Perioperative Management for Complex Spine Fusion Surgery

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The number of complex spine surgeries performed worldwide on an annual basis continues to rise at a remarkable rate, with greater than 400,000 spinal fusions estimated to occur annually throughout the United States.[1] Some of the purported reasons for this trend include an aging population, with a concomitant higher preponderance of degenerative spinal conditions in the general population, and an increasing number of medically appropriate candidates for these interventions, due to improved overall medical therapies and perioperative optimization of comorbidities. Improvements in surgical technology, including minimally invasive techniques, and radiographic navigation tools have expanded the candidacy pool for complex multilevel spine fusion procedures even further.[2] Perhaps the most important reason for the rise in eligible patients, however, is the incorporation of proactive, patient-centered, and value-based perioperative protocols that are being increasingly implemented at many high-volume spine centers. These strategies have been adopted to optimize patient preparation and mitigate morbidity and mortality, thus creating "safer" spaces for complex surgical procedures in patients who would have previously been deemed medically inappropriate for surgery. Major complex spine fusion operations carry significant risk of postoperative complications with a mortality rate published in a retrospective cohort study of 1,288,496 patients reaching 0.2%.[1] Furthermore, several recent large prospective studies in patients undergoing spine fusion operations have included populations that clearly demonstrate increasing ages, a higher number of cardiac risk factors, and higher American Society of Anesthesiologists (Schaumburg, Illinois) physical classifications.[3–5] As this surgical population continues to grow, and become more complex, perioperative optimization and total care pathways are not only preferred methods, but essential elements in the care of the complex spine patient.

This clinical focused review presents and summarizes perioperative management recommendations with literature support and evidence based on guidelines, clinical trials, systematic review articles, and expert opinion. At times, various recommendations are supported by levels of evidence described as level of evidence A noting support with multiple randomized controlled trials, B-Randomized with at least one randomized controlled trial, B-Non-randomized from data supported by nonrandomized studies or meta-analysis, or C-Expert opinion based on expert opinion.

Special Considerations

Although most complex spine surgeries are performed for degenerative disease, there are additional considerations for patients who require surgical management of spinal trauma, infections, and metastatic or primary tumors. For instance, spine trauma patients are not afforded the ability to undergo preoperative screening or optimization of comorbidities. They also may present with trauma-induced coagulopathy or acute spinal cord injury, with or without neurogenic shock. These patients often benefit from hyperdynamic therapy with blood pressure augmentation to support spinal cord perfusion, overcome spinal cord edema, and hence mitigate secondary spinal cord injury. The most recent guidelines for spinal cord injury sponsored by the American Association of Neurological Surgeons (Rolling Meadows, Illinois) and Congress of Neurological Surgeons (Schaumburg, Illinois) recommend maintaining a mean arterial blood pressure greater than 85 mmHg for at least the first 7 days after acute injury (Class III evidence based on case series and expert opinion).[6,7] A recent review article reported the results of several comparative trials for vasopressor preference in the setting of acute spinal cord injury.[8] In summary, norepinephrine, dopamine, and phenylephrine all effectively augment mean arterial pressure. However, dopamine carries significant risks of arrhythmia and was found to increase intrathecal pressure, thereby impeding spinal cord perfusion. Norepinephrine demonstrated superior results in spinal cord blood flow studies and may be preferred over phenylephrine in the setting of high cervical injuries with risk of bradycardia, although both vasopressors are appropriate for hyperdynamic management in the perioperative setting of acute spinal cord decompression and

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fusion.[8] Furthermore, polytrauma patients should be evaluated for additional injuries that would precipitate hemorrhagic or hypovolemic shock, with particular attention to the possibility of traumatic brain injury. The management goals for patients with any degree of traumatic brain injury should follow the clinical care guidelines provided by the Brain Trauma Foundation (Palo Alto, California).[9]

With global advances in the systemic management of cancer, patient survival has improved, but this has resulted in higher rates of eventual metastases as well. Nearly 70% of patients with metastatic disease have spinal involvement, and up to 10% of those patients have a symptomatic lesion.[10,11] Surgical management of spinal oncologic disease has expanded significantly during the last several decades, with improved surgical options that are also able to facilitate radiotherapy, promote spinal stability, and improve pain relief and neurologic recovery, facilitating both curative and palliative goals.[10] The operative approaches range from minimally invasive techniques to extensive bony resections with complex staged surgeries and reconstructive procedures described in table 1. While traumatic and infectious indications for spine surgery should raise concerns about bleeding, poor neurologic outcomes, and an increased rate of postoperative complications overall, spine tumor surgery carries the added risks of thromboembolic disease, immunosuppression, and primary tumor or chemotherapy associated organ dysfunction.[11] The management of oncological spinal disease must consider the patient's history of cancer treatments and comorbidities as many chemotherapeutic agents are associated with cardiogenic, hepatic, and renal toxicity, or myelosuppression, which increases surgical risks and requires additional considerations for the patient's blood management plan.

