Original Article

Sugammadex and blood loss during cervical spine fusion surgery

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Abstract

Background and Aims: Sugammadex (SUG) has been associated with changes in coagulation studies. Most reports have concluded a lack of clinical significance based on surgical blood loss with SUG use at the end of surgery. Previous reports have not measured its use intraoperatively during ongoing blood loss. Our hypothesis was that the use of SUG intraoperatively may increase bleeding.

Material and Methods: This was a single site retrospective study. Inclusion criteria were patients undergoing a primary posterior cervical spine fusion, aged over 18 years, between July 2015 and June 2021. The primary outcomes compared were intraoperative estimated blood loss (EBL) and postoperative drain output (PDO) between patients receiving SUG, neostigmine (NEO) and no NMB reversal agent. The objective was to determine if there was a difference in primary endpoints between patients administered SUG, NEO or no paralytic reversal agent. Primary endpoints were compared using analysis of variance with a *P* value of 0.05 used to determine statistical significance. Groups were compared using the Chi-squared test, rank sum or student's *t* test. A logistic regression model was constructed to account for differences between the groups.

Results: There was no difference in median EBL or PDO between groups. The use of SUG was not associated with an increase in odds for >500 milliliters (ml) of EBL. Increasing duration of surgery and chronic kidney disease were both associated with an increased risk for EBL >500 ml.

Conclusion: Intraoperative use of SUG was not associated with increased bleeding. Any coagulation laboratory abnormalities previously noted did not appear to have an associated clinical significance.

Keywords: Neostigmine, neuromuscular blockade, spinal fusion, sugammadex, surgical blood loss

Introduction

Sugammadex (SUG) (Bridion®, Merck, Netherlands) can be administered for the reversal of neuromuscular blockade (NMB) with rocuronium (ROC).[1] Sugammadex may reverse NMB more rapidly with a possibly better side-effect profile than the classical reversal agent, neostigmine (NEO).[2,3] There have been reports of changes in coagulation studies shortly after the administration of SUG.[4–8] The clinical significance of the coagulation measurement abnormalities associated with SUG has been questioned. Most reports to date concluded a lack of clinical significance of the abnormalities based on surgical blood loss.[5–8] All of the studies dismissing a significant impact on blood loss involved the use of SUG at the end of a surgical procedure when hemostasis was presumably achieved, except one. Zhao *et al.*[8] Measured the effect of the intraoperative

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use of SUG during thyroidectomies. Blood loss was similar between groups in the report by Zhao *et al.*, but the amount of blood loss associated with a thyroidectomy limits the value of this conclusion.[9] The current literature related to the clinical impact of SUG on surgical blood loss is limited, particularly concerning its intraoperative use while bleeding may still be occurring.

During cervical spine surgery, patients commonly undergo monitoring of the spinal cord with motor evoked potentials (MEPs) or electromyography (EMG). There is a frequent need to reverse NMB intraoperatively while there may still be significant bleeding. As a result, any effect on coagulation ability from SUG may be more noticeable in this patient population. At our institution, we routinely perform posterior cervical spinal fusions. Our surgical team's preference is to perform a posterior fusion from the second cervical vertebrae to the second thoracic vertebrae (C2–T2). It is an operation where a moderate-to-significant amount of blood loss may be expected. We also routinely monitor spinal cord function. Our surgeons also uniformly place a drain which would allow us to measure the effect beyond the intraoperative period. We retrospectively examined these cases at our institution to assess for any possible increase in intraoperative or postoperative bleeding associated with the administration of SUG. If there is any impact from the previously noted, short-lived abnormality in coagulation studies, it may be apparent in intraoperative blood loss. The universal use of a drain would allow us to compare SUG to other treatments over a longer time period, when coagulation studies should have normalized after SUG. The objective of the current study was to compare primary endpoints between patients who received SUG, NEO, or no NMB reversal agent. The primary endpoints were the volume of blood loss during surgery and postoperative drain output. The secondary endpoint was the odds ratio for bleeding associated with the use of SUG, NEO or no reversal agent.

