hours. Pad weights were measured to evaluate the blood loss at first 24 hours.

Main Points

- Sugammadex prolongs activated partial thromboplastin and prothrombin time, but the association between prolongation and effect on postoperative bleeding remains unknown in cesarean section patients.
- Sugammadex was evaluated, for the first time, in cesarean section patients, in terms of alterations in coagulation parameters and postoperative bleeding.
- In this study, we found that sugammadex is safe to use in cesarean section, because it did not cause an increase in activated partial thromboplastin and prothrombin time.

Statistical Analysis

The data were analyzed using IBM SPSS Corp.; Armonk, NY, USA. The alterations in aPTT, PT, INR, Hgb, Htc, and Plt values according to group and time were examined with generalized linear models (Wald Chi-square test). Demographic characteristics, intraoperative bleeding, and pad weight comparisons of groups were evaluated with independent t-test. The Mann–-Whitney U test was used to examine gravida, parity, and number of CS between the groups. *P* value of <.05 was considered statistically significant. Power analysis was performed using the G-power software (G-power v3.1.9.2, Universitat Kiel, Kiel, Germany). Post hoc power analysis demonstrated that we achieved a power of 0.83 with a 5% level of significance and a 0.60 effect size to use one-tailed two independent mains t-test.

Hemostatic Tests

Preoperative and postoperative aPTT and PT blood samples were taken into citrate-included tubes and centrifuged at 2,000 × *g* for 10 minutes at 4° C, and plasma samples were analyzed by original reagent on ERBA analyzer.

RESULTS

A total of 76 patients who met the criteria were included. Comparison of groups demographic data and amount of bleeding is shown in Table 1. There were no differences between the groups in terms of age, BMI, gravida, parity, and amount of intraoperative bleeding and duration of surgery. At the first 24 hours of postoperative period, mean pad weights of groups were significantly higher in group I (*P* = .037). aPTT, PT, and INR values were evaluated in terms of time, group, and group–time interaction effect. The group and time interaction had no significant effect on the aPTT and PT mean values (*P* = .986 and .549, respectively) (Table 2). Main effect of time on aPTT and PT was statistically significant within the groups themselves (*P* = .022 and <.001, respectively) (Table 2). But, upper or lower limit of aPTT, PT, and INR values did not exceed at any time of sugammadex administration (Table 3). Main effect of group and time on INR mean values showed no significant differences (*P* > .05). Also, the effect of group and time interaction on INR mean values was similar between the groups (*P* > .05) (Table 2). While the main effect of groups on Hgb and Htc values was not significant, the main effect of time on Hgb, Htc, and Plt values

Table 1. Comparison of Demographic and Operative Data between the Groups

	Sugammadex (n = 39)	Neostigmin (n = 37)	Total (n = 76)	*P*
Age (year)	27.9 ± 5.3	29.4 ± 5.2	28.6 ± 5.3	.217*
Height (cm)	163.6 ± 4.1	163.2 ± 6.1	163.4 ± 5.1	.757
Weight (kg)	77.5 ± 6.8	73.6 ± 10.5	75.6 ± 8.9	.062
BMI	28.9 ± 2.5	27.6 ± 3.5	28.3 ± 3.1	.056
Gravity, n	3 (1–6)	2 (1–5)	2 (1–6)	.199**
Parity, n	2 (0–5)	1 (0–4)	1 (0–5)	.251**
Number of C/S, n	2 (1–4)	2 (1–3)	2 (1–4)	.836**
Amount of intraoperative bleeding (mL)	513.6 ± 191.5	547.7 ± 203.7	530.2 ± 196.9	.454*
Ped weight (mg)	433.5 ± 150.7	365.9 ± 124.6	400.6 ± 141.8	**.037***

*Independent samples t test (mean ± SD).
**Mann–Whitney U test [median (min – max)].
Note: Statistically significant values are indicated in bold.

