



Fetal outcomes with and without the use of sugammadex in pregnant patients undergoing non-obstetric surgery: A multicenter retrospective study

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Background

■ Sugammadex, a modified gamma-cyclodextrin, provides rapid and reliable reversal of neuromuscular blockade by encapsulating steroidal neuromuscular blocking agents (NMBAs). According to the manufacturer of sugammadex, it can bind not only NMBAs but also other molecules, including progesterone, and may decrease the levels of unbound progesterone following administration.¹

■ Maintenance of progesterone levels throughout pregnancy, particularly in the first trimester, is known to be essential for the maintenance of pregnancy.² Progesterone withdrawal in studies with pregnant rats resulted in the termination of pregnancy.³ Despite the absence of corresponding evidence in humans, sugammadex exposure during early human pregnancy may theoretically cause progesterone withdrawal and result in stillbirth or miscarriage. Since clinical data on the effects of sugammadex on human fetal development and pregnancy maintenance are limited, the Society for Obstetric Anesthesia and Perinatology released a statement in 2019 advising avoidance of sugammadex usage in early pregnancy.⁴

■ We aimed to compare fetal outcomes between pregnant patients who received sugammadex and those who did not during non-obstetric surgery. On the basis of the results of previous clinical reports, we hypothesized that sugammadex administration to pregnant patients would not affect fetal outcomes and pregnancy maintenance.

Methods

■ IRB approval: #2580 the Saitama Medical Center Clinical Research Ethics Committee

■ Consent: Informed consent was waived, due to the study's retrospective design. (Opt Out)

■ Inclusion: Pregnant women who underwent non-obstetric surgery at three tertiary perinatal care centers from January 2013 to December 2020.

■ Data source: We retrospectively reviewed the medical charts and sent a postal survey to related delivery hospitals when the medical data stated below were not included in our charts.

■ Outcomes: Miscarriages and preterm births after the surgeries were investigated as the primary outcomes. The administration of sugammadex, procedures, anesthetic methods, surgical indications, maternal and pregnancy characteristics, duration of surgery and anesthesia, dose of NMBAs and neuromuscular block reversal agents, and the usage of train of four monitoring, obstetric outcomes after the surgeries, including gestational age at childbirth, delivery mode, birth weight, and neonatal abnormalities were investigated as exploratory outcomes.

■ Groups: We divided the pregnant women into those who underwent non-obstetric surgery under general anesthesia with sugammadex (GA with SGX group), and those who received general anesthesia without sugammadex (GA without SGX group), and non-obstetric surgery under neuraxial or local anesthesia only (NA/LA group).

■ Analysis: We compared the rates of miscarriage or preterm birth after surgery in the two groups: GA with SGX group and GA without SGX group. The same analyses were repeated between the two: GA with SGX group and without SGX group (NA/LA group plus GA without SGX group) and were repeated between GA and NA/LA. We also analyzed other fetal outcomes in the two groups: neonatal abnormalities and low birth weight for gestational age, defined as newborns whose birth weight was below the 10th percentile of the weight distribution that accounts for 90% of infants at the same fetal age.

■ Statistical methods:

Data are presented as means and standard deviations or median and Interquartile range for continuous variables and as numbers and percentages for categorical variables. Differences in patient demographic characteristics were compared using an unpaired t-test or Mann Whitney U test for continuous variables. Fisher's exact test was used to analyze categorical data. Intergroup differences in primary and secondary outcomes were analyzed using Fisher's exact test. Missing data were excluded from the analysis. Statistical significance was defined by P values less than 0.05. Statistical analyses were performed using SAS statistical software package (version 9.4; SAS Institute, Cary, NC, USA).