Preoperative Optimization and Risk Stratification

The importance of a robust and multidisciplinary preoperative assessment in minimizing potentially avoidable and catastrophic perioperative morbidity for patients who present for complex spine fusion surgery cannot be overstated. Most patients undergoing complex spine fusion are referred for surgery for longstanding pain or instability secondary to kyphoscoliosis, spinal stenosis, or spinal lesions. Neurologic deficits may be associated with degenerative spinal disease, but most complex spine fusion operations are elective and thus benefit from adequate time for preoperative optimization of patient comorbidities and mitigation of modifiable risk factors.[1,7,12] In addition to standard preoperative assessment, patients anticipating complex spine surgery should be evaluated for the ability to tolerate prone positioning and all of its physiologic sequelae, acute blood loss anemia and hypovolemia, and longer operative durations.

It is critical to assess patients' functional status and proceed with cardiovascular stress testing for patients with risk factors for major adverse cardiac events who are unable to achieve 4 metabolic equivalents due to pain, immobility, or neurologic dysfunction. The commonly used Revised Cardiac Risk Index does not predict major adverse cardiac events in patients undergoing multilevel spine fusion operations and should not be used alone for cardiovascular risk assessments in this patient population.[13] The Charleston Comorbidity Index and the American College of Surgeons (Chicago, Illinois) National Surgical Quality Improvement

Table 1. Description of Open Spine Procedures for Complex Deformity Correction[10]

Surgical Procedure	Description and Notes
Anterior cervical discectomy and fusion	Supine positioning. Minimal blood loss. Emphasis on spinal cord perfusion and protection. May require blood pressure augmentation with higher MAP goals.
Anterior lumbar interbody fusion	Supine positioning. Minimal blood loss. Transperitoneal or retroperitoneal access with small risk of injury to the major vessels and visceral organs. Consider lower extremity pulse oximeter to continuously monitor perfusion.
Transforaminal lumbar interbody fusion	Prone positioning. May be conducted with a minimally invasive technique.
Direct lateral interbody fusion or lateral lumbar interbody fusion	Lateral decubitus positioning. May be conducted with a minimally invasive technique. Small risk of injury to great vessels that would be difficult to control surgically.
Extreme lateral interbody fusion or oblique lumbar interbody fusion	Lateral decubitus positioning. This exposure often does not require intraoperative neuromonitoring, but the risk of vascular injury and sympathetic plexus disruption is higher than with other approaches.
Posterior spinal fusion or posterior lumbar interbody fusion	Most common surgical approach for open multilevel fusion. Prone positioning. Highest risk of dural tear and nerve injury due to retraction.
Osteotomies	
Smith-Peterson osteotomy or Pointe osteotomy	Resection of posterior elements including facets, lamina, and ligaments. Often performed at multiple adjacent levels. May achieve up to 10 degrees of correction per level. Associated with moderate blood loss.
Pedicle subtraction osteotomy	Involves a 3-column osteotomy with resection of posterior spinal elements, pedicles, and part of the vertebral body. May provide up to 30 degrees of correction. Associated with significant blood loss (1,000–2,000 ml).
Vertebral column resection	Complete removal of a vertebral body. Associated with significant blood loss (1,000–2,000 ml) with risk to major vessels during resection.

MAP, mean arterial pressure.

Program calculator, which includes age, functional status, serum creatine, and American Society of Anesthesiologists Physical Status, offer reasonable predictive power for general complications and discharge to a skilled nursing facility after spine surgery. However, these calculators are not specific for spine surgery patients *per se*, and should not be used for organ-centered risk assessment.[14,15] The Risk Assessment Tool, derived and validated with a single-center cohort of spine surgery patients, provides a comprehensive risk assessment for adverse events after spine surgery with an area under the receiver operating curve of 0.7.[16] Independent risk factors identified in the Risk Assessment Tool include cardiovascular disease, diabetes, smoking history, systemic malignancy, obesity, substance abuse, and psychiatric disorders. The Risk Assessment Tool provides a risk score based on a calculation of comorbidity burden, age, sex, surgical complexity, and spinal disease diagnosis, and accounts for spinal tumor surgery, osteomyelitis, and acute spinal trauma.[16]

