Efficacy of intraoperative cell salvage in spine surgery: a meta-analysis

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OBJECTIVE Intraoperative cell salvage systems, or cell savers, are widely used for the management of blood loss in patients undergoing spine surgery. However, recent studies report conflicting evidence of their efficacy. The purpose of the meta-analysis was to investigate the efficacy of cell savers in reducing blood transfusion requirements in patients undergoing spine surgery.

METHODS Both retrospective and prospective studies that investigated the efficacy of cell savers in reducing transfusion requirements in spine surgery patients when compared with control patients were identified from MEDLINE, Embase, Cochrane Collaboration Library, Google Scholar, and Scopus databases. Outcome data extracted included number of patients receiving allogenic transfusions (transfusion rate); units of allogenic transfusions; postoperative hemoglobin; costs; operative time; and complications. RevMan 5 software was used to perform statistical analyses. A random-effects model was used to calculate pooled odds ratios (with 95% CIs) and weighted mean differences (WMDs [95% CI]) for dichotomous and continuous variables, respectively.

RESULTS Eighteen studies with 2815 patients in total were included in the meta-analysis. During spine surgery, the use of intraoperative cell salvage did not reduce the intraoperative (OR 0.66 [95% CI 0.30, 1.41]), postoperative (OR –0.57 [95% CI 0.20, 1.59]), or total transfusion (OR 0.92 [95% CI 0.43, 1.98]) rate. There was a reduction in the number of allogenic units transfused intraoperatively by a mean of 0.81 (95% CI –1.15, –0.48). However, there were no differences in the number of units transfused postoperatively (WMD –0.02 [95% CI –0.41, 0.38]) or the total units transfused (WMD 0.08 [95% CI –1.06, 1.22]). There were also no differences in operative time (WMD 19.36 [95% CI –2.43, 42.15]) or complications reported (OR 0.79 [95% CI 0.46, 1.37]) between groups. A difference in postoperative hemoglobin (WMD 0.54 [95% CI 0.11, 0.98]) between both groups was observed.

CONCLUSIONS Cell saver is efficacious at reducing intraoperative allogenic units transfused. There is no difference in transfusion rates, postoperative units transfused, and the total number of units transfused. Further cost analysis studies are necessary to evaluate the cost-effectiveness of this method of blood conservation.

■ **CLASSIFICATION OF EVIDENCE** Type of question: therapeutic; study design: meta-analysis; strength of recommendation: low.

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KEYWORDS cell saver; cell salvage; spine surgery; blood conservation strategy

SPINE surgeries, particularly deformity correction surgery, may result in major blood loss due to the long operative times, extensive muscle stripping, and large wound surfaces involved.¹⁵ Several blood conservation strategies are employed to minimize blood loss and the requirement for allogenic blood transfusions. Though rare, complications associated with allogenic blood transfusions include infection transmission, fluid over-

load, hemolytic reactions, and transfusion-related acute lung injury.² In addition, blood products may impair the body's natural immune responses, increasing the risk of postoperative bacterial infection.²⁷ Intraoperative cell salvage is a blood loss management strategy in which blood collected from the operative field or postoperatively from suction drain is anticoagulated and centrifuged to isolate red blood cells, which are then washed and filtered before

ABBREVIATIONS AIS = adolescent idiopathic scoliosis; QALY = quality-adjusted life year; WMD = weighted mean difference.

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■ CLASSIFICATION OF EVIDENCE

Type of Question Therapeutic

Study Design Meta-Analysis

Strength of Recommendation Low

Summary Statement

This meta-analysis of 15 observational and 3 randomized controlled trials examining the use of intraoperative cell salvage in patients undergoing various spine procedures found no convincing evidence of benefit, and it underscores the need for further well-designed trials.