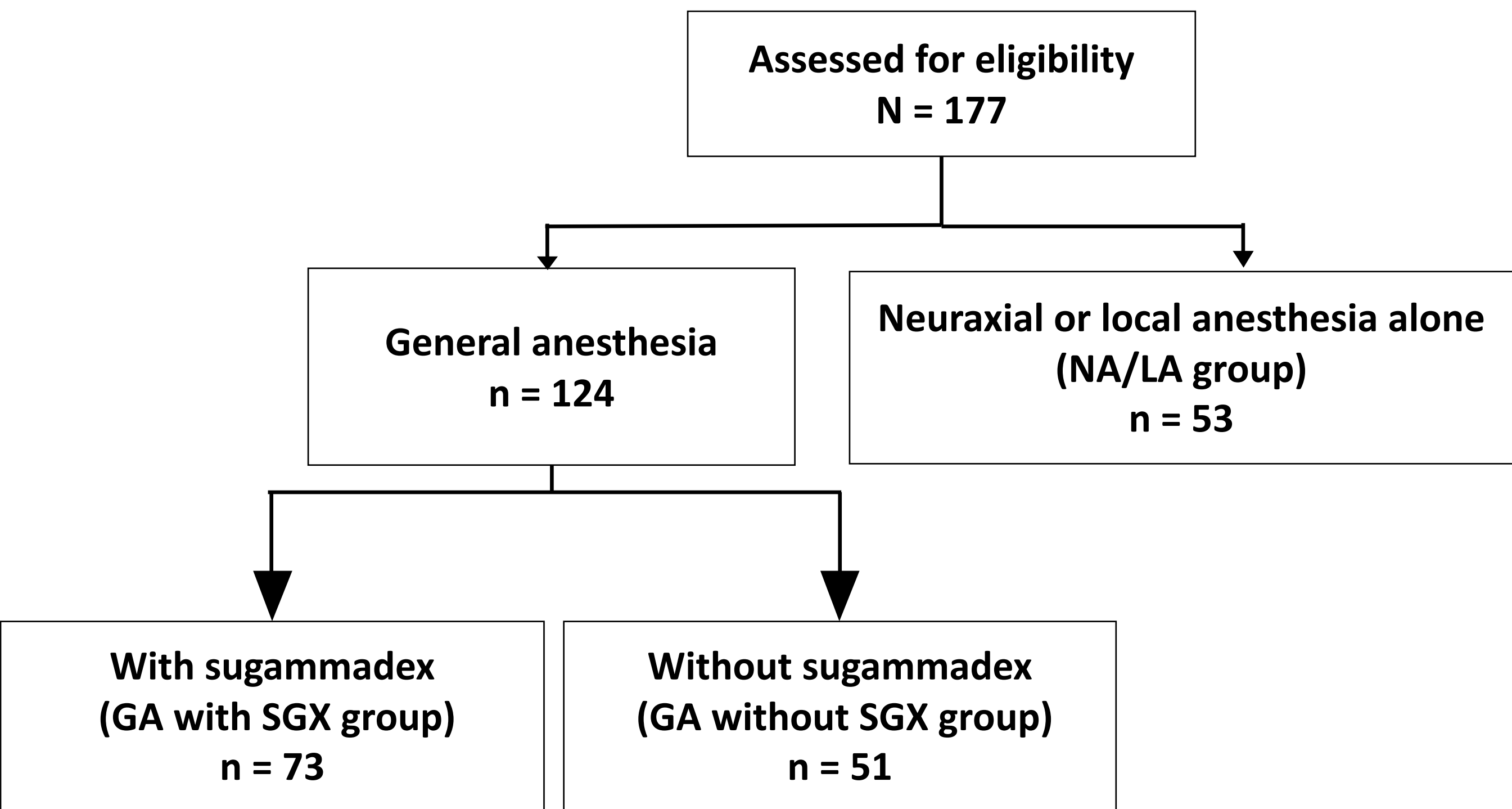


Figure 1. The constitution of the study cohort

Table 1. Demographic, surgical, and obstetric characteristics

	GA with SGX (n = 73)	GA without SGX (n = 51)	Total (N = 124)	P value
Indications, n (%)				0.1819 ¹
Ovarian cyst	59 (80.8)	47 (92.2)	106 (85.5)	
Appendicitis	7 (9.6)	1 (2.0)	8 (6.5)	
Fracture, dislocation	0 (0.0)	1 (2.0)	1 (0.8)	
Cholecystitis	2 (2.7)	0 (0.0)	2 (1.6)	
Breast cancer	4 (5.5)	1 (2.0)	5 (4.0)	
Others (subarachnoid hemorrhage, adrenal tumor)	1 (1.4)	1 (2.0)	2 (1.6)	
Laparoscopic surgery, n (%)				0.6065 ¹
No	12 (16.4)	6 (11.8)	18 (14.5)	
Yes	61 (83.6)	45 (88.2)	106 (85.5)	
Age				0.3247 ²
Mean (SD)	30.4 (5.7)	31.3 (4.6)	30.8 (5.3)	
Height (cm)				0.6624 ²
Mean (SD)	157.9 (5.0)	158.3 (5.4)	158.1 (5.2)	
Weight (kg)				0.4394 ²
Mean (SD)	55.1 (9.7)	53.8 (8.6)	54.6 (9.2)	
BMI				0.3115 ²
Mean (SD)	22.1 (3.6)	21.5 (3.2)	21.8 (3.5)	
Fetus number, n (%)				1.0000 ¹
Singleton	72 (98.6)	50 (98.0)	122 (98.4)	
Twins	1 (1.4)	1 (2.0)	2 (1.6)	
Pregnancy weeks at surgery (wk)				0.0062 ²
Mean (SD)	15.0 (5.1)	12.8 (3.1)	14.1 (4.5)	

	GA with SGX (n = 73)	GA without SGX (n = 51)	Total (N = 124)	P value
Duration of anesthesia (min)				0.5770 ²
