Effect of Reversal of Neuromuscular Blockade with Sugammadex *versus* Usual Care on Bleeding Risk in a Randomized Study of Surgical Patients

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ABSTRACT

Background: Previous studies show a prolongation of activated partial thromboplastin time and prothrombin time in healthy volunteers after treatment with sugammadex. The authors investigated the effect of sugammadex on postsurgical bleeding and coagulation variables.

Methods: This randomized, double-blind trial enrolled patients receiving thromboprophylaxis and undergoing hip or knee joint replacement or hip fracture surgery. Patients received sugammadex 4 mg/kg or usual care (neostigmine or spontaneous recovery) for reversal of rocuronium- or vecuronium-induced neuromuscular blockade. The Cochran–Mantel–Haenszel method, stratified by thromboprophylaxis and renal status, was used to estimate relative risk and 95% confidence interval (CI) of bleeding events with sugammadex *versus* usual care. Safety was further evaluated by prespecified endpoints and adverse event reporting.

Results: Of 1,198 patients randomized, 1,184 were treated (sugammadex n = 596, usual care n = 588). Bleeding events within 24 h (classified by an independent, blinded Adjudication Committee) were reported in 17 (2.9%) sugammadex and 24 (4.1%) usual care patients (relative risk [95% CI], 0.70 [0.38 to 1.29]). Compared with usual care, increases of 5.5% in activated partial thromboplastin time ($P < 0.001$) and 3.0% in prothrombin time ($P < 0.001$) from baseline with sugammadex occurred 10 min after administration and resolved within 60 min. There were no significant differences between sugammadex and usual care for other blood loss measures (transfusion, 24-h drain volume, drop in hemoglobin, and anemia), or risk of venous thromboembolism, and no cases of anaphylaxis.

Conclusion: Sugammadex produced limited, transient (<1 h) increases in activated partial thromboplastin time and prothrombin time but was not associated with increased risk of bleeding *versus* usual care. **(Anesthesiology 2014; 121:969-77)**

SUGAMMADEX (Bridion®; MSD, Oss, The Netherlands) is a selective relaxant-binding agent for the rapid reversal of neuromuscular blockade induced by rocuronium and vecuronium.[1] Studies in animal models show that sugammadex acts by chemical encapsulation of unbound neuromuscular-blocking agents in the plasma.[1,2] Clinical studies show that sugammadex is effective and well tolerated for the reversal of moderate and deep neuromuscular blockade induced by rocuronium and vecuronium,[3–8] and it reverses neuromuscular block more rapidly than does neostigmine.[9]

Early, preclinical *in vitro* spiking studies demonstrated an increase in activated partial thromboplastin time (aPTT) with sugammadex. Two clinical trials revealed limited aPTT and prothrombin time (international normalized ratio) (PT[INR]) prolongations, after 16 mg/kg and after 4 mg/kg sugammadex, which resolved quickly (*i.e.*, ≤30 min).[10,11] Although sugammadex is administered at the end of surgery, even these minor and transient prolongations have the potential to increase the risk of postoperative bleeding. To further investigate the potential clinical relevance of these

What We Already Know about This Topic

- Sugammadex prolongs activated partial thromboplastin and prothrombin time, but the clinical relevance of these transient prolongations remains unknown, particularly when considering the risk of perioperative bleeding

What This Article Tells Us That Is New

- In a randomized, double-blind trial performed in patients undergoing hip/knee surgery or hip fracture surgery (n = 1,198) and comparing sugammadex (4 mg/kg) and usual care, sugammadex induced limited (<8% at 10 min) and transient (<1 h) increases in activated partial thromboplastin time and prothrombin time but was not associated with an increased incidence of bleeding (2.9 *vs.* 4.1%; relative risk, 0.70; 95% CI, 0.38 to 1.29) or increased severity of bleeding

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findings, the current study examined the effect of reversal of neuromuscular blockade with sugammadex 4 mg/kg *versus* usual care (defined as neostigmine or spontaneous reversal) on adjudicated events of bleeding and coagulation variables in surgical patients at increased risk for bleeding events due to the type of surgery and concomitant administration of thromboprophylaxis.

Materials and Methods

Study Design and Patient Selection

This was a randomized, parallel-group, double-blind trial conducted at 22 centers in Austria, Belgium, and Germany between October 2011 and September 2012 (NCT01422304). The primary objective was to provide a precise estimate of the relative risk (RR) of sugammadex *versus* usual care on events of bleeding. The protocol was approved by the appropriate national drug authority and by the Independent Ethics Committee at each study center, and the study was conducted in accordance with the principles of Good Clinical Practice and current regulatory requirements. All patients provided written informed consent before study participation.

