



Is there consensus on the perioperative management of Xa inhibitors in patients undergoing elective spine surgery? – A survey of current spine surgeon practices

Ashley E. Xiong^{1^}, Taylor J. Jackson¹, Bryan Kinsey Lawson^{1,2}, Navid Khezri¹, Arjun Sebastian¹, Brett Freedman¹, Benjamin Elder¹, Bradford Currier¹

¹Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA; ²Department of Orthopedics, Mike O'Callaghan Federal Hospital, Las Vegas, NV, USA

Contributions: (I) Conception and design: BK Lawson, A Sebastian, B Freedman, B Elder, B Currier; (II) Administrative support: AE Xiong, BK Lawson, N Khezri, A Sebastian, B Freedman, B Elder, B Currier; (III) Provision of study materials or patients: BK Lawson, AE Xiong, A Sebastian, B Freedman, B Elder, B Currier; (IV) Collection and assembly of data: AE Xiong, BK Lawson, N Khezri, A Sebastian, B Freedman, B Elder, B Currier; (V) Data analysis and interpretation: AE Xiong, TJ Jackson, N Khezri; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ashley E. Xiong, BS. Mayo Clinic, 200 First St SE, Rochester, MN 55905, USA. Email: ashleyxiong5@gmail.com.

Background: Factor Xa inhibitors (Xai) are an increasingly common consideration in perioperative anticoagulation management. However, there no existing guidelines established for use in Spine Surgery. This survey study aims to capture current practice trends regarding the perioperative management of Xai among spine surgeons.

Methods: An 11-question survey was sent to all surgeon members of 3 spinal surgery societies. Responses were remitted anonymously. Questions characterized the background and experience of the respondent and inquired into their current perioperative Xai and other anticoagulant management. Questions were all single-best option, multiple-choice.

Results: A total of 116 surveys were received. Twenty-six (22.4%) were from neurosurgeons and 90 (77.6%) were from orthopedic surgeons. Practiced preoperative Xai hold length tended to be longer than recommended by the respondent's medical colleagues. Only 65.2% ($P \leq 0.0001$) of respondents practiced in agreement with the recommendations of their medical colleagues. Postoperative Xai holds trended toward longer holds than that of other anticoagulants with 37.9% ($P = 0.0125$) of respondents showed differences within their own practice between length of Xai hold and length of other anticoagulant holds. One out of four respondents reported noticing a change in the rate of perioperative bleeding complications among Xai patients. Despite reported increased bleeding issues, only 39% of those who noted this increase in bleeding complications reported they would hold a Xai longer than other anticoagulants.

Conclusions: There exists a wide range of recommended and practiced chronic anticoagulant hold lengths. This inconsistency likely highlights conflicting risk aversion among surgeons, between complications which are viewed as medical (i.e., thromboembolism and stroke) *vs.* surgical (i.e., compressive hematoma). Yet, survey responses suggest the length of Xai hold times did not necessarily reflect the surgeon's experience with postoperative bleeding complications in Xai patients. These inconsistent practices highlight the need for further research that can establish guidelines for perioperative management of Xai patients undergoing spine surgery.

Keywords: Anticoagulants; factor Xa inhibitors (factor Xai); spine; orthopedic surgery; neurosurgery

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[^] ORCID: 0000-0002-0081-4157.

Introduction

Venous thromboembolism (VTE) incidence following elective spine surgery can range from 0.3% to 31%. Even at the lowest incidence rates, VTEs represent a serious postoperative risk (1). For patients with a history of thromboembolic conditions, the risk of perioperative thrombotic event is higher than the general population and perioperative anticoagulation management poses a challenge (2). A balance must be struck between preventing another VTE and causing a bleeding complication of surgery. The North American Spine Society's Evidence-Based Clinical Guideline notes that the safety and efficacy of chemoprophylaxis in spine surgery is countered by the risk of bleeding complications and thus timing of anticoagulant use is controversial—offering no definitive guideline for surgical practice (3). In fact, to the authors' knowledge, the best practice for management of chronic anticoagulation medications perioperative to elective spine surgery marks a current gap in the literature. In situations such as this, a poll of active spine surgeons who have earned membership into spine surgery societies offer the opportunity to obtain a cross-section of current practice that can then inform future directed clinical research on the subject.