Material and Methods

We retrospectively analyzed charts of patients undergoing posterior C2–T2 spinal fusions after receiving institutional approval (approval number NCR213565). The requirement for written patient consent was waived. Inclusion criteria were patients, aged over 18 years, undergoing a C2–T2 posterior cervical fusion, between July 2015 and June 2021. Exclusion criteria were use of a NMB other than rocuronium or succinylcholine, missing values for intraoperative estimated blood loss (EBL) or total postoperative drain output (PDO) from the patient's chart, or the administration of both SUG and NEO for NMB reversal.

Standardized protocol: Our neurosurgical team used a standardized surgical approach for C2–T2 fusions. Anesthesia protocols were also standardized with respect to conditions for reversal of neuromuscular blockade. All patients were monitored intraoperatively using both motor and sensory evoked potentials as well as EMGs. During the initial dissection of muscle and soft tissue, residual paralysis after intubation was tolerated without intervention. Patients were administered a neuromuscular reversal agent if any residual paralysis was detected after soft tissue dissection was completed and prior to work on the spinal canal itself. Muscle paralysis was detected using EMG monitoring at both the gastrocnemius and adductor pollicis muscles bilaterally. The anesthesia provider was free to select the reversal agent, if one was indicated. Patients were not administered a reversal agent if full muscle strength was detected via EMG after soft tissue dissection was complete. As a result, any administration of NMB reversal agent was standardized to use at the same point in the operation for all patients. An initial dose of SUG, if chosen by the provider, was administered in a standard dose of 2 milligrams (mg) per kilogram. A repeat dose would be administered if residual muscle paralysis was still detected via EMG 10 minutes after the initial dose. EBL was determined by combining the amount captured by a Neptune suction machine (Stryker Corporation, Kalamazoo, Michigan) plus the estimated blood volume collected in sponges or on the drapes. Drains were left in place for three to four days until PDO was less than 50 milliliters (ml) in 12 hours. The only alteration of the protocol over the course of the period studied was a switch from using tranexamic acid (TXA), based on the surgeon's perception of intraoperative bleeding, to preemptive use in patients believed to be at high risk of bleeding (uremic patients or patients with preoperative coagulation abnormalities). To account for this change in protocol, we performed a regression analysis of the data once compiled.

Data extraction and analysis: We extracted the patient's age, weight, height, preoperative and postoperative laboratory studies (hematocrit (HCT), hemoglobin (HGB), platelet count (PLT), prothrombin time (PT), activated partial prothrombin time (aPTT), and creatinine), preoperative use of anticoagulants, administration of TXA, comorbid diseases at the time of surgery (hypertension (HTN), congestive heart failure (CHF), chronic kidney disease (CKD), use of dialysis, liver disease, or diabetes (DM)) from the patient's medical records. We also recorded the length of surgery in minutes, EBL, and PDO. Patients were divided into groups for comparison based on which NMB agent and which NMB reversal medication were used. The groups were as follows: those who received succinylcholine (SUC) without ROC or

NMB reversal, those who received ROC with reversal using SUG, those who received ROC with reversal using NEO, those who received ROC without any NMB reversal agent, and patients who did not receive a neuromuscular blocker or reversal agent. Patients who received SUC followed by ROC were categorized as having received ROC and then placed into a final group based on the reversal agent administered or lack thereof. The data was prepared using Microsoft Excel (Microsoft Corporation, Redmond, Washington) and analyzed using SigmaPlot version 14 (Systat Incorporated, San Jose, California). Groups were compared using the Chi-squared test, analysis of variance (ANOVA), student's *t* test, or Wilcoxon rank-sum test as appropriate. A *P* value of 0.05 was used to determine statistical significance. In a post hoc power analysis, assuming an alpha value of 0.05, our sample was sufficiently powered (0.983) to detect a difference of 100 ml (assuming a standard deviation of 100 ml) of blood loss between the SUG and NEO groups. Odds ratios (OR) for blood loss greater than 500 ml were calculated using the collected data points as independent variables in a logistic regression model.