Classification of Evidence

Cheriyian and colleagues have undertaken a very timely and comprehensive quantitative systematic review of English-language studies evaluating the potential benefit of intraoperative cell salvage in patients undergoing spine surgery. The authors identified 18 studies that fulfilled their inclusion and exclusion criteria, and they calculated summary statistics for 9 prespecified primary and secondary outcomes using Cochrane Collaboration software. When performed to exacting standards on an adequate body of evidence, meta-analyses have the potential to provide the most comprehensive and precise evidence-based estimates of the true clinical effect of a given intervention. The key word in the preceding sentence is “precise.” The primary contribution of a meta-analysis is to increase the precision (i.e., narrow the confidence interval) of an effect size estimate. Meta-analyses, no matter how well performed, cannot improve the quality of the existing evidence, and they do not create new evidence. Unfortunately, despite good statistical technique, the authors of this paper were not able to provide an answer to their questions about the value of cell salvage technology. They found no benefit of cell salvage for 7 of their 9 prespecified outcomes. In the two outcomes for which a benefit was documented, the improvement in postoperative hemoglobin (0.54 g/dl) was statistically significant but of minimal clinical importance, and the reduction in mean units of blood transfused intraoperatively was modest (0.81 units), marred by a substantial risk of bias and marginalized by the lack of difference in postoperative or overall units transfused. As mentioned, meta-analyses cannot improve the quality of the evidence they analyze. Cheriyian and colleagues identified 15 observational studies relevant to their question. Because of their retrospective nature and unmasked primary outcome measure (decisions regarding blood transfusion were made by unmasked treating physicians), all 15 of these studies constitute class III evidence at best and more likely class IV evidence using AAN/AANS/CNS criteria. For similar reasons, the 3 randomized controlled trials also provide only class III evidence. In addition, for 8 of the 9 outcomes analyzed, heterogeneity among included studies was high (this was expressed mathematically by an I^2 value > 50% and qualitatively by the substantial differences among studies in patient populations, interventions, outcome measures, and study methodologies). The other unique threat to reliability that meta-analyses are subject to is publication bias—the selective omission from publication of small, negative trials. Although the authors acknowledge this risk, they do not provide data (from funnel plots or quantitative

calculations) regarding the degree of potential publication bias. Because of the limitations of their data, the authors’ meta-analysis cannot provide strong guidance for clinicians regarding the usefulness of cell salvage during spine surgery. This does not mean that their meta-analysis is of no value. On the contrary, it emphasizes the paucity of good evidence and should be taken as a call to clinicians to support high-quality randomized trials. Until data from such studies become available, however, practitioners must rely on clinical judgment, unsupported by compelling evidence.

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reinfusion. This method has been shown to salvage 60%–80% of red cells lost during surgery.⁵ Early studies on efficacy^{25,26} found this method to be beneficial for children and young adults undergoing spinal surgery. Furthermore, the authors found cell saver to be more cost-effective than allogenic transfusions in patients with operative blood loss greater than 2000 ml, due to the high costs of these transfusions. More recent studies, however, have reported conflicting evidence on the efficacy of cell savers and the cost-effectiveness in reducing blood transfusion requirements in spine surgery. The purpose of this meta-analysis was to investigate the efficacy of cell savers in reducing allogenic transfusion rates in patients undergoing spine surgery. A review of cost analysis studies was also performed.

Methods

The meta-analysis was performed according to the PRISMA requirements for quality reporting of systematic reviews and meta-analyses.¹⁹

Electronic Literature Search

We conducted a systematic review of the published literature through January 2019 on the efficacy of cell savers in spine surgery. Our results were limited to studies published in the English language over the past 30 years. Databases searched included MEDLINE, Embase, Cochrane Collaboration Library, Google Scholar, and Scopus. In addition, we examined reference lists of included articles for any studies missed on our initial search. Search terms included “intraoperative cell salvage,” “cell saver,” and “spine.”

Study Selection

We performed a systematic review of all prospective and observational studies, assessing the efficacy of cell savers compared with no cell savers on the transfusion requirements in patients undergoing spine surgery. We included all age groups and all spinal procedures, excluding spinal tumor and trauma surgery. Studies were excluded if they did not have a control cohort. In addition, we excluded review articles, case reports, and case series. Eligible publications were selected by two independent reviewers,

and any disagreement was settled after discussion with a third reviewer.

Quality Assessment

Assessments of quality were done for each published study by two independent reviewers. Assessment of non-randomized studies was done using a modified Newcastle-Ottawa scale. Using this assessment each study is judged based on 9 items in 3 different categories: selection of study groups (4 items), comparability of study groups (2 items), and ascertainment of outcomes of interest (3 items). Points are awarded in each section, with a maximum of 9 points awarded for lowest-bias observational studies. Bias of study was categorized as high (0–3), medium (4–6), or low (6–8). Prospective studies were assessed as outlined by Jadad et al.¹³ Included studies were graded in 3 categories: randomization, comparability, and outcome. Studies graded with a score of 0–1, 2–3, or 4–5 (out of a maximum score of 5) were considered to be of high, medium, or low bias, respectively. Studies graded as having a high risk of bias according to either scale were discussed among all reviewers to decide on inclusion.