Should provocative cardiac testing be indicated based on the stepwise approach to perioperative assessment outlined in the American College of Cardiology (Washington, D.C.) and the American Heart Association (Dallas, Texas) guidelines for perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery,[17] stress echocardiography is the initial methodology of choice (as opposed to nuclear medicine testing). It not only provides risk assessment for ischemic heart disease but also provides an assessment of right ventricular function, pulmonary hypertension, and valvular disease. Patients with right-sided systolic dysfunction may not tolerate the right ventricular strain associated with prolonged prone positioning. The prone position can reduce stroke volume and increase right atrial and ventricular pressures, in the setting of higher intrathoracic pressure causing increased afterloads, with subsequent decrease in cardiac output.[7,18] Additionally, right ventricular strain that occurs with acidosis, and associated increases in pulmonary vascular resistance, create a precarious hemodynamic scenario for patients with a history of heart failure, or restrictive or obstructive lung disease. Obesity and its association with diabetes mellitus and sleep-disordered breathing can also introduce significant perioperative risk for major adverse cardiac events.[19] In light of these considerations, there should be a low threshold for patients to undergo investigation by echocardiography to determine both the presence and extent of systolic and diastolic heart dysfunction, given the risks of increased pulmonary vascular resistance associated with acute blood loss, rapid intravascular volume shifts, and mixed acidosis, which frequently occur during multilevel spine fusion procedures.

Preoperative patient education and counseling regarding smoking cessation and alcohol and illicit substance intake reduction or abstinence strategies should be a focus for risk modification in anticipation of complex spine surgery. This assessment process has a Class 1 recommendation from the most recent guidelines for perioperative care of patients undergoing major complex spinal instrumentation surgery published by the Society for Neuroscience in Anesthesiology and Critical Care (Raleigh, North Carolina).[1] Tobacco smoking represents an independent risk factor for postoperative delirium, pulmonary complications, major adverse cardiac events, and worse functional outcomes from surgery. Alcohol use is less strongly associated with postoperative complications, but may be linked to delirium, cardiopulmonary complications, postoperative infections, and pseudoarthoses.[2] Marijuana is the most prevalent psychotropic substance used throughout the United States, with a rising number of users given the widespread decriminalization of the use of cannabis products. A recent retrospective review of the National Inpatient Sample of elective spine procedures, from 2012 to 2015, demonstrated increased risk for postoperative thromboembolic events, adverse pulmonary complications, and higher rates of stroke in patients with preoperative cannabis use.[20] Thus, elective surgery should be delayed until patients demonstrate abstinence from smoking nicotine, cannabis, and minimal alcohol intake for at least 4 weeks before surgery.[12] Urine toxicology screening can detect drugs of abuse, and urine nicotine samples will demonstrate compliance with smoking cessation, while urine anabasine may be used for patients on nicotine replacement therapies to evaluate for active tobacco intake.[21]

Prehabilitation, while certainly a promising prospect, has not been shown to definitively improve outcomes in clinical trials, and the evidentiary support for prehabilitation protocols is moderate in recent systematic reviews of enhanced recovery after surgery protocols for spine procedures.[12] However, nutritional assessment with correction of vitamin deficiencies, especially vitamins D and B12, and caloric supplementation for malnourished states have been shown to improve surgical outcomes, reduce inpatient lengths of stay, and facilitate patient engagement with rehabilitation.[2,12] The most recent Society for Neuroscience in Anesthesiology and Critical Care guidelines emphasize the greater relevance of preoperative physiotherapy (including massage, stimulation, heat treatment, and exercise) as opposed to simple prehabilitation as a means to decrease pain and improve behavioral habits that promote early rehabilitation and improved quality of recovery. Furthermore, these guidelines also advise protein supplementation to improve muscle mass and endurance in frail and/or elderly patients anticipating spine fusion surgery (Class I, Level of Evidence C-Expert opinion).[1]

As the average age of patients undergoing spine surgery increases, the concern for frailty as a measure of high vulnerability to low-power stressors should be a focus of all preoperative assessment and risk stratification strategies for these patients. Calculated frailty indices are positively correlated with postoperative morbidity and mortality after spine surgery and have more predictive power than simple age or comorbidity index metrics for complications associated

with spine procedures.[3–5] There are several available tools that assess frailty in the preoperative setting and are specifically validated for these patients, including the modified Frailty Index, the Adult Spine Deformity Frailty Index, and the Spinal Tumor Frailty Index. Although there are multiple frailty assessment tools that are available and validated in this patient population, the question remains as to which tool is the best predictive metric. Future studies are needed to determine the most robust assessment tool that is both reliable and feasible to administer in the preoperative setting. At the current time, however, perhaps the most important goal should be to emphasize the highly significant role of preoperative frailty assessment as a component of preoperative risk stratification in patients anticipating spine surgery.[4,5]