Among the anticoagulants used for chronic management of VTE and prophylaxis for other common conditions, such as atrial fibrillation, Xa inhibitors (Xai) are the newest class of medication. Likely due to the standard oral dosing regimen and no need for laboratory monitoring, Xai use has become more and more prevalent. Xai work by inhibiting Xa which reduces thrombin and prevents the formation of clots. Common Xai medications include rivaroxaban, apixaban, and edoxaban. Considering their cost-effectiveness, ease of use, and equivalent, or even superior, prevention of thromboembolic events and all-cause mortality, it can be expected that the usage of Xai will continue to grow. This rising prevalence has introduced a new variable for surgeons to consider (4-6). An international consensus statement by the European Association of Cardiothoracic Anaesthesiology recommended Xai be held for 2-4 days prior to surgery, while other guidelines offer a range of 1 to 5 days depending on factors, such as anti-factor Xa plasma level assay availability (6-8). The variance among these recommendations reflect an attempt to standardize guidelines based on the half-life of Xai's similar to their currently approved dosing regimens, while at the same time allowing for some manner of individualization based on a patient's risk both for a thrombotic and a

bleeding event.

Adding to this uncertainty is the absence of an affordable, widely available laboratory assessment for Xai activity. Though Anti-Factor Xa Assays have been created, they are not widely accessible. More commonly available tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) are not sensitive (8,9). Additionally, the lack of a readily available anticoagulant reversal agent increases the difficulty in decision making when using these drugs (10). Without clear guidelines, a widely available test to directly measure Xai activity, nor a cost-effective reversal agent, it is unclear how spine surgeons are currently striking their own balance in regards to perioperative Xai management. The purpose of this study is to capture current practice trends regarding the perioperative management of Xai and other anticoagulation medications among spine surgeons.

We present the following article in accordance with the SURGE reporting checklist (available at <https://dx.doi.org/10.21037/jss-20-637>).

Methods

This study and its components were reviewed and approved by Mayo Clinic Institutional Review Board (Registration No. IRB00000020). Subject's participation in the study was entirely voluntary with consent to participate received upon subject's submission of survey answers. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). An electronic survey was sent through SurveyMonkey® to all surgeon members of AOSpine North America, Cervical Spine Research Society (CSRS), and Lumbar Spine Research Society (LSRS). Responses were submitted anonymously. All responses were voluntary and respondents were not compensated for completing the survey. The surveys were sent out to the society members twice, with reminders, before being closed to further responses.

The survey was comprised of 11 questions (*Table 1*) that were designed to characterize the medical training of the respondent, their current practice regarding perioperative anticoagulants, and discuss future options for perioperative anticoagulant management. The survey asked questions related to their pre- and post-operative practices with patients who were taking Xai or other chronic anticoagulants. Questions were all single-best option, multiple-choice. A 100% response rate was required for each survey submitted.

Table 1 Survey questions

#	Question
1	Please describe your training background?
2	Approximately how many years have you been practicing Spine Surgery?
3	Please describe your practice?
4	How long do your medical colleagues recommend holding direct factor Xa inhibitors pre-operatively (e.g., 2 days means 2 full days off inhibitors prior to date of surgery)?
5	How long do you personally require patients to remain off of their direct factor Xa inhibitor pre-operatively (e.g., 2 days means 2 full days off inhibitors prior to date of surgery)?
6	On average how long do you hold your patients direct factor Xa inhibitor post-operatively (e.g., 2 days means no anticoagulation on the day of surgery plus one full day)?
7	In general how long do you hold all chemical anticoagulation post-operatively (e.g., 2 days means no anticoagulation on the day of surgery plus one full day)?
8	Have you noted a change in the rate of perioperative bleeding complications (epidural hematoma, wound drainage, etc.) in your patients taking direct factor Xa inhibitors, when compared to other chemical anticoagulants (i.e., warfarin, heparin, LMWH, etc.)?
9	If readily available and the cost is acceptable, would you routinely obtain a laboratory study to determine if your patient has cleared their direct factor Xa inhibitor prior to surgery?
10	If the proposed factor Xa inhibitor test demonstrated active metabolites of the direct factor Xa inhibitor, would you consider canceling or postponing surgery?
11	Does a patient's pre-operative stroke risk assessment (CHADS2 score) factor into how you will hold anticoagulation post-operatively?

