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Perspective

Research Challenges Relating to Immune-Related Patient Outcomes During Blood Transfusion for Spine Surgery

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Abstract: Background: In this manuscript, the challenges encountered during research into patient outcomes following transfusion during spine surgery are explored. **Method:** A narrative review of transfusion research over decades. **Results:** An estimated 310 million major surgeries occur in the world each year, and 15% of these patients experience serious adverse outcomes (the United States of America, n 5,880,829). Many adverse outcomes are associated with allogeneic blood transfusion (ABT) and are potentially avoided by intraoperative cell salvage (ICS). The incidence of perioperative transfusion in patients who undergo spine surgery varies between 8 and 36%. **Conclusions:** Knowledge gaps remain due to the complexity of the field of study, confounding factors, the inability to define optimal transfusion triggers, challenges countered in study design, requirements for large sample sizes, and the inability to conduct randomised controlled trials (RCTs). The surgical complexity, subtle patient factors, and differences in policies and procedures across hospitals and countries are difficult to define and add further complexity. Solutions demand well-designed prospective collaborative research projects.

Keywords: blood transfusion; spine surgery; research design; cell salvage; clinical outcomes

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1. Introduction

In this manuscript, the challenges encountered during research into patient outcomes following transfusion during spine surgery are explored, with a particular focus on transfusion-related immune modulation (TRIM). Despite significant advances in medical science, substantial knowledge gaps persist in the field of transfusion medicine. This manuscript aims to explore the fundamental challenges that hinder progress and impede our ability to answer critical research questions related to TRIM and its effects on patient outcomes. For the purposes of this manuscript, "Downstream Outcomes Potentially Related" to immune modulation and immune competency (DOPR-TRIM) will be the focus. An estimated 310 million major surgeries occur in the world each year, and 15% of these patients experience serious adverse outcomes (the United States of America, n = 5,880,829) [1]. Many adverse outcomes are associated with allogeneic blood transfusion (ABT) and are potentially avoided by intraoperative cell salvage (ICS) [2]. The incidence of perioperative transfusion in patients who undergo spine surgery varies between 8 and 36% [3]. Knowledge gaps remain due to the complexity of the study field, confounding factors, the inability to define optimal transfusion triggers, challenges encountered in study design, requirements for large sample sizes, and the inability to conduct randomised controlled trials (RCTs). The surgical complexity, subtle patient factors, and differences in policies and

procedures across hospitals and countries are difficult to define and add further complexity. Solutions demand well-designed prospective collaborative research projects.

2. Risk Factors Associated with Transfusion During Spine Surgery

Spine surgery for multilevel posterior fusion, revision, tumour, major trauma, and complex spine surgery (i.e., technically difficult) will most likely require transfusion. ICS is booked for these indications at the Royal Brisbane and Women's Hospital (RBWH). When considering the international literature on factors associated with the need for transfusion, Polo et al. used a national database (n = 2302, Poland) to study multilevel fusion (more than four levels), correction of deformity, and the anterior approach in elective surgery [4,5]. Risk factors for transfusion included surgery involving the thoracic and lumbar spine or sacrum and osteotomies [6], revision surgeries, a longer operative time [5,7], surgeries to treat major deformity (in particular cases involving corrective vertebral osteotomies), tumours of the vertebral column [8,9], metastatic tumours, greater surgical complexity, emergency room admission [7], and greater hospital volume [9]. Patient factors were advanced age, ASA $\geq$ 3, pulmonary disease, preoperative haematocrit less than 36% [5], diabetes with chronic complications [9], a higher body mass index (BMI) [7], and female sex [4]. The transfusion incidence during revision surgeries to treat deformity ranged between 8 and 30% [7].

3. Transfusion Thresholds and Spine Surgery

"When to transfuse" (i.e., the transfusion trigger) has been a topic of conversation and controversy for decades. This section is included in this manuscript as an example of one of the challenges experienced in transfusion research. Internationally accepted conservative transfusion triggers are now universally adopted. The American Association of Blood Banks recommends that blood transfusion should be considered for stable patients with haemoglobin (Hb) levels less than 7 g/dL; surgical patients with Hb levels less than 8 g/dL; or patients with symptoms such as chest pain, unresponsive tachycardia, or congestive heart failure [10]. In the absence of ongoing haemorrhage, most patients tolerate haemoglobin thresholds within the range of 7.0 g/dL to 8.0 g/dL. Even though this research is challenging and complicated due to many confounding factors and high heterogeneity across studies, there is agreement among clinicians to no longer aim for a higher Hb. In standard clinical care, anaesthetists do consider international guidelines and standard transfusion triggers. Exceptions that may demand a higher Hb target are ongoing haemorrhage, specific risks of hypotension to an individual patient considering their unique comorbidities and the complexity of ongoing surgery, the resources in their hospital, and the specific available expertise. There are subtle differences in care among anaesthetists with differing experiences and education that are commonly not assessed in these studies.

Clinical implications that are specific to spine surgery may require changes to the traditional transfusion triggers (restrictive Hb 7 g/dL vs. liberal Hb 10 g/dL) [11]. Restrictive triggers may improve outcomes in some instances (i.e., the length of hospital stay (LOS), infection rate, or thrombotic events) [12]; however, they may be associated with postoperative delirium [13]. However, when considering the potential hypoxic threshold in the spinal cord [14,15], clinicians prefer more liberal transfusion triggers.