Table 2. Comparison of aPTT, PT, and INR Values between the Groups in Terms of Group and Time

	APTT*	PTZ*	INR*
Group	0.263	0.997	0.190
Time	**0.022**	**<0.001**	0.333
Group × time	0.986	0.549	0.396

*Generalized linear models *P* value.
Note: Statistically significant values are indicated in bold.

was significantly different between the groups ($P < .001$, <.001, and .020, respectively) (Table 4). The effect of group and time interaction on Hgb, Htc, and Plt was also similar between the groups ($P > .05$) (Table 4). Descriptive statistics and multiple comparison results of hemoglobin, Hct, and Plt values by group and time were shown in Table 5.

DISCUSSION

In this study, we found that coagulation parameters showed no significant differences after the administration of sugammadex at a dose of 2 mg kg^{-1} when compared to neostigmine. Also, postoperative hemoglobin, hematocrit, and platelet values were similar between the groups.

Literature about sugammadex is relatively new. The effect of sugammadex on coagulation parameters was documented with in vitro studies, which showed a limited and transient increase in both aPTT and PT values via the inhibition of factor Xa activity.[23] This effect was first observed at 10 minute after the administration and resolved within 60 minutes. For the last 10 years, several studies have been showed this effect with in vivo research. In 2013 and 2014, De Kam et al.[21,22] showed a transient and limited increase in aPTT and PT related to sugammadex use. However, this increment was not associated with more postoperative bleeding. Studies were randomized and double-blinded, sugammadex was administered at doses of 4 mg kg^{-1} or 16 mg kg^{-1} to patients, and also each patient was taking aspirin alone or enoxaparin and unfractioned heparin. In another study, Rahe-Meyer et al.[20] found similar results in patients with increased risk of bleeding because of concomitant use of thromboprophylaxis agent. They revealed a transient (<1 hour) and limited (<%8) rise in aPTT and PT. Also, their results were not accompanied by an arise in postoperative bleeding. In current study, we did not observe any increase in aPTT and PT. In the assessment of postoperative bleeding, hemoglobin, hematocrit, and platelet levels showed similar alteration between the groups. However, mean pad weights were significantly higher in sugammdex group. In 2015, Taş et al.[24] investigated the effect of sugammadex on coagulation parameters and postoperative bleeding in patients who had septoplasty surgery. They found no difference in terms of coagulation parameters, while the amount of postoperative bleeding was higher in sugammadex group. Their results were similar to ours, but they measured amount of postoperative bleeding by nasal tip dressing, which is more objective to accurately detect the amount of bleeding than our method. Also, the effect of sugammadex on Hgb and Htc values was similar compared to neostigmine administration in our study, which is more objective criteria to evaluate the amount of postoperative bleeding. One prospective observational study published in 2015 investigated the patients who underwent open abdominal cancer surgery.[25] In their study, cohort divided into three groups: neostigmine, sugammadex 2 mg kg^{-1}, and sugammadex 4 mg kg^{-1}. At the end of the study, they did not observe

Table 3. Descriptive Statistics and Multiple Comparison Results of APTT(sn), PTZ(sn), and INR Values by Group and Time

Group	Time	APTT	PTZ	INR
Sugammadex	Preoperative	26.5 ± 2.4	11.1 ± 0.8	0.969 ± 0.066
	Postoperative 30th minute	25.8 ± 2.2	11.4 ± 0.8	0.992 ± 0.071
	Postoperative 1st hour	25.4 ± 2.4	11.5 ± 1.1	1.006 ± 0.089
	Postoperative 2nd hour	25.7 ± 2.6	11.6 ± 1.0	1.004 ± 0.084
	Total	25.8 ± 2.4	11.4 ± 0.9	0.993 ± 0.078
Neostigmin	Preoperative	26.2 ± 2.2	10.9 ± 0.5	0.951 ± 0.042
	Postoperative 30th minute	25.6 ± 2.1	11.6 ± 0.8	1.265 ± 1.579
	Postoperative 1st hour	25.1 ± 2.2	11.6 ± 0.5	0.955 ± 0.225
	Postoperative 2nd hour	25.3 ± 2.6	11.6 ± 0.6	1.251 ± 1.472
	Total	25.5 ± 2.3	11.4 ± 0.7	1.105 ± 1.085
Total	Preoperative	26.3 ± 2.3[a]	11.0 ± 0.7[a]	0.960 ± 0.056
	Postoperative 30th minute	25.7 ± 2.2ab	11.5 ± 0.8b	1.125 ± 1.104
	Postoperative 1st hour	25.2 ± 2.3[b]	11.5 ± 0.8[b]	0.981 ± 0.170
	Postoperative 2nd hour	25.5 ± 2.6[b]	11.6 ± 0.8[b]	1.124 ± 1.029
	Total	25.7 ± 2.4	11.4 ± 0.8	1.048 ± 0.760