Mean (SD)	149.0 (47.6)	144.2 (46.9)	147.0 (47.2)	
Duration of surgery (min)				0.2736 ²
Mean (SD)	101.4 (42.7)	93.1 (39.8)	98.0 (41.6)	4
Total rocuronium dose (mg)				<.0001 ³
Median (IQR)	70.0 (50.0, 80.0)	50.0 (30.0, 60.0)	57.5 (40.0, 70.0)	
Total suxamethonium dose (mg)				0.9643 ³
Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
Total sugammadex dose (mg)				<.0001 ³
Median (IQR)	200.0 (200.0, 200.0)	0 (0, 0)	175.0 (0, 200.0)	
Total neostigmine dose (mg)				<.0001 ³
Median (IQR)	0 (0, 0)	1.0 (0, 2.0)	0 (0, 0)	
Neuromuscular monitoring use n (%)				0.0806 ¹
No	72 (98.6)	46 (90.2)	118 (95.2)	
Yes	1 (1.4)	5 (9.8)	6 (4.8)	

¹Fisher's exact p-value; ²Equal-variance two-sample t-test; ³Wilcoxon rank sum p-value;

Results

Table 2. Miscarriage or preterm birth within four weeks following sugammadex administration

	GA with SGX (n = 73)	GA without SGX (n = 51)	Total (N = 124)	OR (95% CI)	P value
n (%)				0.34 (0.03 - 3.86)	0.5711 ¹
No	64 (98.5)	45 (95.7)	109 (97.3)		
Yes	1 (1.5)	2 (4.3)	3 (2.7)		
Missing	8	4	12		

	GA with SGX (n = 73)	GA without SGX +NA/LA (n = 104)	Total (N = 177)	OR (95% CI)	P value
n (%)				0.47 (0.05 to 4.59)	1.0000 ¹
No	64 (98.5)	96 (97.0)	160 (97.6)		
Yes	1 (1.5)	3 (3.0)	4 (2.4)		
Missing	8	5	13		