Table 2 Respondent demographics by training background and years of practice

Practice	1–2 years (%)	3–10 years (%)	11–20 years (%)	>20 years (%)	Total
Academic Neurosurgery	2 (1.7)	6 (5.2)	5 (4.3)	7 (6.0)	20 (17.2)
Private Neurosurgery	1 (0.9)	1 (0.9)	1 (0.9)	3 (2.6)	6 (5.2)
Academic Orthopedic Surgery	4 (3.4)	14 (12.1)	14 (12.1)	17 (14.7)	49 (42.6)
Private Orthopedic Surgery	5 (4.3)	15 (12.9)	7 (6.0)	14 (12.1)	41 (35.3)
Total	12 (10.3)	36 (31.0)	27 (23.3)	41 (35.3)	116 (100.0)

Statistical analysis

Statistics were performed utilizing JMP Pro 14 (SAS Institute Inc., Cary, NC, USA). Univariate comparisons of respondent demographics, recommended and reported practices, and reported bleeding complications were conducted. Wilcoxon Rank-Sum tests compared continuous variables while Chi-square and Fisher exact tests compared categorical variables. Alpha level was set to $P < 0.05$ for significance.

Results

Demographics

There was a total of 116 unique completed surveys

submitted, all of which were included in analysis. Of the 116 respondents, 26 (22.4%) were neurosurgeons and 90 (77.6%) were orthopedic surgeons. Demographics of the respondents, by practice, are illustrated in *Table 2*.

Pre-operative practices regarding Xai

The recommended pre-operative window for holding Xai provided to respondents by their medical colleagues varied widely from 0 to >7 days. Among all respondents, 73.28% reported that their medical colleagues recommended holding Direct Factor Xai preoperatively for anywhere between 2–5 days. The most commonly recommended Xai preoperative holds were 3 days (24.1%), 2 days (23.3%),

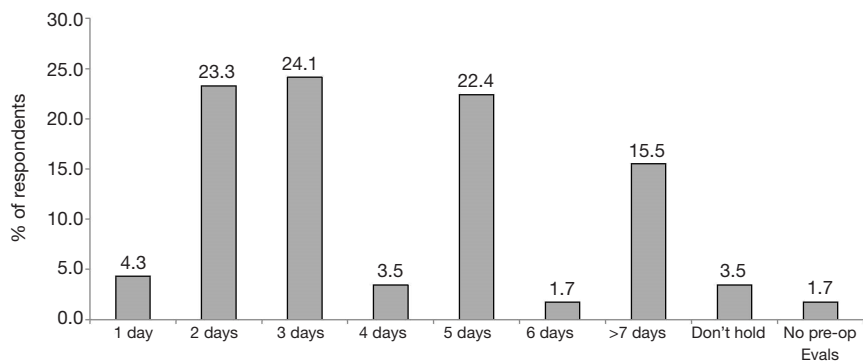


Figure 1 Colleague-recommended pre-operative hold for Xai. Response rate for Question 4 of the survey demonstrates a distribution of recommendations for colleague-recommended pre-operative hold for Xai. Of particular interest is the similar frequency of recommendation to hold Xai pre-operatively between 2, 3, and 5 days. Xai, Xa inhibitors.