Adult patients (≥18 yr of age) of American Society of Anesthesiologists class 1 to 3 undergoing joint (hip or knee) replacement surgery/revision or intracapsular or extracapsular hip fracture surgery and planned to receive thromboprophylaxis and neuromuscular blockade with either rocuronium or vecuronium were eligible to participate in this trial. Thromboprophylaxis was defined as ongoing or planned pre- or intraoperative chemical thromboprophylaxis with an anticoagulant/antiplatelet agent (such as low-molecular-weight heparin, unfractionated heparin, vitamin K antagonists, and/or aspirin). Joint (hip or knee) replacement surgery included partial (*e.g.*, resurfacing), total replacement/revision, and stage 1 revision only. Patients must have been eligible for planned extubation in the operating room. Patient recruitment was most frequently handled by a member of the anesthesia team during the anesthetic preassessment, which occurred from several weeks preoperatively to the day before surgery; at some study sites, the surgical team identified potential patients. Only patients who had provided written, informed consent were included in the study.

Patients who met all randomization criteria were assigned to receive sugammadex 4 mg/kg or usual care (neostigmine with glycopyrrolate or atropine, or placebo/spontaneous recovery) for reversal of rocuronium- or vecuronium-induced neuromuscular blockade in a 1:1 ratio. Randomization was stratified according to planned thromboprophylaxis (including low-molecular-weight heparin, unfractionated heparin, or neither) and renal function (estimated creatinine clearance <60 or ≥60 ml/min, using the Cockcroft–Gault formula)[12] using a centralized interactive voice and Web response system.

Patients were excluded from the study if they had suspected anatomical malformations that could make endotracheal intubation more difficult; neuromuscular disorders that might affect neuromuscular blockade; medical history of coagulation disorder, bleeding diathesis, systemic lupus erythematosus, or antiphospholipid syndrome; history or evidence of active abnormal bleeding or blood clotting (*e.g.*, thrombosis) within the 30 days before screening; severe hepatic dysfunction; active hip or knee infection scheduled for revision surgery; known or suspected severe renal insufficiency (estimated creatinine clearance of <30 ml/min); family history of malignant hyperthermia; or morbid obesity (body mass index >35). Patients were excluded if they had hypersensitivity to or conditions that would contraindicate the use of sugammadex, muscle relaxants or their excipients, or other medication(s) used during general anesthesia. Patients were excluded if they received treatment with toremifene and/or fusidic acid intravenously within 24 h before or after study medication administration because of potential drug–drug interaction, as were those who had been previously treated with sugammadex, had participated in a previous sugammadex trial, or had participated in another clinical trial within 30 days of this trial. Female patients who were pregnant or breast-feeding also were excluded.

Endpoints

The primary endpoint was the proportion of patients with at least one adjudicated event of bleeding that occurred within 24 h after trial medication administration and was outside the usual boundaries of expectations, for example, with regard to the amount of blood lost, the duration of bleeding or other relevant factors, considering the type of procedure, the underlying risk of bleeding and the surgeon's specific surgical experience. The initial determination was made by a Blinded Safety Assessor at the site, who was a medically qualified member of the surgical team. The sites were instructed to report any event of bleeding that was unanticipated and to err on the side of false-positive reporting. For all bleeding events thus identified, the available medical information was submitted for adjudication to the independent, blinded Primary Adjudication Committee, consisting of external experts in the field (appendix). The Primary Adjudication Committee classified the event as "a major bleeding event," "a nonmajor bleeding event," or "not an unanticipated event of bleeding" based on the Recommendation from the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee Subcommittee on Control of Anticoagulation.[13] The Adjudication Committee also determined if the event occurred within 24 h of study drug. All personnel involved in the adjudication process were blinded to treatment allocation throughout the trial. The primary analysis for clinical bleedings was based on the adjudicated bleeding events (major or nonmajor). In addition, all events as submitted by the site investigator to the Adjudication Committee and major bleedings within the specified time frames (24 h and within 14 days) were analyzed.