Intraoperative Management

Aside from homeostatic and autonomic maintenance goals for intraoperative management during complex spine fusion operations, the anesthetic regimen must ensure a rapid postoperative recovery for motor and sensory assessment. Patients undergoing these surgeries are oftentimes exposed to significant risk of postoperative neurologic dysfunction, especially when the surgical plan entails correction of kyphoscoliosis, an intradural component, or vertebral body tumor resection. Continuous intraoperative neuromonitoring with somatosensory evoked potentials (SSEPs) and motor evoked potentials as well as electromyography is often employed to detect spinal cord ischemia or nerve root injury, respectively, in "real-time" in which reversal of a previous surgical maneuver or a change in the amount of sagittal surgical correction can avoid a neurologic injury. Thus, one of the main objectives of the maintenance anesthesia for complex spine surgery is to facilitate and optimize intraoperative neuromonitoring. Volatile anesthetics cause a dose-dependent decrease in the amplitude and increase in the latency of SSEPs, with an even more profound and qualitatively similar effect on motor evoked potentials.[22] Accordingly, many practitioners elect to maintain general anesthesia with total intravenous anesthesia. Although total intravenous anesthesia may represent the most facilitating regimen for patients with baseline neurologic deficits (*e.g.*, secondary to severe spinal canal stenosis, myelopathy, diabetic or intrinsic peripheral neuropathy, and so forth), or in the very young (less than 7 yr) or elderly (greater than 70 yr), a balanced approach with volatile anesthetics limited to 0.5 minimum alveolar concentration (MAC; excluding nitrous oxide) or less conserves the integrity of intraoperative neuromonitoring in most cases and may be associated with smoother and more rapid emergence.[1,2,7,22] Supplementary intravenous sedatives and hypnotics (most commonly propofol) are usually required, and a judicious opioid strategy, often in the form of a continuous infusion, is frequently employed, not only for adequate analgesia in the intraoperative and postoperative periods but also to prevent the movement response to noxious stimuli in the setting of absent or severely reduced neuromuscular blockade.[22] Bolus dosing of opioids (including remifentanil), sedative, hypnotics, and adjuncts for multimodal analgesia such as ketamine or dexmedetomidine may impact neuromonitoring signals with transient changes to the latency and amplitude of SSEPs that may be wrongfully attributed to surgical changes, or may reduce the ability to detect a meaningful change in motor or sensory signals.[23] Thus, medication boluses should be used with caution (and proactive team communication) or avoided, with a preference for infusions in the intraoperative period (Class I recommendation, Level of Evidence B-Non-randomized).[1]

Continuous intraarterial hemodynamic monitoring and frequent arterial blood gas sampling are recommended for most multilevel spinal fusion operations.[7] It not only provides consistent measure of systemic perfusion, dynamic assessment of systolic pressure, and pulse pressure variation but also allows ready access to arterial blood gas sampling for frequent monitoring of acidosis, hemoglobin, and electrolytes.[1] This is especially important in those patients with a history of pulmonary hypertension or right ventricular dysfunction, so as to avoid acute increases in pulmonary vascular resistance. Fluid resuscitation with a balanced crystalloid solution such as Plasma-Lyte (Baxter International Inc., USA) or Normosol (Pfizer Inc., USA) is preferred greater than 0.9% normal saline as these solutions contain less than 110 mEq chloride, and are thus less likely to precipitate a hyperchloremic metabolic acidosis and carry a lower risk of postoperative acute kidney injury.[1,24,25] Lactated Ringer's solution, also a balanced crystalloid solution, has a lower tonicity, and thus may contribute to detrimental soft-tissue swelling and spinal cord edema for patients who receive large-volume resuscitations or several liters as a maintenance fluid in the prone position for lengthy surgical procedures.[26] Although the literature is inconclusive, there are retrospective studies that support the use of colloids to supplement volume resuscitation in long spine surgeries (lasting more than 6 h) to mitigate the risk of postoperative visual loss (Class IIa recommendation, Level of Evidence C-Expert opinion).[1] Postoperative visual loss is a rare complication of complex spine surgery, but independent risk factors were identified as male sex, obesity, use of the Wilson frame for prone positioning, higher estimated blood loss, surgical duration, and fluid management using crystalloid without the administration of some nonblood colloid solutions.[27–29]

Intravascular volume assessment is challenging for patients in the prone position and requires the use of dynamic measurements of cardiac preload. Static values such as central venous pressure are not reliably accurate with the increase in intrathoracic pressure associated with prone positioning.[30] Multiple prospective trials have independently demonstrated the value of using dynamic measures of volume status, including systolic blood pressure, pulse pressure, and stroke volume variation, for patients undergoing posterior spinal fusions.[7] Although there are available monitoring systems for continuous noninvasive

measures of cardiac output and stroke volume, a simple observation of systolic blood pressure or pulse pressure variation from an indwelling arterial line as it responds to positive pressure ventilation will suffice. These metrics can be monitored continuously with an indwelling arterial catheter for reliable prediction of patients who will have a blood pressure response to fluid resuscitation. A prospective, nonrandomized, crossover study by Biais *et al.* demonstrated that a pulse pressure variation in excess of 15% with positive pressure ventilation predicts blood pressure augmentation with volume expansion for patients in the prone position.[30,31] While goal-directed fluid therapy based on these metrics aims to maintain euvolemia, it is also important to avoid hypotension that may be associated with prolonged general anesthesia in the prone position. Farag *et al.* recently established that the use of vasopressors does not promote acute kidney injury and should be considered a valuable tool to support and maintain systemic blood pressure.[32]