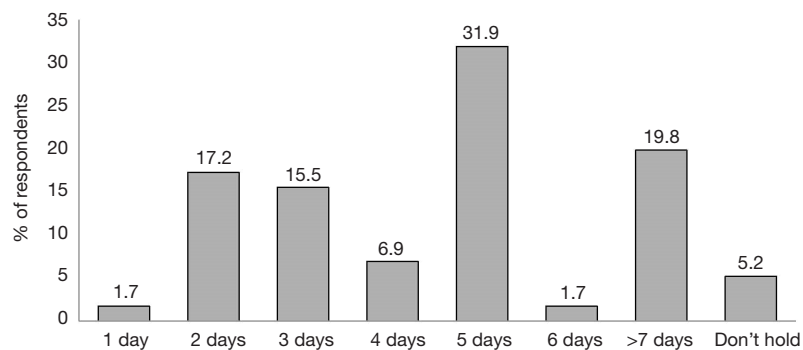


Figure 2 Practiced pre-operative hold for Xai. Response rate for Question 5 of the survey. Respondents reported a wider range of practiced pre-operative Xai hold than would be expected given the majority distribution of recommended pre-operative Xai hold between 2, 3, and 5 days seen in *Figure 1*. Responses demonstrate that surgeons report practicing a more conservative pre-operative Xai hold than recommended. Xai, Xa inhibitors.

and 5 days (22.41%) (*Figure 1*).

Similar to the recommended pre-operative hold length, 71.56% of respondents reported that they personally require patients to remain off of their Direct Factor Xai preoperatively for anywhere between 2–5 days. The most commonly used preoperative Xai holds were 5 days (31.9%), >7 days (19.8%), and 2 days (17.2%) (*Figure 2*).

Though there was a similar quantity of respondents recommending 2–5 days of Xai hold, only 65.2% of respondents reported that their practice was in agreement with the recommendations of their medical colleagues ($P \leq 0.0001$). Of the 41.2% whose practice was different than recommended by colleagues, 35.6% recommended a hold of greater length, while 5.6% recommended a shorter hold length than what their medical colleagues recommended (*Figure 3*). Among orthopedic surgeons, there was a greater

disagreement between recommendation and practice with 57.8% of respondents practicing in agreement with recommendations, 35.6% requiring a longer Xai hold and 6.6% requiring a shorter Xai hold (*Figure 4*).

When compared by specialty and years of experience, there was no distinguishable trend, or preference, when it came to the chosen number of days for pre-operative Xai hold.

Post-operative practices regarding Xai

Respondents were asked about their post-operative practices with regards to both patients on Xai and patients who were on any anticoagulants (*Figure 5*). Postoperative Xai practices varied widely, with an overall trend toward longer holds than that of other anticoagulants. The three most frequently

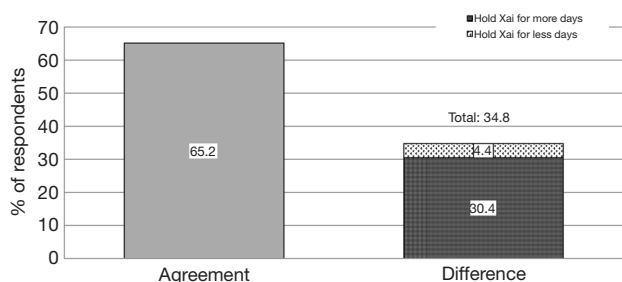


Figure 3 Agreement between recommendations and practice. Individual responses to survey questions 4 and 5 were compared across all surgical specialties. While 65.2% of respondents practiced pre-operative Xai holds according to what was recommended to them by colleagues, 34.8% practiced differently, with 30.4% of all respondents practicing a longer pre-operative Xai hold than recommended by colleagues. Xai, Xa inhibitors.

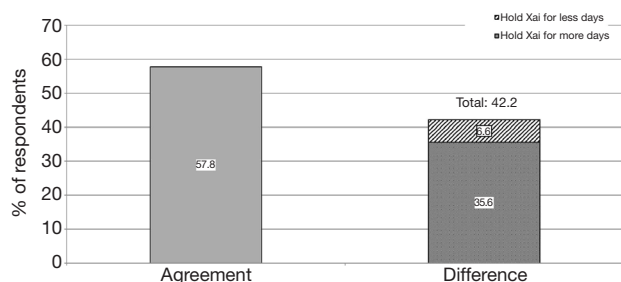


Figure 4 Agreement among orthopedic surgeons between recommendation & practice. Individual responses to survey questions 4 and 5 were compared among orthopedic surgeons alone. Fewer orthopedic surgeons practiced pre-operative Xai holds in agreement with their colleague's recommendations than seen among all surgical specialty respondents (57.8% vs. 65.2%). 42.2% of orthopedic surgeons practiced different pre-operative Xai holds than recommended by their colleagues, with 35.6% of respondents practicing longer pre-operative Xai holds. Xai, Xa inhibitors.