The key secondary endpoint of the trial was change from baseline in aPTT at 10 and 60 min after trial medication administration; PT(INR) was analyzed as a secondary endpoint. Additional endpoints related to blood loss and anemia included postoperative drainage volumes within the first 24 h after trial medication administration; the rates of postoperative transfusion (initiated after sugammadex or placebo/neostigmine was given) and the respective transfusion volumes; postoperative changes in hemoglobin using the bleeding index (calculated as change from baseline of hemoglobin level at the visit performed 24 to 48 h after surgery, adjusted for the amount of erythrocytes transfused). Also, the incidence of anemia with an onset within 72 h after administration of trial medication was analyzed; for anemia, no objective criterion was used, but was recorded if considered clinically relevant by the blinded safety assessor as part of mandatory general adverse event (AE) recording.

Safety was further evaluated by prespecified endpoints and AE reporting, including those that were serious and at least possibly drug related. A posttreatment follow-up evaluation was performed by a blinded safety assessor at least 14 days after administration of treatment by telephonic contact to collect serious AEs and AEs of special interest, including venous thromboembolic events, and events related to hypersensitivity or anaphylaxis. For most patients, the follow-up period was longer, and an actual visit to the site was performed at 4 to 7 weeks after the surgery (as travel was not encouraged for hip and knee surgery shortly after the procedure). The Primary Adjudication Committee evaluated suspected symptomatic venous thromboembolic events. A Hypersensitivity Adjudication Committee evaluated serious AEs suggestive of hypersensitivity and/or suspected events of anaphylaxis to identify those events that met the Sampson criteria.[14] Hypersensitivity included any clinically suspicious symptoms, especially dermatologic, cardiovascular, or respiratory symptoms, which in the opinion of the investigator, may have been related to study medication.

Procedures

Induction and maintenance of anesthesia (including the use of opioids) and induction and maintenance of neuromuscular blockade proceeded according to usual practice; each site was preassigned to use either rocuronium or vecuronium for all patients. Whereas all patients had to be appropriate candidates for rapid reversal of neuromuscular blockade (in the event they were randomized to receive sugammadex), before randomization, the anesthesiologist determined whether active reversal or spontaneous reversal would have been the patient's usual care. When active reversal was chosen, patients were randomized (1:1) to receive either neostigmine or sugammadex. When spontaneous reversal was chosen, patients were randomized (1:1) to receive either placebo or sugammadex. Trial medication was administered in a blinded manner by the anesthesiologist after preparation in an unblinded manner by the pharmacist, according to the randomization schedule and using a double-dummy approach: sugammadex and placebo to neostigmine/atropine or neostigmine/atropine and placebo to sugammadex in the active reversal arm and sugammadex and placebo to sugammadex or two administrations of sugammadex placebo in the spontaneous reversal arm. To further maintain blinding, opaque, colored syringes were used to mask any potential differences in the tint of the study treatments.

Blood samples for analysis of aPTT and PT(INR) were collected at screening, just before the start of administration of trial medication (baseline) and at 10 and 60 min after administration of trial medication using heparin-free lines/materials. Measurements of aPTT and PT(INR) were performed by a central laboratory (Quest Diagnostics Clinical Trials, Collegeville, PA).

Study Organization

The complete list of primary investigators is provided in the appendix. A Data Monitoring Committee was formed to oversee patient safety and make recommendations to the sponsor, as appropriate. Two Clinical Adjudication Committees were formed: one to evaluate bleeding events and venous thromboembolic events (the Primary Adjudication Committee; see appendix) and the other to evaluate serious AEs suggestive of hypersensitivity or anaphylaxis (the Hypersensitivity Adjudication Committee; see appendix). These committees were responsible for confirming the events according to predetermined criteria and evaluating the presence of confounding factors.

Statistical Analyses

Because all endpoints were safety related, analyses were performed on the all-patients-as-treated population, consisting of all randomized patients who received blinded trial medication, and who were analyzed according to the actual treatment they received. The RR and 95% CI of adjudicated bleeding events with sugammadex compared with usual care was calculated using the Cochran–Mantel–Haenszel method, stratified by thromboprophylaxis strategy and renal status. The relative increase (%) of aPTT with sugammadex compared with usual care for the percentage change from baseline of aPTT at 10 and 60 min after administration was calculated using the constrained longitudinal data analysis method, adjusted for site, strata, and type of surgery. PT(INR) data were analyzed analogous to that of aPTT. All proportions were analyzed based on the risk difference using the Miettinen–Nurminen method. The transfusion volume (log scale), drainage volume, and bleeding index were analyzed using a general linear model, all adjusted for strata and investigational site. All analyses were performed using SAS/STAT® software (SAS Institute, Cary, NC).