Results

We identified 225 patients undergoing C2–T2 fusion surgery during the time period studied. There were 33 patients excluded because they were undergoing repeat cervical fusion surgery with a final total of 192 patients studied. All patients who met the inclusion criteria and did not meet the exclusion criteria were included in the analysis. The groups were similar in age, weight and gender ratio without any attempt to match the groups for comparison [Table 1]. Nearly all of the patients in the study were continuously administered a propofol infusion and nearly all received sevoflurane. The groups did not differ significantly in type of anesthesia. There was a difference in preoperative HCT and duration of surgery discovered using one-way ANOVA. There were not any outliers identified for either variable when using Dunn's correction for multiple pairwise comparisons. The five groups had significant outliers in two variables. Patients who received only ROC without reversal were administered TXA more frequently. There was also a higher rate of CKD among patients who received only SUC or no NMB. EBL was different between groups as determined by a one-way ANOVA, but there was not an outlier identified using Dunn's correction. The use of SUG was not associated with a change in OR for EBL >500 mL in a regression model controlling for covariates [Table 2]. Among patients receiving SUG, the average dose was 2.83 mg/kg (standard deviation of 0.98). The administration of TXA was associated with an increased OR for >500 mL of EBL.

Discussion

Patients who received SUG had a median EBL of 250 mL compared to 350 mL in the NEO group. We did not find an increase in PDO with SUG either. Our results suggest there was not a significant increase in bleeding with SUG. Sugammadex had been linked to short-lived, dose-dependent changes in coagulation studies. De Kam *et al*.[4] reported the effects of SUG on coagulation studies in healthy volunteer patients not receiving an NMB. De Kam *et al*.[4] described an increase in PT and aPTT with SUG compared with the placebo, which resolved within 60 minutes. The greatest change was seen in the highest dose group (16 mg SUG/kg). Rahe-Meyer *et al*.[5] studied the effect of SUG in a prospective, double blinded study of hip and knee surgery patients. Rahe-Meyer *et al*.[5] found a transient increase in PT and aPTT with a dose of 4 mg/kg of SUG. In opposition, Raft *et al*.[7] found no difference in PT or aPTT with 2 and 4 mg/kg doses in a prospective, observational study. Abnormalities in thromboelastography (TEG) have also been noted.[10–13] Chang *et al*.[10] measured the impact of SUG on TEG in a prospective, double blinded study. They described a difference in K times at 10 minutes between the SUG group and a group which received NEO, but K time in the SUG group was not different from the baseline value. In the Chang *et al*.[10] report, the K time in the NEO group decreased at 10 minutes compared to baseline, as opposed to the K time changing in the SUG group. Kang *et al*.[11] described an increase in R time with a 4 mg/kg SUG dose and a trend towards a greater R time in a 2 mg/kg dose group ($P = 0.06$). The nature of these laboratory abnormalities has been questioned. Dirkmann *et al*.[12] postulated that the abnormalities were the result of SUG binding to phospholipid testing reagents as opposed to a true alteration in coagulation.

Several authors had previously attempted to determine if the abnormalities in coagulation studies were clinically significant, but none used SUG intraoperatively during surgery with the potential for significant blood loss. Raft *et al*.[7] described a lack of difference in blood loss with SUG. Rahe-Meyer *et al*.[5] found no difference in surgical blood loss despite the transient change in coagulation studies they noted. In these reports, SUG was administered at the end of the surgery when hemostasis was presumably achieved. In contrast, Zhao *et al*.[8] compared SUG to NEO after intubation but prior to the end of thyroid surgery. Zhao *et al*. mentioned there was no difference in blood loss but they did not present their data. In opposition, Tas *et al*.[13] did find a statistically significant difference in blood loss after the administration of SUG. Tas *et al*. measured blood loss into nasal drip pads after septoplasties when SUG was administered at the