	GA (N = 124)	NA/LA (N = 53)	Total (N = 177)	OR (95% CI)	P value
n (%)				0.78 (0.08 to 7.63)	1.0000 ¹
No	109 (97.3)	51 (98.1)	160 (97.6)		
Yes	3 (2.7)	1 (1.9)	4 (2.4)		
Missing	12	1	13		

¹Fisher's exact p-value

Table 3. Neonatal outcomes at birth following sugammadex administration

	GA with SGX (n = 73)	GA without SGX (n = 51)	Total (N = 124)	OR (95% CI)	P value
Light for date, n(%)				0.69 (0.13 to 3.54)	0.6868 ¹
No	53 (94.6)	36 (92.3)	89 (93.7)		
Yes	3 (5.4)	3 (7.7)	6 (6.3)		
Data missing	17	12	29		
Abnormalities, n (%)				1.42 (0.25 to 8.06)	1.0000 ¹
No	58 (93.5)	35 (94.6)	93 (93.9)		
Yes	4 (6.5)	2 (5.4)	6 (6.1)		
Data missing	11	14	25		

¹Fisher's exact p-value

Discussions

■ An in vivo study in pregnant rats did not show a significant decrease in progesterone levels following a single dose of 30 mg·kg⁻¹ sugammadex in the first trimester of pregnancy.² In that study, all the rats completed pregnancy without stillbirth or miscarriage. One clinical study measured the levels of steroidal endogenous hormone following administration of 4 mg·kg⁻¹ sugammadex.⁷ In that study, the serum progesterone level did not show a significant decrease at 15 min and 4 h after sugammadex administration. These observations indicate that the effect of sugammadex on serum progesterone levels may be insignificant

■ A few case series describing the use of rocuronium and sugammadex in pregnant patients undergoing general anesthesia have been reported.^{5,6} The most extensive of these reports describes the use of sugammadex in 25 pregnant patients.⁵ In that study, four, 19, and two pregnant patients received sugammadex at the first, second, and third trimesters, respectively. In another report of 6 cases, 2 and 4 pregnant patients received sugammadex during non-obstetric surgery in the first and second trimesters, respectively.⁶ In both studies, pregnancy complications related to the administration of sugammadex were not reported..

■ In this study, one fetus in the GA with SGX group showed intrauterine fetal demise at 15 gestational weeks (2 weeks after sugammadex administration). Induction of delivery was conducted two days after the recognition of the demise, but the putative cause was umbilical cord stricture. As mentioned above, the clinical concern associated with sugammadex administration is a reduction in serum progesterone concentration, which could cause laboring. In this case, the fetal demise did not result in laboring without medical induction. Therefore, it is less likely that the reason for the demise was related to sugammadex administration.

Limitations

■ First, although this study included the largest population on the use of sugammadex in pregnant patients undergoing non-obstetric surgery, the number of cases in our study may not have been sufficient to draw definitive conclusions. However, we believe that it is important to share cases with similar circumstances to build evidence.

■ Second, most patients in our study did not undergo neuromuscular monitoring. Since different sugammadex doses are recommended depending on the depth of the neuromuscular block, the amount of free unbound sugammadex molecules remaining in circulation after reversal is unpredictable.

■ Third, none of the patients received high-dose sugammadex (e.g., 16 mg/kg) for rescue reversal. High-dose sugammadex may cause greater progesterone withdrawal and have a more noticeable effect on pregnancy maintenance in comparison with the usual reversal dose. But, it is a potentially life-saving strategy to manage “cannot ventilate cannot intubate” situations in pregnant patients.

Conclusion

This multicenter retrospective study demonstrated no difference in fetal outcomes between pregnant women undergoing non-obstetric surgery with and without sugammadex. Although miscarriages related to sugammadex administration were not observed in this study, further studies are required to draw conclusions regarding the safety of sugammadex in pregnant patients.

GA: general anesthesia, NA/LA: neuraxial anesthesia and/or local anesthesia, SGX: sugammadex, SD: standard deviation OR: odds ratio, CI: confidence interval

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