The sample size was based on a desired precision of the RR, whereby precision was defined as the upper limit of the 95% CI divided by the RR; the sample size was chosen to result in a precision of two or better. Based on the literature

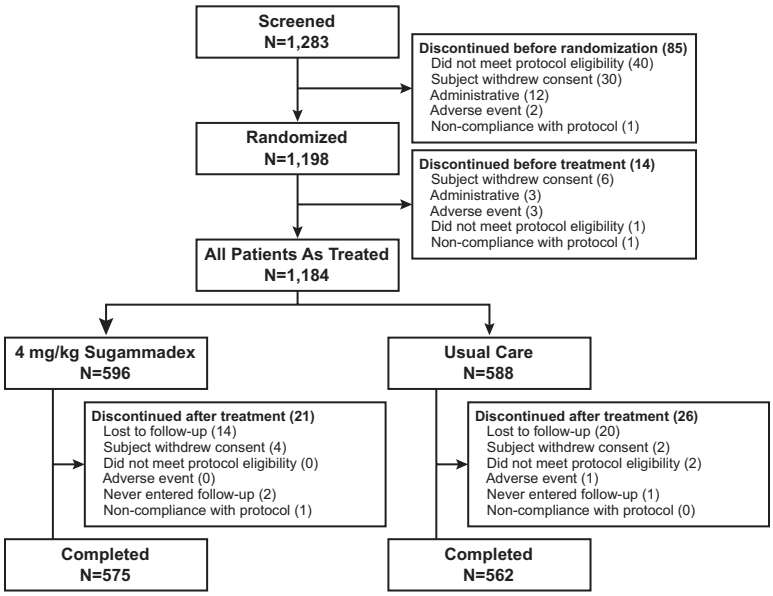

Fig. 1. Patient accounting.

review of hip fracture surgery and joint (hip or knee) replacement procedures, the incidence of bleeding events in the sugammadex development program, and the duration of the primary observation period in this study, the incidence of bleeding events was expected to be approximately 5%. A sample size of 800 patients would provide sufficient statistical power to achieve the desired precision. During the trial, it was observed that the overall bleeding event rate was substantially lower than the anticipated 5%. Therefore, the protocol was amended to extend the enrollment of surgical patients until the number of adjudicated events reached 33 (to obtain the desired precision), or a maximum of approximately 1,200 patients had been enrolled. This protocol amendment also included additional variables as exploratory endpoints to help characterize potential clinical effects related to bleeding events.

Results

Of the 1,198 patients randomized, 1,184 were treated (sugammadex n = 596, usual care n = 588) from October 2011 to September 2012. For usual care patients, 52% received neostigmine and 48% underwent spontaneous recovery. Overall, 1,137 patients completed the trial: 575 (96.5%) in the sugammadex group and 562 (95.6%) in the usual care group. Patient disposition by treatment group is illustrated in figure 1. Baseline characteristics were similar across the treatment groups (table 1).

Primary Endpoint: Bleeding

Bleeding events within 24 h were reported in 17 (2.9%) sugammadex and 24 (4.1%) usual care patients (table 2). The results of the analysis of bleeding events, according to the investigator's assessment, were consistent with that of the primary analysis and with the analysis of major adjudicated bleeding events (table 2). The risk of a bleeding event was higher for those with moderate renal impairment than for those without (RR = 2.4; 95% CI, 1.3 to 4.5; $P < 0.01$), but there was no interaction with treatment ($P = 0.85$; table 2). There was no heterogeneity of effect of sugammadex on incidence of bleeding across subgroups by age (<75, ≥75 yr), usual care (active reversal, spontaneous recovery), sex, American Society of Anesthesiologists class (1, 2, 3), and surgical location (hip or knee) (table 3). The incidence of bleeding events up to 14 days after treatment was similar with sugammadex and usual care (table 2). The cumulative incidences of bleeding events overall and those according to the investigator's assessment were similar, with no significant difference between the sugammadex and usual care treatment groups.