Table 1: A comparison of the five groups studied

Variable	Succinylcholine only	Rocuronium, no reversal	Rocuronium, neostigmine reversal	Rocuronium, sugammadex reversal	No NMB	*P*
Number of Patients	5	69	34	82	2	
Age in years	67 (67-85)	64 (56-70)	62 (55-69)	64 (55-68)	58 (39-68)	0.15
Weight (kg)	80.3 (73.3-99.8)	76.1 (65.7-91.3)	78.5 (65.8-93.0)	77.1 (68.0-89.8)	78.7 (64.8-98.4)	0.62
BMI	27.5 (25.2-31.7)	26.0 (22.9-31.7)	26.9 (23.4-30.3)	25.8 (23.4-29.2)	20.0 (16.7-23.3)	0.40
Male gender	60.0%	66.7%	62.2%	65.0%	36.4%	0.28
HCT	32.5 (30.2-38.5)	36.4 (31.4-40.0)	38.5 (34.1-41.7)	38.6 (34.5-42.0)	33.0 (24.5-41.5)	0.03*
PLT	157,000 (110,000-245,500)	213,000 (167,000-269,000)	246,000 (190,000-324,500)	216,000 (172,000-275,000)	249,000 (188,000-310,000)	0.11
PT	13.7 (12.8-14.3)	13.5 (12.8-14.6)	13.4 (13.0-13.7)	13.5 (12.8-14.0)	13.4 (12.9-13.9)	0.93
PTT	34.7 (29.5-41.8)	31.3 (28.9-35.9)	32.1 (29.6-34.5)	31.3 (29.0-35.3)	31.5 (30.0-33.0)	0.82
Minutes of surgery	179 (154-217)	241 (172-320)	275 (222-339)	187 (140-311)	179 (109-248)	0.03*
Propofol infused	100%	95.6%	100%	100%	100%	0.25
Volatile anesthetic used	80%	76.8%	91.8%	87.8%	50%	0.16
TXA	0%	88.9%	11.1%	0%	0%	0.02
Preoperative heparin	20%	13.0%	8.8%	14.6%	0%	0.87
CHF	0%	5.8%	2.9%	7.3%	0%	0.86
CKD	40%	7.2%	2.9%	8.5%	50.0%	0.01
HTN	80.0%	56.5%	47.1%	51.2%	100%	0.39
Diabetes	20%	24.6%	17.6%	22.0%	0%	0.87
Liver disease	20.0%	7.2%	2.9%	7.3%	0%	0.67
EBL in ml	100 (40-550)	300 (200-600)	350 (237-500)	250 (187-400)	450 (400-500)	0.01*
PDO in ml	290 (115-552)	632 (317-927)	635 (403-9860	630 (347-870)	436 (353-520)	0.25

*Data presented as median (interquartile range) or percentage of group. * = No outlier found using Dunn's correction for multiple pairwise comparisons. kg=kilograms, BMI=Body mass index, HCT=preoperative hematocrit, PLT=preoperative platelet count, PT=prothrombin time, PTT=activated partial thromboplastin time, TXA=administration of tranexamic acid, CHF=congestive heart failure, CKD=chronic kidney disease, HTN=hypertension, EBL=estimated blood loss, PDO=postoperative drain output*

conclusion of surgery. The increased blood loss with SUG was less than 2 ml but statistically significant. Observations from thyroidectomies or nasal surgeries may not project well to surgeries involving significant muscle interruption with bleeding from raw surfaces, such as spine surgery. Moon *et al*. looked at blood loss after the administration of SUG after liver transplant surgery. Moon *et al*.[14] retrospectively analyzed patients undergoing liver transplants and found no difference in postoperative drainage or need for reoperation for bleeding with SUG. Their study may have missed any significant impact on bleeding due to the transient nature of the coagulation abnormalities.

We found a lack of difference in EBL with the use of SUG intraoperatively during posterior C2–T2 cervical spine fusions. Ours is the only report where SUG was administered intraoperatively when blood loss was ongoing, and the surgery was associated with potentially significant blood loss. We also noted a lack of difference in PDO associated with the administration of SUG which was consistent with the report by Moon *et al*. We conclude a lack of clinical effect related to the short-term laboratory abnormalities associated with SUG. The study abnormalities may be related to the interaction between SUG and components of the test as opposed to a real phenomenon. The lab abnormalities may also represent a real phenomenon, but it does not appear to be clinically significant.