Data Extraction

Each study was thoroughly reviewed independently by two reviewers to ensure complete and accurate data extraction. General study characteristics extracted were as follows: study design and purpose, study group size, mean age, sex distribution, geographical location, inclusion/exclusion criteria, and publication date. Primary outcomes extracted included number of patients who received allogenic transfusions (transfusion rate), units or volume of allogenic transfusions, and postoperative hemoglobin concentration. Secondary outcomes of interest included operative time and transfusion-related complications, such as immunological reactions, hemodynamic overload, transfusion-related acute lung injury, and postoperative bacterial infection. In cases of insufficient data, the corresponding author was contacted for clarification and information.

Statistical Analysis

Meta-analysis was performed using Review Manager Software 5.0 (Cochrane Community). Weighted mean differences (WMDs) with 95% CIs and pooled odds ratios with 95% CIs were used to assess effect size of continuous data (e.g., volume of blood loss, hemoglobin concentration) and dichotomous data (e.g., number of transfusions, incidence of complications), respectively. A random-effects model was used in all analyses. Publication bias was assessed by funnel plot and I^2 statistic for heterogeneity. An $I^2 > 50\%$ was considered suggestive of substantial heterogeneity.

Results

Study Selection

Our search resulted in a total of 9550 citations. After screening by title, abstract, and entire article, 18 studies were identified that met all inclusion criteria and had us-

FIG. 1. PRISMA flow diagram of study selection.

able data. Figure 1 shows the method of study selection and inclusion. Study characteristics of included studies are described in Tables 1 and 2.

Quality Assessment

The modified Newcastle-Ottawa scale score of retrospective studies varied between 7 and 8 (low bias) (Table 3). The two prospective studies had a Jadad score of 0 and 2 (high and medium bias, respectively) (Table 3). Sample size varied between 42 and 680 patients, with a mean of 156 patients in each study.

Effect on Transfusion Rate

Thirteen^{3,4,6,8,11,12,14,16,18,21–23,30} studies (n = 2118; cell saver/control = 1078/1040) reported on the number of patients transfused in each group. Eight studies^{4,6,8,11,14,21–23} (n = 1205; cell saver/control = 444/761) reported data on intraoperative transfusion rate. The cell saver group did not show a significant difference in intraoperative transfusion rates (OR 0.66 [95% CI 0.30, 1.41]; p = 0.28; I^2 = 81%). There was also no difference in the postoperative transfusion rates among the 5 studies^{8,14,18,21,22} (n = 920; cell saver/control = 364/556) that reported on outcomes (OR 0.57 [95% CI 0.20, 1.59]; p = 0.28; I^2 = 79%). Similarly, in the 7 studies^{3,4,6,12,16,22,27} (n = 920; cell saver/control = 364/556) that reported on total transfusion rates, there was no significant difference between cell saver and control cohorts (OR 0.92 [95% CI 0.43, 1.98]; p = 0.84; I^2 = 83%) (Fig. 2).

TABLE 1. Assessment study of bias using Newcastle-Ottawa scoring for retrospective studies

Authors & Year	Criteria for Study Bias in Retrospective Studies			Total Score	Bias Assessment
	Selection	Comparability	Outcome		
Akgül et al., 2014	4	1	3	8	Low
Behrman & Keim, 1992	3	1	3	7	Low
Bowen et al., 2010	4	1	3	8	Low
Canan et al., 2013	4	1	3	8	Low
Choi et al., 2019	4	1	3	8	Low
Ersen et al., 2012	4	1	3	8	Low
Gause et al., 2008	3	1	3	7	Low
Gum et al., 2017	4	1	3	8	Low
Kelly et al., 2015	4	0	3	7	Low
Miao et al., 2014	4	1	3	8	Low
Mirza et al., 2009	3	1	3	7	Low
Oliveira et al., 2017	4	1	3	8	Low
Owens et al., 2013	3	1	3	7	Low
Reitman et al., 2004	3	1	3	7	Low
Weiss et al., 2007	3	1	3	7	Low