Secondary Endpoint: Coagulation

For aPTT, the average percentage change from baseline was increased with sugammadex as compared with usual care treatment by 5.5% (95% CI, 3.7 to 7.3%; $P < 0.001$) at 10 min after administration of trial medication and by 0.9% (95% CI, −0.9 to 2.8%; $P = 0.33$) at 60 min after administration of trial medication (fig. 2A). For PT(INR), the average percentage change from baseline was increased with sugammadex *versus* usual care of 3.0% (95% CI, 1.3 to 4.7%; $P < 0.001$) at 10 min after administration of trial medication and by 0.9% (95% CI, −1.0 to 2.9%, $P = 0.35$) at 60 min after administration of trial medication (fig. 2B).

Blood Loss Endpoints

For all endpoints related to the amount of blood lost (the 24-h drain volume, the need for any transfusion after treatment with sugammadex or usual care and the volume

Table 1. Baseline Characteristics

	Sugammadex N = 596	Usual Care N = 588
Age (yr), mean (range)	67 (18–92)	67 (24–93)
Sex, n (%)		
Male	270 (45%)	248 (42%)
Female	326 (55%)	340 (58%)
Race, n (%)		
Caucasian	595 (100%)	584 (99%)
Other	1 (<1%)	4 (1%)
Body mass index, mean (range)	28 (17–35)	28 (17–38)
Creatine clearance* (ml/min)		
Median (IQR)	100 (80–123)	99 (79–124)
Missing, n	26	36
<60 ml/min, n (%)	103 (17)	105 (18)
≥60 ml/min, n (%)	493 (83)	483 (82)
ASA class, n (%)		
1	92 (15)	69 (12)
2	411 (69)	412 (70)
3	93 (16)	107 (18)
Type of surgery, n (%)		
Hip fracture, intracapsular, dis- and replaced with total hip replacement, or hemiarthroplasty	12 (2)	11 (2)
Hip fracture, intracapsular, fixed with internal fixation	6 (1)	7 (1)
Hip revision arthroplasty	33 (6)	32 (5)
Knee revision arthroplasty	28 (5)	29 (5)
Primary total hip arthroplasty	324 (54)	305 (52)
Primary total knee arthroplasty	193 (32)	204 (35)
Antithrombotic therapy, n (%)†		
LMWH	498 (84)	492 (84)
Antiplatelet agent	15 (3)	14 (2)
LMWH and antiplatelet agent	73 (12)	71 (12)
No LMWH and/or antiplatelet agent	10 (2)	11 (2)
aPTT, mean ± SD, s	31 ± 4	31 ± 4
PT(INR), mean ± SD	1.1 ± 0.2	1.1 ± 0.1
Hemoglobin, mean ± SD, g/l	113 ± 16	113 ± 16

* By protocol, patients with known or suspected severe renal insufficiency (estimated creatinine clearance of <30 ml/min by Cockcroft–Gault) were excluded from participation in the study. † Defined as any antithrombotic medication in the period from 2 days (for LMWH) or 5 days (for ASA) before trial medication administration to start of trial medication administration.

aPTT = activated partial thromboplastin time; ASA = American Society of Anesthesiologists; INR = international normalized ratio; IQR = interquartile range; LMWH = low-molecular-weight heparin; PT(INR) = prothrombin time (international normalized ratio).

transfused in those situations, and the incidence of anemia and the decline in hemoglobin levels using the bleeding index), there was an advantage with sugammadex compared with usual care (table 2). For the risk of venous thromboembolism, there were no significant differences between sugammadex and usual care (table 2). There were no adjudicated cases of anaphylaxis.

Safety Assessment

Sugammadex was generally well tolerated in patients receiving thromboprophylaxis and undergoing hip fracture surgery or joint (hip or knee) replacement/revision. The incidences of AEs and treatment-related AEs were similar in the sugammadex and usual care treatment groups (table 4). The most frequent AEs (≥10% incidence in either group) were procedural pain (34.1% sugammadex, 39.8% usual care), constipation (21.5% sugammadex, 24.8% usual care), nausea (20.8% sugammadex, 23.6% usual care), pain (15.4% sugammadex, 17.2% usual care), sleep disorder (14.6% sugammadex, 14.3% usual care), anemia (12.2% sugammadex, 12.8% usual care), vomiting (10.7% sugammadex, 11.9% usual care), postoperative anemia (10.6% sugammadex, 11.2% usual care), and hematoma (10.4% sugammadex, 9.4% usual care). Most AEs were of mild to moderate intensity. All six cases of treatment-related serious AEs were related to bleeding and were included in the adjudication process. None of the sugammadex-treated patients died during the trial. One pretreatment and three posttreatment deaths occurred in patients assigned to usual care. The pretreatment death occurred secondary to pulmonary embolism. All postrandomization deaths (ventricular fibrillation, metastatic renal cell carcinoma, and cardiac arrest) were considered unlikely to be related to trial medication by