used lengths of hold for Xai were 2 days (24.14%), 3 days (20.69%), and 7–14 days (19.83%). The three most frequently used hold lengths for patients on any other anticoagulant were 2 days (28.45%), 7–14 days (17.24%), and 1 day (12.93%). 66.38% of respondents held Xai for 3 or more days postoperatively. When asked about holding other anticoagulants for 3 or more days postoperatively, the percentage of respondents dropped to 51.72%.

Individual responses revealed that 37.93% of respondents showed differences within their own practice

between length of Xai hold and length of holding other anticoagulants (Figure 6) ($P=0.0125$). Of respondents who had a difference in their postoperative practices, 68.2% held Xai longer than other anticoagulants, while 31.8% held Xai for a shorter postoperative period.

Opportunities for rational consensus and future clinical research

One out of four respondents reported noticing a change in the rate of perioperative bleeding complications among patients who used Xai (Figure 7). Of those who noticed a change, 86.2% reported an increase and 13.8% reported a decrease. However, those who reported noticing an increase in bleeding complications only accounted for 39% of those who held direct Xai longer than other anticoagulants preoperatively. Further, only 44% of those who reported noticing an increase in bleeding complications for Xai patients described a difference in their practice between Xai and other anticoagulant holds following surgery.

When respondents were asked if they would routinely use an easily accessible and affordable lab test that would measure Xai clearance, 80.2% of respondents said yes. If the proposed test existed, and they had a patient who had Xai test results indicating on-going activity of the drug, 96.55% of respondents reported they would cancel or postpone surgery for one of four reasons. These four reasons were: (I) yes, unequivocally; (II) yes, but only if the patient's other coagulation tests were abnormal or scientific evidence demonstrated heightened bleeding risk; (III) yes, but only if the patient's other coagulation tests were also abnormal; (IV) yes, but only if there is scientific evidence demonstrating heightened bleeding risk.

Discussion

This survey reveals that there is a vast range of practice surrounding perioperative Xai management and a clear need for evidence based direction on management as Xai use continues to grow. There exists a wide range of recommended and practiced chronic anticoagulant hold lengths in elective spine surgery with no clear preference. Most surgeons appear to rely upon the recommendations from their medical colleagues regarding preoperative holding length for Xai. However, there were discrepancies between the medical consultant recommended hold length and the practiced hold length, particularly among Orthopedic surgeons, who were more likely to opt for a

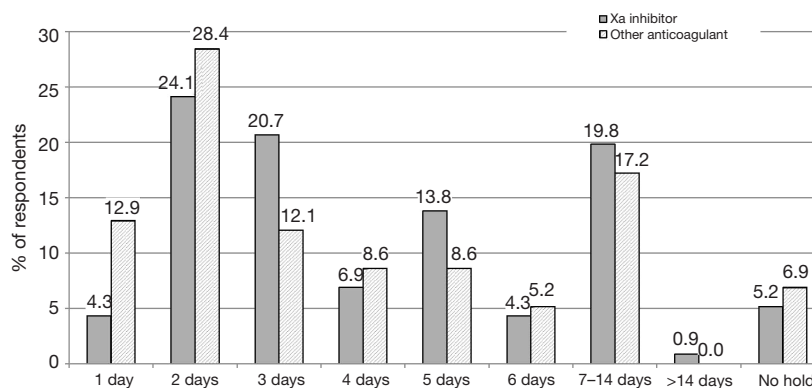


Figure 5 Practiced post-operative hold lengths. Response rates to survey questions 6 and 7 comparing practiced post-operative Xai and other anticoagulant holds. Represented is a wide distribution of post-operative hold lengths for both Xais and other anticoagulants. However, Xai inhibitors were more frequently held for 2, 3, 5, or 7–14 days postoperatively while other anticoagulants were most frequently held 1, 2, 3, or 7–14 days postoperatively. Xai, Xa inhibitors.