Perioperative Patient Blood Management

Spinal deformity correction surgery is often associated with acute blood loss ranging from less than 500 ml for simple one- to two-level fusions to more than 2,000 ml for complex multilevel instrumentation procedures with osteotomies.[33] Patient blood management requires proactive strategies to minimize perioperative bleeding and decrease the need for allogeneic erythrocyte transfusion. In the preoperative period, diagnosing and treating anemia with iron supplementation and erythrocyte-stimulating agents (*e.g.*, epoetin alfa) when appropriate significantly reduces the incidence of transfusion in spine surgery and reduces the risks of hospital readmission and prolonged length of stay associated with anemia.[34] Additional measures including active warming of the patient, the use of intraoperative cell salvage techniques, and proactive management of acute blood loss and coagulopathy have also been shown to reduce perioperative transfusion requirements.[35,12] Accordingly, it is imperative that active blood loss during surgical exposure, spinal instrumentation, or osteotomy correction be followed with frequent hemoglobin assessments every 1 to 2 h, and treated with volume resuscitation and blood product transfusions (Class I recommendation, Level of Evidence C-Expert opinion).[1] Blood loss can occur rapidly during spinal fusion operations with a risk of severe anemia and dilutional coagulopathy if acute bleeding is not anticipated and managed proactively. Cell salvage technology provides reliable assessment of acute blood loss as well as a meaningful strategy for return of salvaged autologous red blood cells.[1] Deliberate hypotension as a means of minimizing acute blood loss is no longer advised in the setting of spine surgery as it has been associated with postoperative morbidity, including major adverse cardiac events, and postoperative neurologic complications such as postoperative visual loss.[12,29] In accordance with the Society for Neuroscience in Anesthesiology and Critical Care guidelines for perioperative management of patients undergoing complex spine fusion procedures, blood pressure goals should be individualized to maintain adequate end-organ perfusion depending on the patient's preoperative comorbidities and risk for perioperative myocardial ischemia, stroke, or acute kidney injury.[1]

There is an extensive and recent body of literature investigating the prophylactic administration of antifibrinolytic agents such as tranexamic acid in spine surgery. Tranexamic acid is effective at minimizing total blood loss and significantly reducing the need for perioperative erythrocyte transfusion (Class I recommendation, Level of Evidence A).[1] However, there is wide variation (and wide institutional variability) on a purported ideal dosing regimen.[36,37] In most studies, administration typically entails a preincision loading dose of 10 to 30 mg/kg followed by an infusion with doses generally ranging from 1 to 3 $mg \cdot kg^{-1} \cdot h^{-1}$, although the literature also demonstrates significant outliers from these parameters.[38] "Low-dose" regimens are described in meta-analyses as less than 15-mg/kg loading dose with 1 $mg \cdot kg^{-1} \cdot h^{-1}$ or lower infusion rates, and are effective at reducing blood loss and transfusion requirements.[39] Large meta-analyses have also demonstrated improved efficacy and maintenance of safety with "high-dose" tranexamic acid regimens (greater than 30-mg/kg loading dose or an initial dose in excess of 2,000 mg) without associated increased incidences of thromboembolic phenomena, seizures, or nonbleeding mortality in populations of spine surgery patients as well as general noncardiac surgery patients.[38–40] While there is no clear consensus on the optimal dosing of tranexamic acid, one commonly employed and reported regimen for adult patients undergoing open spinal instrumentation of three or more vertebral levels is the administration of a 15-mg/kg intravenous loading dose with an intraoperative infusion of 1 $mg \cdot kg^{-1} \cdot h^{-1}$ until surgical closure.[36,37]

Blood product transfusion algorithms based on goal-directed therapy with conventional coagulation studies (*e.g.*, prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen concentration, and so forth) can be used to direct blood product administration, but more functional studies of whole blood hemostasis based on viscoelastography may be preferred for complex spinal deformity correction surgeries that incorporate osteotomies and severe angular corrections, and hence significant anticipated blood losses.[41] Figure 1 demonstrates one such algorithm for blood product transfusion that emphasizes a proactive approach to patient blood management with recommendations using conventional coagulation assays, as well as "trigger" events that should prompt the use of rotational thromboelastometry or thromboelastometry to guide further blood product management. Viscoelastography-based transfusion algorithms have not demonstrated significant reductions in transfusion requirements, or improved outcomes in the spine surgery population thus far, and should only be considered for the extraordinary circumstances of major bleeding and massive transfusion.[42] The suggested