Interestingly, TXA was associated with an increased risk for EBL >500. Initially in this study period, TXA was reserved for use in patients experiencing significant intraoperative bleeding during complex spine surgery at our institution. Our practice concerning the use of TXA changed gradually over the course of the study epoch based on emerging literature on the topic.[15] We moved from its use as a rescue intervention to a prophylactic intervention. Patients who received TXA as a rescue intervention early in the study period possibly skewed the results towards TXA being associated with a higher risk for EBL >500 ml.

A noteworthy finding was the association between the preoperative diagnosis of CKD and increased odds for EBL >500. Kidney disease has been associated with worse outcomes after spine surgery, including a greater need for a transfusion.[16] Previously, CKD had not been linked to greater EBL. Greater EBL in the patients with CKD may be partially responsible for the increase in transfusions. This logically follows from reports that thrombocytopenia has been associated with a greater need for a transfusion

Table 2: The odds ratios for <500 ml of blood loss for variables measured

Independent Variable	Odds Ratio (95% Confidence Interval)	*P*
Sugammadex*	0.84 (0.38-1.88)	0.67
Succinylcholine	0.72 (0.06-8.34)	0.79
Rocuronium	1.29 (0.58-2.87)	0.54
Propofol infusion	1.11 (0.04-30.28)	0.95
Volatile anesthetic use	1.11 (0.36-3.37)	0.86
Tranexamic acid	13.41 (2.16-83.14)	0.01
PLT <100,000	5.66 (0.33-97.24)	0.23
PT >16	0.55 (0.12-2.44)	0.43
PTT >40	0.64 (0.15-2.76)	0.55
Preoperative heparin	1.48 (0.46-4.75)	0.51
CHF	1.27 (0.23-6.95)	0.79
CKD**	9.97 (3.06-32.52)	<0.01
BMI >30	1.48 (0.62-3.55)	0.38
Hypertension	0.40 (0.18-0.89)	0.03
Diabetes	0.74 (0.27-2.07)	0.57
Liver disease	3.23 (0.73-14.42)	0.12
Surgery length (per minute)	1.01 (1.01-1.01)	0.01

*Data presented as odds ratio (95% confidence interval). PLT=Platelet, PT=Prothrombin time, PTT=Activated partial thromboplastin time, CHF=Congestive heart failure, CKD=Chronic kidney disease, BMI=Body mass index. *When neostigmine administration used as independent variable OR 0.85 (0.36-1.97 95% CI), P=0.68. When no NMB reversal used as independent variable OR 1.73 (0.88-3.42 95% CI), P=0.11. ** When preoperative creatinine level of ≥2 used as independent variable OR 5.70 (2.32-13.95 95% CI), P<0.01.*

after spinal surgery.[17] The qualitative impact of CKD on platelets may have a similar effect as a low absolute number. The association between CKD and blood loss was even greater when an independent variable of creatinine ≥2 was substituted for the diagnosis of CKD. This suggests uremia may be the mediator. The exact effect should be evaluated in future research.

While this report suggests SUG is safe, it has several limitations. First, this was a retrospective report with inherent limitations. There may have been confounders such as intraoperative blood pressure swings for certain patient groups we may have failed to identify. Additionally, only associations can be identified retrospectively as opposed to causal relationships. Second, determining EBL is subjective. Third, our institutional preference for the use of TXA changed during the study epoch. Fourth, patients who received SUG received an average of less than 3 mg/kg and we can't comment on the effect of higher doses. Finally, provider bias may have driven decisions on the use of SUG or NEO which were missed in the data analysis. Despite its limitations, we feel our report is the strongest to date on the impact of the intraoperative use of SUG on bleeding. We find no reason to modify the practice of using SUG intraoperatively while blood loss may be occurring currently. The limitations of our analysis point out the need for a prospective control study to determine the true impact of SUG on intraoperative bleeding in order to draw a final conclusion on safety.

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Conflicts of interest
There are no conflicts of interest.

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