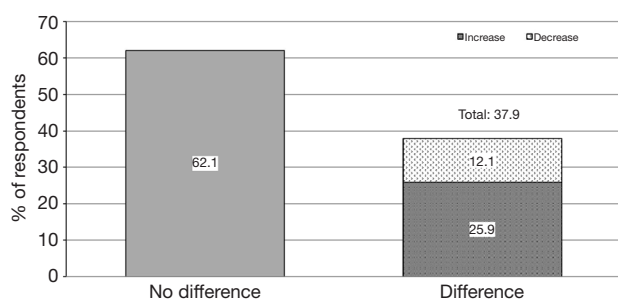


Figure 6 Surgeon's differences between Xai and other anticoagulant holds within their practice. Individual responses to survey questions 6 and 7 were compared. 62.1% of respondents reported no difference between Xai and other anticoagulant holds within their practice. 37.9% of respondents reported a difference in Xai and other anticoagulant holds with 25.9% practicing a longer post-operative hold and 12.1% practicing a shorter post-operative hold. Xai, Xa inhibitors.

pre-operative hold longer than what was recommended by a medical consultant. This inconsistency may highlight conflicting perspectives of risk aversion between the medical doctor and surgeon in chronic anticoagulant use—thrombotic events *vs.* postoperative hemorrhage/hematoma. Conversely, patients who require long term Xai usually have comorbidities that place them at the highest risk for perioperative thrombotic events, further complicating the medical decision making. The novelty of Xai leaves surgeons with little evidence for differences in outcomes for Xai patients, let alone the impact of premature or delayed holds or resumption, with which to make practice decisions.

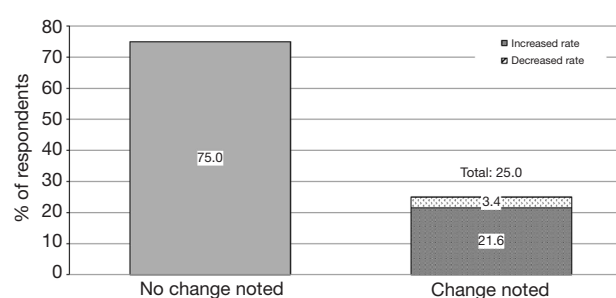


Figure 7 Respondent noted change in rate of perioperative bleeding for Xai patients. Response rate to survey question 8 regarding respondent noted change in rate of perioperative bleeding for Xai Patients. 25% of respondents noted a change with 21.6% indicating a noted increase and 3.4% indicating a noted decrease rate of perioperative bleeding for Xai patients. Xai, Xa inhibitors.

The true rate of adverse postoperative events in chronic Xai users is unclear. Unfortunately, there is little evidence regarding the use of Xai in orthopaedic surgery, outside of arthroplasty surgery where there is significant information on the topic (11,12). Even among the arthroplasty patient population there is little consensus on the optimal perioperative management of anticoagulation. A survey of the American Association of Hip and Knee Surgeons (AAHKS) membership revealed wide variability in practice patterns, highlighting the need for ongoing research (12).

One of the most interesting findings in this study was that 25% of respondents reported observing changes in postoperative bleeding complications for patients on Xai,

yet the length of Xai hold times did not reflect the surgeon's experience with postoperative bleeding complications. In fact, more than half of those who held Xai longer than other anticoagulants postoperatively did not report noticing an increase in postoperative bleeding complications. The cause of this trend was not informed by this study, though it may be related to perceived risks and tendency towards risk aversion in the setting of a lack of availability of Xai level and reversal agents. The rapid onset of activity of Xais may also have been a factor in decision making for when to restart the medication, since other anticoagulants take much longer to become effective than the Xais. Additionally, the literature has conflicting evidence regarding differences in bleeding risk between Xai and more conventional chemoprophylaxis agents (13).