Table 2. Study Endpoints

Bleeding within 24 h	Sugammadex (N = 596)	Usual Care (N = 588)	Relative Risk Sugammadex *vs.* Usual Care (95% CI)*
Adjudicated bleeding	17 (2.9%)	24 (4.1%)	0.70 (0.38–1.29)
Bleeding per investigator	20 (3.4%)	31 (5.3%)	0.64 (0.37–1.11)
Adjudicated major bleeding	12 (2.0%)	20 (3.4%)	–1.4 (–3.4 to 0.5)
Adjudicated bleeding by renal status, n/N (%)			
Normal renal function (≥60 ml/min)	11/493 (2.2%)	16/483 (3.3%)	0.67 (0.31–1.45)†
Impaired renal function (<60 ml/min)	6/103 (5.8%)	8/105 (7.6%)	0.77 (0.27–2.21)†
Bleeding within 14 Days	**Sugammadex (N = 596)**	**Usual Care (N = 588)**	***P* Value**
Adjudicated bleeding	24 (4.0%)	27 (4.6%)	0.63
Adjudicated major bleeding	18 (3.0%)	23 (3.9%)	0.40
Bleeding per investigator	32 (5.4%)	45 (7.7%)	0.11
Adjudicated symptomatic venous thromboembolism	5 (0.8%)	3 (0.5%)	0.49
Blood loss endpoints			
Postoperative drainage volume (ml),‡ median (interquartile range)	395 (200–650)	400 (200–670)	0.71
Patients transfused postoperatively	221 (37%)	227 (39%)	0.59
Total transfusion volume§ for patients who received postoperative transfusion (ml), median (interquartile range)	378 (195–596)	400 (217–545)	0.07
Patients with postoperative anemia‖	124 (21%)	132 (22%)	0.49
Postoperative change in hemoglobin using the bleeding index,# mean ± SD	–16 ± 167	–17 ± 17	0.12

All values are n (%), unless otherwise specified.

* Relative risk and associated 95% CI as computed by the Cochran–Mantel–Haenszel method, stratified for renal status (creatinine clearance <60 or ≥60 ml/min) and planned thromboprophylaxis therapy (low-molecular-weight heparin or other). † The interaction test for bleeding by renal status was not significant ($P = 0.85$). ‡ Onset within 24 h after trial medication administration. § The volume was transformed to the log scale. ‖ With onset within 72 h after trial medication administration. # Bleeding index was calculated as the hemoglobin level in g/l at the baseline visit minus the hemoglobin level at visit 3 adjusted for the amount of red cells transfused.

the investigator. No AEs indicating delayed or insufficient neuromuscular blockade, recurrence of neuromuscular blockade, slow recovery from neuromuscular blockade, or light anesthesia were reported. No significant differences between treatment groups were observed for laboratory variables or vital signs.

Discussion

This dedicated, randomized, double-blind study assessed the incidence of bleeding events with sugammadex *versus* usual care in patients undergoing major orthopedic surgery while receiving commonly prescribed thromboprophylaxis to reduce the risk of thromboembolism.[15] The results

Table 3. Incidence of Adjudicated Events of Bleeding by Treatment for Subgroups

	Sugammadex			Usual Care		
	N	n	%	N	n	%
Age category, yr	428	7	1.6	437	13	3.0
<75						
≥75	168	10	6.0	151	11	7.3
Usual care	292	7	2.4	319	12	3.8
Active reversal						
Spontaneous recovery	304	10	3.3	269	12	4.5
Sex	326	6	1.8	340	15	4.4
Female						
Male	270	11	4.1	248	9	3.6
ASA class	92	3	3.3	69	2	2.9
1						
2	411	9	2.2	412	16	3.9
3	93	5	5.4	107	6	5.6
Surgical location	375	7	1.9	355	12	3.4
Hip						
Knee	221	10	4.5	233	12	5.2

ASA = American Society of Anesthesiologists.