There is no difference between times with the same letter (a, b) in each parameter.

Table 4. Comparison of Hgb, Htc, and Plt Values by Group and Time

	Hemoglobin*	HTC*	PLT*
Group	0.714	0.575	**0.005**
Time	**<0.001**	**<0.001**	**0.020**
Group × time	0.963	0.754	0.922

*Generalized linear models *P* value.
Note: Statistically significant values are indicated in bold.

any significant difference between the groups in terms of coagulation parameters and postoperative hemoglobin concentrations. Relative weakness of this study is that they had small number of patients in neostigmine group (n = 11), which were 37 in our study.

To our knowledge, this is the first study in the literature that evaluated the effect of sugammadex in C/S patients in the context of coagulation parameters and postoperative bleeding. However, the effect of sugammadex on coagulation parameters only has been seen so far with doses of 4 mg kg^{-1} and 16 mg kg^{-1}.[26] Mean prolongations of aPTT and PT were both by 22%.[26] Our study was conducted with doses of 2 mg kg^{-1}, which is advised by ASA for C/S patients.

In conclusion, our prospective observational study demonstrated that sugammadex is not related to a significant increase in aPTT and PT or decrease in postoperative hemoglobin, hematocrit, and platelet levels. This study is the first one that investigated coagulation parameters and postoperative bleeding among C/S patients. But, further studies are needed to investigate the relation between the sugammadex and postcesarean patients particularly with patients who use thromboprophylaxis during the pregnancy.

Table 5. Descriptive Statistics and Multiple Comparison Results of Hgb (g dL^{-1}), Htc (%), and Plt Values by Group and Time

Group	Time	Hgb	Htc	Plt
Sugammadex	Preoperative	12.2 ± 1.4	37.2 ± 3.2	236,948.7 ± 67,050.2
	Postoperative 6 hours	10.9 ± 1.4	33.4 ± 3.8	214,256.4 ± 66,148.4
	Postoperative 24 hours	10.5 ± 1.3	32.6 ± 3.5	222,128.2 ± 59,198.2
	Total	11.2 ± 1.5	34.4 ± 4.0	224,444.4 ± 64,369.3
Neostigmin	Preoperative	12.4 ± 1.4	37.3 ± 3.4	219,405.4 ± 56,810.8
	Postoperative 6 hours	11.0 ± 1.5	33.2 ± 3.9	191,162.2 ± 50,417.4
	Postoperative 24 hours	10.6 ± 1.5	31.8 ± 3.7	197,324.3 ± 50,666.7
	Total	11.3 ± 1.7	34.1 ± 4.4	202,630.6 ± 53,634.6
Total	Preoperative	12.3 ± 1.4*	37.3 ± 3.3*	228,407.9 ± 62,489.5*
	Postoperative 6 hours	10.9 ± 1.4b	33.3 ± 3.8**	203,013.6 ± 59,767.2**
	Postoperative 24 hours	10.6 ± 1.4**	32.2 ± 3.6**	210,052.6 ± 56,245.4**
	Total	11.3 ± 1.6	34.3 ± 4.2	213,824.6 ± 60,255.4

There is no difference between times with the same letter *,**in each parameter.

Ethics Committee Approval: Ethical committee approval was received from the Niğde Ömer Halisdemir University (2019/34).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.D., D.D., F.K.; Design - E.D., D.D., F.K.; Data Collection and/or Processing - E.D., D.D., F.K.; Literature Search - E.D., D.D., F.K.; Writing Manuscript - E.D.; Critical Review - D.D., F.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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