Currently, the literature suggests that there are significant variations in bleeding risk demonstrated in patients taking Xais. In one study, fondaparinux and rivaroxaban were shown to increase the risk of major/clinically relevant non-major (CRNM) bleeding compared to E40 and increase the incidence of major/CRNM bleeding when compared to a variety of enoxaparin doses. However, in the same study, apixaban had a lower risk than enoxaparin for major/CRNM bleeding (14). There is also evidence that bleeding risk for a single Xai varies by site—further confounding the process of perioperative Xai management. In a study comparing rivaroxaban versus warfarin, rates of bleeding were similar across all three bleeding classification types: major bleeding, major or CRNM bleeding, and CRNM bleeding. Yet, there was higher incidence of major GI bleeding among the rivaroxaban population than those on warfarin (15,16). There is limited literature specifically addressing rates of bleeding complications at the spine or following spinal surgery. Beyond considering the Xai, or the rate of bleeding complications across sites, there is also variation in bleeding complication rates across dosage. Edoxaban 30 mg has been shown to have an increased rate of Major or CRNM bleeding when compared to warfarin, while edoxaban 60 mg was shown to have a decreased rate of Major or CRNM bleeding, but a significantly increased rate of major GI bleeding (17,18). When comparing the rate of major postoperative bleeding across rivaroxaban doses in patients who underwent THA, there was a significant dose trend. Those at the lowest and top three dosing tiers had higher incidences of major postoperative bleeding than patients on enoxaparin (19). A dose-response meta-analysis of both enoxaparin and Xai dosing also demonstrated the complex balance between efficacy and

risk of major bleeding complication in use of apixaban, edoxaban, rivaroxaban, and dabigatran following orthopedic surgeries (20). Other studies on rivaroxaban in arthroplasty surgery suggest rivaroxaban incurs no more significant rates of major bleeding than enoxaparin, despite having increased rates of bleeding complications (21,22). Importantly, the relative prevalence of studies surrounding rivaroxaban in the orthopedic setting highlights the scarcity of literature on bleeding risks and complications for other Xais. Overall, this plethora of conflicting and contingent literature, without a comprehensive summary, leaves spinal surgeons without a clear understanding to guide perioperative Xai management.

The desire for more information regarding the optimal perioperative management of Xai is clear. Xai testing appealed to over 80.2% of respondents. If such a test was scientifically substantiated, our results indicate that surgeons would almost unanimously use it and patient's care would be directly influenced by it. However, the practicality and utility of such tests would still depend upon further research into the correlation between Xai activity levels and perioperative bleeding and thrombotic risk. A key limitation with current tests is the high cost and limited availability of these tests. Increased Xai use will likely necessitate better availability of tests and reversal agents, and clear guidelines.

There are several limitations inherent to survey methodology. This survey is representative of those who were willing to voluntarily complete the series of questions. As a multiple choice format, only a limited number of choices can be presented which may not accurately represent the full breadth of clinical scenarios or capture the nuances of these complex medical treatment decisions. Additionally, this survey is not meant to reflect the relative effectiveness of or endorse any particular treatment strategy. Rather, it was meant only to illustrate the current practice strategies among spine surgeons today. Despite these limitations, this survey does help to demonstrate the ongoing controversies and lack of consensus among surgeons and physicians regarding the use of direct factor Xai for perioperative anticoagulation in spine surgery.

Conclusions

In summary, there continues to be wide variability in the perioperative use of Xai among spine surgeons. The need for clear guidelines regarding the use of these medications is of increasing importance as the use of these medications becomes increasingly common. As testing for Xai levels

becomes more available, surgeons are likely to incorporate that data into their clinical practice, which will impact patient care. Management of Xai and prevention of thromboembolism is a particularly challenging task that should be well informed. Research into the current practices of spine surgeons would be further supported by increased survey participation and further questions regarding the perceived risks and advantages to increased or decreased perioperative Xai holds. The lack of established risks and guidelines for spine surgical patients taking Xai should be addressed with further research into Xai patient outcomes and optimal perioperative Xai hold length.

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Footnote

Reporting Checklist: The authors have completed the SURGE reporting checklist. Available at <https://dx.doi.org/10.21037/jss-20-637>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study and its components were reviewed and approved by the Mayo Clinic Institutional Review Board (Registration No.

IRB00000020). Subject's participation in the study was entirely voluntary with consent to participate received upon subject's submission of survey answers. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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