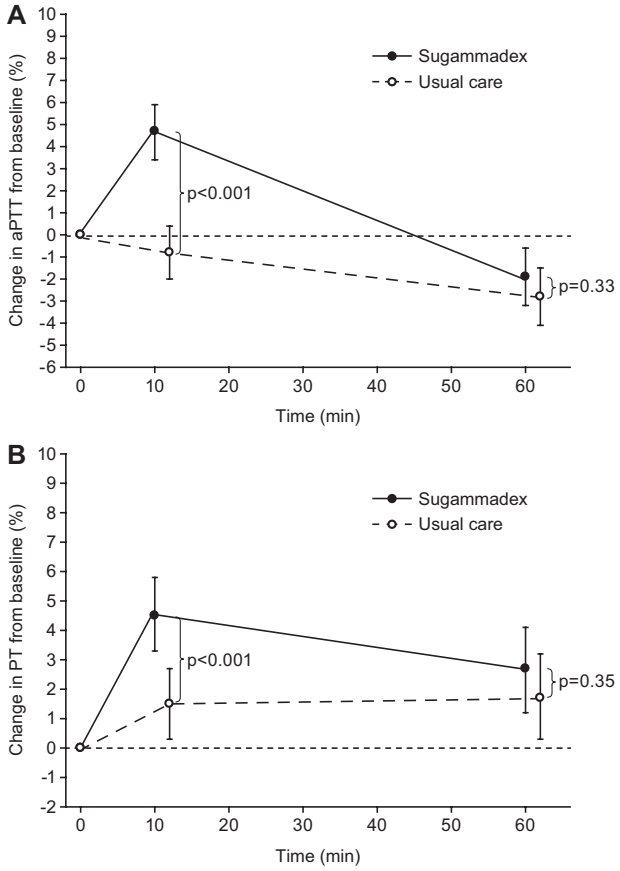

Fig. 2. Changes from baseline (95% CIs) over time for (*A*) activated partial thromboplastin time (aPTT) and (*B*) prothrombin time (international normalized ratio) (PT[INR]) (all-patients-as-treated population), using a constrained longitudinal data analysis method. For sugammadex, N = 567, and for usual care, N = 545.

demonstrate that treatment with sugammadex 4 mg/kg was not associated with an increased bleeding risk in surgical patients as compared with usual care. This finding was robust insofar as it was observed across all endpoints of bleeding and blood loss (*i.e.*, transfusion, drainage volume, anemia, and hemoglobin drop). The drop in hemoglobin, as reflected in the bleeding index, is of particular interest, as each patient contributes to this endpoint and thus it has greater discriminatory power than the binary, more clinically relevant, endpoint of bleeding events. The average drop in the bleeding index was 15.7 g/l for sugammadex-treated patients *versus* 17.4 g/l for the usual care group, showing that, on average, treatment with sugammadex did not result in a larger decrease in hemoglobin compared with usual care. Treatment with sugammadex was associated with limited mean increases in aPTT and PT(INR) at 10 min after administration compared with usual care; these increases resolved within 60 min. *In vitro* experiments suggest that sugammadex exerts its effects on coagulation variables *via* transient inhibition in formation and activity of factor Xa.[16] Two randomized, double-blind trials in healthy volunteers showed that sugammadex 4 mg/kg added to background aspirin or sugammadex 4 or 16 mg/kg added to background enoxaparin and unfractionated heparin was associated with limited (≤25%) and transient (≤1 h) increases in aPTT and PT(INR), which were not considered clinically relevant.[10,11] Importantly, in the current study, the observed increases were not only limited and transient but were not associated with a coincident or subsequent increased risk of bleeding or amount of blood lost.

The lack of an association between the highest dose of sugammadex (4 mg/kg) and increased bleeding risk in patients for whom bleeding can be of clinical concern is consistent with findings from the sugammadex clinical development program. Pooled analysis of clinical trial data from surgical patients treated with sugammadex did not show an increased incidence of hemorrhage as compared with patients treated with either placebo or neostigmine (Merck & Co., Inc., Whitehouse Station, NJ, data on file). In addition, a retrospective, 1-yr study in patients who underwent laparotomy for cancer surgery requiring suction drains and, as such, were considered at high risk of postoperative bleeding demonstrated that sugammadex at doses of 2 and 4 mg/kg was not associated with increased bleeding.[17]

This study included some limitations. The current results are specific to patients undergoing major orthopedic surgery and may not be generalizable to patients having other surgical

Table 4. Adverse Events Occurring after Trial Medication Administration up to and Including 14 Days after Trial Medication Administration