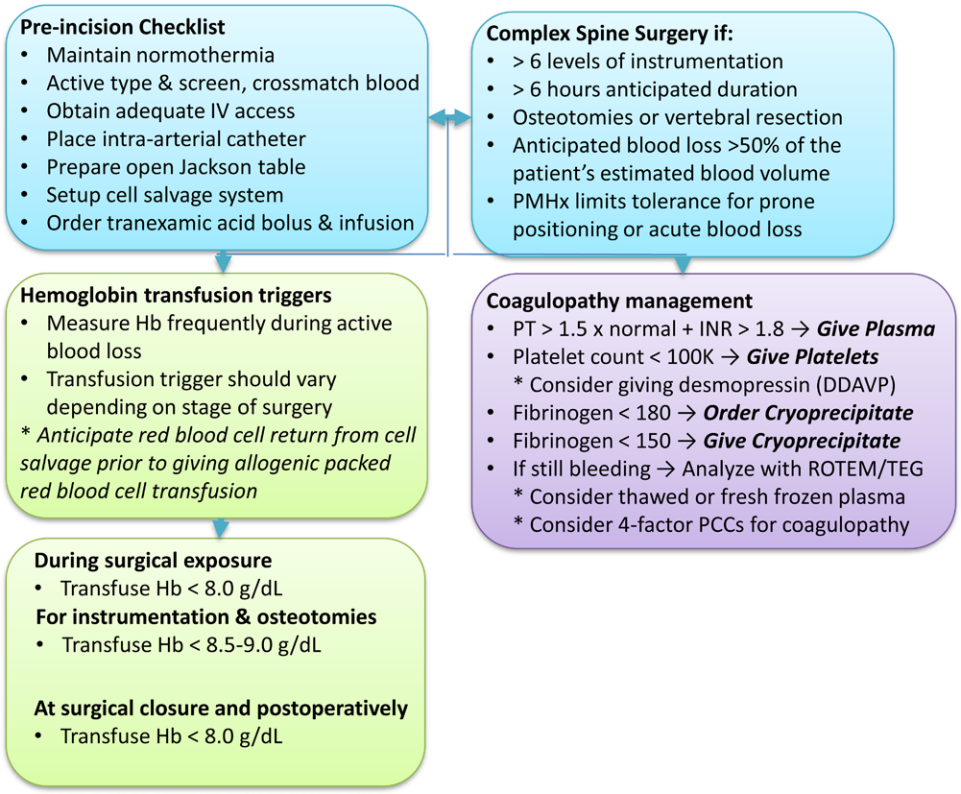

Fig. 1. Algorithm for patient blood management during spine surgery. Tranexamic acid bolus (10 to 15 mg/kg) and infusion (1 to 2 mg · kg^{-1} · h^{-1}) from incision to skin closure. Hb, hemoglobin; INR, international normalized ratio; IV, intravenous; PCCs, prothrombin complex concentrates; PT, prothrombin time; ROTEM, rotational thromboelastometry; TEG, thromboelastogram.

hemoglobin transfusion trigger of 8.0 g/dl during surgical exposure and the immediate postoperative period is based on the most recent guidelines from the American Association of Blood Banks (Arlington, Virginia) for major orthopedic surgery and patients with active blood loss (strong recommendation with moderate quality evidence).[42] Maintaining a higher hemoglobin (greater than 8.5 to 9.0 g/dl) during pedicle screw instrumentation and osteotomies or vertebral column resection is supported by the European guideline for management of major bleeding and coagulopathy after trauma (strong recommendation with low-quality evidence).[43] This algorithm also emphasizes aggressive treatment of hypofibrinogenemia with the use of cryoprecipitate as a low-volume alternative to plasma for fibrinogen repletion and hemostatic control, and has been shown to reduce overall transfusion requirements in spine procedures that are associated with significant blood loss.[35,44,45] Given the risk of catastrophic neurologic complications associated with epidural hematomas, several guidelines recommend maintaining a plasma platelet count of at least 100,000/μl for surgeries involving or adjacent to the nervous system, including spinal instrumentation.[46] The algorithm presented in figure 1 also suggests the use of desmopressin and prothrombin complex concentrates where appropriate as adjuvants to improve platelet function and mitigate severe dilutional coagulopathy, respectively.[35]