Effect on Units Transfused

Six studies,^{6,7,10,16,17,21} which included 515 patients (cell saver/control = 301/214) reported on the mean units of blood products transfused intraoperatively. The cell saver usage reduced the number of units transfused intraoperatively by an average of 0.81 units (95% CI -1.15, -0.48; $p < 0.01$) when compared to controls (Fig. 3A). However, data from 6 studies^{1,7,10,16,17,21} comprising 470 patients (cell saver/control = 269/201) did not show a significant difference in the mean number of units transfused postoperatively (WMD -0.02 [95% CI -0.41, 0.38]; $p = 0.93$) (Fig. 3B). There was also no difference in total units transfused (WMD 0.08 [95% CI -1.06, 1.22]; $p = 0.89$) between the two groups in the 5 studies^{1,8,10,17,21} that reported on these outcomes (Fig. 3C). There was a statistically significant and modest difference in postoperative hemoglobin by an average WMD of 0.54 (95% CI 0.11, 0.98; $p = 0.01$) between the cell saver and control groups (5 studies;^{1,4,8,16,21} $n = 334$) (Fig. 4).

Effect on Operative Time and Complications

Eight studies^{1,4,6-8,14,16,21} ($n = 1033$; cell saver/control =

394/639) reported on the operative time between the cell saver and control groups (WMD -19.36 [95% CI -2.43, 41.15]; $p = 0.08$) (Fig. 5A). There was no difference in complications (OR -0.78 [95% CI 0.36, 1.68]; $p = 0.57$) reported in 5 studies^{6,7,14,16,23} ($n = 957$; cell saver/control = 369/588) (Fig. 5B).

Discussion

This meta-analysis supports modest efficacy of intraoperative cell salvage systems in reducing intraoperative units transfused in patients undergoing spine surgery. No significant effects were observed for any other primary outcomes, including intraoperative, postoperative, and total transfusion rates or postoperative and total units transfused. There was a small benefit with respect to postoperative hemoglobin. However, there was no difference in any secondary outcomes, including operative time and the incidence of complications.

To our knowledge, this is the first meta-analysis to investigate the efficacy of cell savers in reducing the transfusion burden in patients undergoing spine surgery. A 2010 systematic review by Elgafy et al.⁹ reported that there was little evidence to support its cost or effective use during routine spine surgery. This recommendation was based on a review of 3 retrospective studies of poor methodological quality.

One would expect cell savers to reduce the units transfused, since much of the patient's blood loss is returned intraoperatively, and our results support this intuition. However, we did not observe any reduction in transfusion rates in the cell saver group, leaving both patient cohorts equally exposed to the potential dangers and complications associated with allogenic blood transfusions. However, the advantage of a reduction in units transfused may improve patient outcomes by decreasing the risk of the dose-dependent complications of transfusions, such as hemodynamic overload, and the odds of transmitting blood-

TABLE 2. Assessment of study bias using Jadad scoring for prospective studies

Authors & Year	Criteria for Study Bias in Prospective Studies			Total Score	Bias Assessment
	Randomization	Blinding	Dropout		
Djurasovic et al., 2018	1	0	1	2	Medium
Liang et al., 2015	2	0	0	2	Medium
Savvidou et al., 2009	0	0	0	0	High