Parameter	Sugammadex (N = 596) n (%)	Usual Care (N = 588) n (%)	Risk Difference (95% CI)*
Patients with at least one AE	551 (92.4)	549 (93.4)	−0.9 (−3.9 to 2.0)
Patients with at least one drug-related AE†	64 (10.7)	72 (12.2)	−1.5 (−5.2 to 2.1)
Patients with at least one SAE	39 (6.5)	40 (6.8)	−0.3 (−3.2 to 2.6)
Patients with at least one drug-related SAE†	4 (0.7)	2 (0.3)	0.3 (−0.6 to 1.4)
Patients who died‡	0 (0.0)	3 (0.5)§	−0.5 (−1.5 to 0.1)

* Risk difference and associated 95% CI (Miettinen–Nurminen method). † Relationship to trial medication specified as "probable" or "possible" by the blinded safety assessor. ‡ Any death occurring poststudy drug administration. § One additional death due to pulmonary embolism occurred after randomization to the usual care treatment group but before treatment.

AE = adverse event; SAE = serious adverse event.

procedures with an increased risk of bleeding, such as cancer surgery, reconstructive plastic surgery, and cardiac, intracranial, or spinal surgery. In addition, this study was conducted in patients who were treated with commonly prescribed thromboprophylaxis, and not with newer oral anticoagulants (although these are not known to increase bleeding relative to low-molecular-weight heparin after hip or knee arthroplasty). Finally, this study was conducted in an adult (*vs.* a pediatric) population, as there is no surgical procedure performed frequently enough in children to provide a sufficient sample size and with an increased risk of bleeding; nevertheless, the current results may not be generalizable to pediatric populations. It may be argued that the study should have been conducted using a noninferiority design in which an absence of risk of excess bleeding is concluded if the 95% CI is below a prespecified margin. This design was not chosen because establishing a suitable margin is not trivial, and even fairly liberal margins require large sample sizes (*e.g.*, to rule out a 50% increase of an incidence of 3.5% as observed here would require a total sample size of 7,000 for a power of 90%). Nonetheless, the study design does not affect the interpretation of the current results; the RR of 0.70 of sugammadex *versus* usual care with the 95% CI of 0.38 to 1.29 indicates that any excess bleeding risk with sugammadex would not exceed 29% compared with usual care.

In conclusion, the results of the current study in surgical patients who were at an increased risk of bleeding and blood loss due to the intraoperative thromboprophylaxis combined with a major surgical procedure confirm that sugammadex increases aPTT and PT(INR) to a limited degree (<8% at 10 min) and duration (<1 h), but is not associated with either an increased incidence of bleeding or increased severity of bleeding, as assessed by measures estimating blood loss.

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Competing Interests

Authors Fennema, Speek, McCrary Sisk, Williams-Herman, Woo, and Szegedi are current or former employees of subsidiaries of Merck & Co., Inc. (Whitehouse Station, New Jersey), and may own stock or hold stock options in the company. Dr. Rahe-Meyer reports receiving honoraria for advisory board membership, lectures, and/or consultancy for CSL-Behring (King of Prussia, Pennsylvania) and Merck (Whitehouse Station, New Jersey). His institution received a grant for the study. Dr. Wulf reports receiving honoraria for advisory board memberships from Boehringer Ingelheim (Ingelheim, Germany), Sintectica (Canton Ticino, Switzerland), and Carefusion (San Diego, California), and for lectures or consultancy from Teleflex (Wayne, Pennsylvania), Sintetica (Canton Ticino, Switzerland), Vygon (Landsdale, Pennsylvania), B. Braun Medical Inc. (Melsungen, Germany), Pajunk GmbH (Geisingen, Germany), SonoSite Inc. (Bothell, Washington), and Merck (Whitehouse Station, New Jersey). Dr. Blobner reports receiving fees from Merck (Whitehouse Station, New Jersey) for consulting, lectures, advisory board membership, and participation in reviews and committees. He reports that his institution received grants and money for travel related to the study from Merck (Whitehouse Station, New Jersey). Dr. Schulman reports receiving travel support from Merck (Whitehouse Station, New Jersey) for investigators' meeting and an honorarium for work in the Adjudication Committee. Dr. Przemeck reports receiving travel support from Merck (Whitehouse Station, New Jersey) for investigators' meeting. His institution received a grant for patient visits and other costs associated with the study. Dr. Klimscha reports his institution received funds from Merck (Whitehouse Station, New Jersey) associated with the study.

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Appendix

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