Perioperative Pain Control

Given both the invasive nature of complex spine fusion surgery and the frequency with which these patients experience significant and chronic preoperative pain, patients are at risk for moderate to severe postoperative pain. Past reports documented a range of preoperative opioid dependence in 46% of patients undergoing spine surgery with 61% of patients using greater than 50 morphine mg equivalents per day, and 23% needing more than 100 morphine mg equivalents per day.[47] Preoperative narcotic use, along with age, history of anxiety or depression, current smoking, and surgical complexity, are all components of the Postoperative Analgesic Intake Needs Score and are risk factors for postoperative pain after spine surgery.[47] Several of these components are modifiable risks, as discussed above, with significant benefits associated with reductions or elimination of opioids in the preoperative setting.[1,2] Unfortunately, greater than 50% of patients who undergo multilevel instrumentation still report inadequate analgesia in the immediate

postoperative period.[48] Severe postoperative pain can lead to chronic pain syndromes, poor engagement with rehabilitation, increased lengths of stay, and overall lower quality of recovery.[2,48] Perioperative multimodal analgesia, incorporating the judicious use of opioids, or an "opioid-sparing" technique, should incorporate preoperative elements such as acetaminophen (Class IIb recommendation, Level of Evidence B-Non-randomized)[1] and nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 specific antagonists (Class IIb recommendations, Level of Evidence B-Randomized).[1] Acetaminophen should be continued into the postoperative period with scheduled dosing. Celecoxib is the most widely studied NSAID in spine surgery trials and has been shown to reduce opioid requirements in the first 24 to 48 h postoperatively without associated bleeding risks or surgical complications.[49–51] It is important to note, however, that the overall risks of bleeding and poor bone healing are mitigated by limiting NSAIDs to a single preoperative dose, or at most limiting its use to less than 2 weeks (strong recommendation based on moderate quality of evidence).[2,7,50]

Gabapentin and pregabalin have been well-studied as components of multimodal analgesia regimens in the spine patient population. Several trials demonstrate opioid-sparing results,[49,51] but more recent meta-analyses and systematic reviews report equivocal pain outcomes and significant concerns for increased risks of sedation with a published number needed to harm of 25.7, and a higher incidence of naloxone use for respiratory depression in the setting of coadministration with long-acting opioids.[49–52] Specifically, a recent population-based cohort study using the Premier Healthcare Database with greater than 265,500 lumbar fusion cases demonstrated an increased odds ratio of naloxone use by 50%, independent of opioid dosing for patient who received gabapentinoids ($P < 0.001$).[49] According to the Society for Neuroscience in Anesthesiology and Critical Care guidelines referenced above, routine use of pregabalin and gabapentin is not well-supported (Class III recommendation, Level of Evidence B-Randomized).[1] Thus, in the naïve patient (*i.e.*, not previously prescribed for chronic neuropathic pain), these medications should be used with great caution and limited to lower preoperative doses given selectively in patients undergoing complex multilevel spinal deformity correction, with particular attention to those patients who will require postoperative intravenous opioids, in whom this class is best avoided.

Ketamine, a *N*-methyl-D-aspartate receptor antagonist significantly improves postoperative pain scores when used in conjunction with long-acting opioids.[48] It is frequently administered as a low-dose infusion (*e.g.*, 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$) from the time of anesthetic induction through the immediate postoperative period. However, ideal dosing regimens for this indication are not clear or consistent in the literature, and further trials are necessary to clarify the best dosing strategies of ketamine for spine surgery patients, especially in the setting of potential hospital restrictions on the use of ketamine infusions for inpatients.[48,51,52]

For most institutions, the judicious use of opioids remains the mainstay of intraoperative analgesia for complex spine surgery, in conjunction with many of the multimodal components mentioned above. Those opioids that are potent and easily and rapidly titratable as intravenous infusions, with favorable pharmacokinetic profiles, such as sufentanil and remifentanil, are generally preferred. The Society for Neuroscience in Anesthesiology and Critical Care guidelines highlight that sufentanil, remifentanil, and fentanyl may all be used for general anesthesia or total intravenous anesthesia without jeopardizing intraoperative neuromonitoring (Class IIb, Level of Evidence C-Expert opinion).[1] However, high-dose remifentanil may impact SSEPs, and thus the infusions rates should be limited to less than 0.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in cases with intraoperative neuromonitoring (Class IIb, Level of Evidence B-Randomized).[1] Furthermore, remifentanil has been associated with hyperalgesia, but this finding is mitigated by the concomitant use of ketamine.[1] Recent trials demonstrate improved pain management in short- and long-term outcome assessments with the use of intravenous methadone, a long-acting opioid with some *N*-methyl-D-aspartate receptor activity, and especially when it is used in conjunction with ketamine.[48,53] In elderly patients, there is concern for certain adverse effects related to methadone (*e.g.*, poorly predicted hepatic metabolism leading to delayed respiratory depression, arrhythmogenic potential, and so forth), but a dose of 0.2 to 0.3 mg/kg administered at the beginning of surgery has not been associated with adverse outcomes in adult patients up to 80 yr old in recent randomized clinical trials.[48,52,53] A clinical focus review of intraoperative methadone for surgical patients by Murphy and Szokol published in this journal in 2019 highlights the safety of methadone for surgical patients but remains cautious about the limited representation of high-risk patients (the elderly, obese patients, and those with a history of cardiovascular disease) in study subjects included in randomized controlled trials.[54]