TABLE 3. Characteristics of included studies

Authors & Year	Country	Sample Size (cell saver/control)	Surgery	Transfusion Criteria	Limitations
Akgül et al., 2014	Turkey	16/17	Posterior spinal fusion	Hb <8 mg/dl w/ clinical findings of anemia; absolute <7 mg/dl	Small sample size
Behrman & Keim, 1992 (i)	USA	25/25	Posterior spinal fusion	Surgeon decision	Small sample size; no transfusion guidelines
Behrman & Keim, 1992 (ii)	USA	25/25	Posterior spinal decompression and fusion	Surgeon decision	Small sample size; no transfusion guidelines
Bowen et al., 2010	USA	33/21	Posterior spinal fusion	Hb <8 mg/dl w/ clinical findings of anemia; absolute <7 mg/dl	Small control group; different between-group surgical blood loss rates
Canan et al., 2013	USA	48/30	Posterior spinal decompression and fusion	Hb <8 mg/dl w/ clinical findings	Different between-group surgical blood loss rates
Choi et al., 2019	Korea	81/32	≥5-level posterior spinal fusion	Hb <7 mg/dl or if anemic symptoms; surgeon decision	Small sample size
Djurasovic et al., 2018	USA	48/47	2- or 3-level posterior spinal fusion	Hb <7 mg/dl or if anemic symptoms; surgeon decision	Small sample size; no postoperative transfusion guidelines
Ersen et al., 2012	Turkey	23/22	Posterior spinal fusion	Hb <8 mg/dl w/ clinical findings of anemia; absolute <7 mg/dl	Small sample size
Gause et al., 2008	USA	141/47	Posterior spinal decompression and fusion	Hb <7 mg/dl; Hct <21; or symptomatic anemia	Selection bias
Gum et al., 2017	USA	427/253	Posterior, anterior-posterior spinal fusion	Surgeon decision	Intercenter variability; no transfusion guideline; preoperative Hb data unavailable
Kelly et al., 2015	USA	86/422	≤3-level laminectomy and fusion	No guideline	Small sample size in cell saver group
Liang et al., 2015	China	55/55	Posterior spinal fusion	Hb <7 mg/dl or symptomatic anemia	Small sample size
Miao et al., 2014	China	67/180	Posterior spinal fusion	Hb <8 mg/dl w/ clinical findings of anemia; absolute <7 mg/dl	Different between-group surgical blood loss rates
Mirza et al., 2009	UK	104/33	Posterior spinal fusion	>1 L operative loss; Hb <7 mg/dl	Small control group
Oliveira et al., 2017	Brazil	27/15	Posterior spinal fusion	Hb <8 mg/dl w/ clinical findings of anemia; or Hb <7 mg/dl	Small sample size
Owens et al., 2013	USA	99/39	Posterior spinal fusion	Hb <7 mg/dl; symptomatic anemia; or preexisting cardiopulmonary disease	Different between-group surgical blood loss rates
Reitman et al., 2004	USA	56/46	Posterior spinal fusion	Not mentioned	Included different procedures; no transfusion guidelines
Savvidou et al., 2009	Greece	25/25	Posterior spinal fusion	Hb <7 mg/dl; Hct <21; or symptomatic anemia	Included different procedures
Weiss et al., 2007	USA	58/37	Posterior spinal fusion	Surgeon decision	No transfusion guidelines

Hb = hemoglobin; Hct = hematocrit.

borne infections. Numerous studies have also shown dose-dependent increases in morbidity, mortality, and cost with each unit of packed red blood cells that is transfused.²⁰

Among the 7 studies that included adolescent idiopathic scoliosis (AIS) patients, 1 study⁴ reported on intraoperative transfusion rate, 1 study¹⁸ on postoperative transfusion rate, and 3 studies^{7,8,9} on total transfusion rate data. The mean number of levels fused among these studies varied from 9.8 to 12.9. There was no significant difference in total transfusion rate (OR = −0.39 [0.13, 1.15]; $p = 0.03$) between cell saver and non-cell saver groups in the AIS cohort. In the AIS cohort, there was a decrease in number

of allogenic units transfused intraoperatively by 0.70 (95% CI 1.22, 0.19; $p = 0.04$, $\chi^2 = 6.34$, $I^2 = 68\%$) among the 3 studies that reported on the outcome.^{11,13,14} However, there was no difference in the postoperative allogenic units transfused (OR 0.10 [95% CI −0.38, 0.58]; $p = 0.005$) or total units transfused (OR = 0.93 [95% CI −0.40, 2.26]; $p = 0.005$). There were 4 studies on patients with adult degenerative spine disease. However, the only outcome that was consistently reported among them was intraoperative transfusion rate. There was no difference in this outcome between the cell saver and non-cell saver groups (OR 1.19 [95% CI 0.41, 3.39]; $p < 0.01$; $I^2 = 84\%$).

FIG. 2. Forest plots showing the effect of cell savers on transfusion rates. M-H = Mantel-Haenszel.

Given that the average reduction in intraoperative allogenic units transfused is less than 1 unit when using the cell saver, this beneficial effect must be balanced against the increased costs in order to make an appropriate recommendation. To better understand the implications of costs, we reviewed 4 studies that investigated the cost-effectiveness of cell saver usage in spine surgery. In a retrospective review of 102 consecutive cases of posterolateral fusion with instrumentation at one institution, Reitman et al.²³ reported an average charge of \$512 per patient for the cell saver and \$270 per patient for autotransfusion in the control group. The cost of transfusion for allogenic blood was \$250. The authors attributed the higher cost of cell saver usage to the fixed cost of the operation, regardless of the amount of blood salvaged and replaced. Due to higher costs for the cell saver, the authors recommended its use only in cases in which anticipated blood loss is extremely high and the expected charge for allogenic transfusion may equal or exceed the fixed cost of using a cell saver, which carries no marginal cost of use.

Savvidou et al.²⁴ evaluated the efficacy and cost-effectiveness of cell saver usage at one European institution. They estimated significantly lower costs associated with

transfusion in the cell saver group than the non-cell saver group ($\text{€}995 \pm \text{€}447$ vs $\text{€}1220 \pm \text{€}269$ per patient). In addition, the authors posited that the potential costs associated with transfusion-related complications, in the patients who received allogenic transfusions, would increase to a greater degree the overall medical charges in the non-cell saver group. However, they did not take into account the cost of the cell saver in the analysis. Miao et al.¹⁷ retrospectively reviewed the total costs of blood products in a Chinese sample of school-aged children undergoing posterolateral fusion with instrumentation. They reported no significant difference between total costs of the perioperative transfusion of all blood products before and after adjusting for the lower cost of allogenic blood products in China, compared with the US, and therefore determined that the use of a cell saver was not a cost-effective practice. It is important to note that it is difficult to calculate costs associated with the avoidance of the rare complications associated with allogenic transfusions. From a retrospective chart review at a single institution, Canan et al.⁶ performed a robust cost-effective analysis to determine the incremental cost-effectiveness ratio of cell saver usage for single-level posterior lumbar decompression and fusion. The authors estimated

FIG. 3. Forest plots showing the effect of cell savers on intraoperative units transfused (A), postoperative units transfused (B), and total units transfused (C). IV = inverse variant.

the total costs of blood products were \$1012 for surgeries without a cell saver versus \$1133 for surgeries with a cell saver available but not used and \$3018 for surgeries with a cell saver used, for an average of \$1736 when the cell saver

was available. The incremental cost-effectiveness ratio was initially calculated as \$55,538.46/transfusion averted, but after converting the denominator to quality-adjusted life years (QALYs) gained (0.01 QALY gained/transfusion

FIG. 4. Forest plot showing the effect of cell savers on postoperative hemoglobin.

FIG. 5. Forest plots showing the effect of cell saver on operative time (A) and complications (B).

averted), the cost increased to \$5,553,846/QALY gained, which is in excess of the advocated willingness-to-pay threshold of \$100,000/QALY and therefore not a cost-effective practice.

The limitations of this meta-analysis were the significant heterogeneity in study design and reported outcome measures. The majority of the outcome data were contributed by AIS studies, and thus the applicability of the results across spine surgery is questionable. Only 3 studies reported specifically on the type of blood product transfused. Furthermore, the majority of studies included in the present analysis were observational and provided lower levels of evidence. Due to the paucity of studies, separate subanalyses on prospective and retrospective studies were not performed. Interpretation of results should take into account the sample size and quality of studies contributing that outcome, since only select studies contributed to each outcome measure.

Future research in this area should be aimed at performing randomized controlled trials to assess the reduction in transfusion rates associated with the use of cell savers in spine surgery. In addition, there is conflicting evidence on the cost-effectiveness of cell savers in spine surgery, with two studies reporting that it is not a cost-effective practice and two reporting the opposite. Therefore, more cost-effective analyses are needed to determine the economic benefit of the use of cell saver.

Conclusions

This meta-analysis supports modest efficacy of intra-

operative cell salvage systems in reducing intraoperative units transfused in patients undergoing spine surgery. However, no significant effects were observed with respect to intraoperative, postoperative, and total transfusion rates or postoperative and total units transfused. Further cost analysis studies are necessary to evaluate the cost-effectiveness of cell saver in spine surgery.

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Disclosures

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Author Contributions

Conception and design: all authors. Acquisition of data: T Cheriyian, J Cheriyian. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: T Cheriyian. Statistical analysis: T Cheriyian, J Cheriyian. Administrative/technical/material support: T Cheriyian, J Cheriyian. Study supervision: T Cheriyian, Dua, Goldstein, Errico, Kumar.

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