With regards to optimal analgesic management, an area of rapid growth and great potential lies within the domain of regional anesthesia. Epidural anesthesia is generally not applicable to complex multilevel spine fusion operations given the duration of surgery, risks of hemodynamic instability, and impact on intraoperative neuromonitoring associated with sympathectomy.[1,7] However, intrathecal morphine has been well-studied and demonstrated reductions in the need for rescue opioids at doses of 0.2 to 0.4 mg, but this method of administration has a risk of delayed respiratory depression.[55] Therefore, the Society for Neuroscience in Anesthesiology and Critical Care guidelines recommend patients who receive intrathecal morphine be monitored with continuous end-tidal capnography in the postoperative setting.[1] More commonly, the practice of wound infiltration with local

anesthetics should be discussed with the surgical team as a component of multimodal analgesia. It has been shown to reduce postoperative pain scores, prevent nausea and vomiting, and shorten inpatient length of stay (Class IIa, Level of Evidence B-Randomized).[1,7] The use of liposomal bupivacaine remains an experimental technique undergoing current investigation in simple spine fusion patients (NCT03745040). Its clinical benefits are not yet supported by the current literature for complex multilevel spinal procedures (Class III, Level of Evidence C).[1]

While most anesthesiologists will be familiar with the use of local anesthetics and neuraxial techniques for postoperative analgesia in this patient population, there have been great advances in other regional techniques, to supplement or substitute intravenous agents. Specifically, there are some high-quality prospective and randomized studies supporting the use of erector spinae blocks in thoracolumbar surgery, with promising data emerging for other cervical and truncal fascial plane blocks (including multifidius cervicis blocks, intersemispinal plane blocks, thoracolumbar interfascial plane blocks, and quadratus lumborum blocks, among others).[56,57] While an exhaustive description of these various regional techniques lies outside of the scope of this review, this is an area that holds great potential within the perioperative care of complex spine surgery patients, becoming part of standard care pathways and algorithms in some institutional practices.

Future Directions

As the population of complex spine surgery patients continues to expand, along with the sheer complexity of the surgeries themselves, there is ongoing need for high-quality research to clarify best practices in all facets of the perioperative care of these patients from preoperative risk stratification and frailty assessment to methods for mitigating postoperative complications. Further research should aim to elucidate the ideal dosing strategy for tranexamic acid to reduce acute blood loss anemia and hypovolemia and should continue to confirm the minimal thromboembolic risk that this therapy incurs. Furthermore, the multimodal analgesic strategies that best suit these patients, including best practice recommendations for the use of various classes of pharmacologic agents such as methadone, ketamine, and gabapentinoids, need to be better supported in high-quality clinical trial results. Finally, the role of various regional anesthetic techniques to provide a vast and unique opportunity to improve outcomes for this vulnerable population remains to be fully appreciated with stringent literature and guideline support.

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Competing Interests

Dr. Koski reports paid consultancy relationships with the following entities: Medtronic (Minneapolis, Minnesota), Nuvasive (San Diego, California), Seaspine (Carlsbad, California), and Alphatec (Carlsbad, California). None of these relationships represents a financial or intellectual conflict of interest with this work. The other authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Jay J. Jacoby, Pied Piper of Anesthesiology

According to German folk legend, the Pied Piper played a magical melody to lure rats, then children, from the town of Hamelin (*right*). The gentle Jay J. "J.J." Jacoby, M.D., Ph.D. (1917 to 2003, *left*), attracted so many medical students into anesthesiology that he was affectionally called the "Pied Piper" of the nascent specialty. Shortly after graduation from the University of Minnesota School of Medicine, the attack on Pearl Harbor had pressed J.J. into military service. His limited experience anesthetizing patients as an obstetrics intern identified him as an "anesthetist," and during World War II, J.J. honed resuscitation and intubation skills in combat zones (*left*, *sitting on an unexploded bomb*). His endotracheal (ET)-tube wizardry not only with difficult airways but also with casks of wine bewitched his fellow officers. By stringing together ET tubes and inserting the end into a barrel, soldiers who bounced along dirt roads could siphon off the precious cargo without spilling it on their uniforms. The war would spark for J.J. and many other novice anesthetists a lifelong passion, and when he returned home, he switched into an anesthesiology residency. At age 29, the whimsical pioneer was recruited to Ohio State University as Professor of Anesthesia. During an enchanting career that involved almost 40 years as a department chair at Ohio State, Marquette University, and Jefferson Medical College, J.J. Jacoby inspired hundreds to follow in his footsteps. (*Bull Anesth Hist* 2003;21(2):8. *Careers in Anesthesiology, Vol. VII,* 2002. Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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