A Cochrane review by Carson et al. (2021) entitled "Transfusion thresholds for guiding red blood cell transfusion" concluded that "further work is needed to improve our understanding of outcomes other than mortality" [16]. What remains unknown is (1) the relevance of specific sub-populations' surgery and (2) the specific outcomes beyond the traditional outcome measures. A major problem with any of the trigger studies is that there is a lack of understanding of the microcirculation and how oxygen delivery is impacted by declining haemoglobin values.

4. TRIM and ABT Outcomes

TRIM describes the delayed (>24 h) modulation of the immune response and subsequent adverse outcomes following allogeneic blood transfusion (ABT) [17–19]. The dysregulation of inflammation and innate immunity leads to susceptibility to microbial infection [20]. In the search to clarify the mechanism of TRIM (still unclear since the 1970s) [21], various postulated mechanisms were investigated. The mechanisms of TRIM are unclear and likely multifactorial [17,22]. At this time, it may not be feasible to confirm the exact pathophysiology, but progress can be made towards that goal while assessing outcomes and relevant associations.

4.1. Downstream Outcomes Potentially Related (DOPR-TRIM)

When hearing the term "transfusion-related outcomes", most clinicians usually consider traditional acute transfusion reactions (e.g., Transfusion-Transmitted Infections, Febrile Nonhaemolytic Transfusion Reaction, Haemolytic Transfusion Reaction, transfusion-related acute lung injury, Transfusion-Associated Circulatory Overload, transfusion-associated graft-versus-host disease [23]) and other cost-related outcomes (e.g., blood product use, LOS, reoperation, readmission after discharge). DOPR-TRIM procedures occur later in the surgical journey, are often complex, hidden within the larger patient risk profile, and are perhaps underestimated (Table 1) [24]. These outcomes include postoperative infection [3,25,26], respiratory failure [27], myocardial infarction, heart failure, stroke [28,29], renal failure, multiorgan failure [30], thromboembolism [31], and other immunological consequences [28].

Table 1. Recommended research for evaluating "Downstream Outcomes Potentially Related" to immune modulation and immune competency (DOPR-TRIM).

Clinical Outcome Categories	Examples
Infection	Wound infection, pneumonia, urinary tract infection
Respiratory	Respiratory failure, pulmonary oedema
Cardiovascular	Cardiac failure, myocardial infarction
Renal	Acute kidney failure
Relevant Surgical Procedure Categories	
Decomp cervical 1 level	
Decomp cervical $\geq$ 2 level	
Posterior Lumbar 1 level	
Posterior Lumbar 2 level	
Posterior Lumbar $\geq$ 3 level	
Pelvis open reduction internal fixation	
Decompression of spine thoracotomy	
Revision spine surgery	

4.2. Infection

Infection is the most common outcome attributed to TRIM. A systematic review by He et al. (2019) confirmed an association between perioperative blood transfusion and postoperative infection during spine surgery [3]. Even with high heterogeneity (I^2 = 86%), this pooled analysis included eight cohort studies and a large number of patients (n = 34,185) (OR, 2.99; 95% CI, 1.95–4.59) and indicated that blood transfusion increased the infection rate (OR, 2.99; 95% CI, 1.95 to 4.59; I^2 = 86%). Interestingly, the removal of two studies reduced the observed heterogeneity but did not change the results overall. Pull et al. (2009) considered retrospective electronic data of 3174 patients following spinal surgery [32]. They found that the rate of clinically significant surgical site infection was 4.3%. Independent statistically significant risk factors included estimated blood loss > 1 L, diabetes, obesity, previous SSI, and longer surgical time. Basques et al., using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, considered patient outcomes following posterior lumbar fusion surgery (2011–2013); 704 (16.7%)

of 4223 patients who received a blood transfusion. Blood transfusion was significantly associated with sepsis, deep surgical site infection, and pulmonary embolism [5].

The spectrum of infection-related outcomes described in the literature varies widely, from wound infection to septic shock. Examples of postoperative outcomes from our own research include pneumonia, urinary tract infection, wound infection, sepsis, gangrene, puerperal sepsis, infection of a prosthetic joint, etc. [33]. Depending on the type of outcome, the impact on patients' experiences is clearly very different. Just counting the number of patients with "infection" within a research project without defining what type of infection or considering the severity of the infection may not be a reliable measure of the extent of this impact or of the potential differences when considering ICS and ABT.

4.3. Outcomes After Transfusion for Spine Surgery

Transfusion-related outcomes go beyond the commonly studied variables (i.e., LOS, infection, and mortality). We previously considered 173 different ICD-10-coded outcomes in transfused patients, all potentially related to the immune consequences of transfusion or DOPR-TRIM [33]. DOPR-TRIM remains unclear during spine surgery.

Relevant studies in adult spine surgery are mostly retrospective, with significant heterogeneity [34]. A systematic review by Blackburn et al. (2019) considered 2759 "unique citations" and included 34 studies. The objectives were to report on the available clinical evidence when considering the association between transfusion timing and clinical outcomes. Only one of the thirty-four studies was prospective. The investigators demonstrated increased rates of postoperative complications, especially infectious complications, and prolonged length of stay following perioperative transfusion. They recommended further research due to a lack of evidence when considering intraoperative versus postoperative transfusions and the effect of transfusion on functional outcomes. Purvis et al. (2017) (n = 6931) considered patients included in a surgical billing database between 2008 and 2015 following anterior and posterior, cervical, and lumbar spine fusion and tumour-related surgeries [12]. Following adjustment for confounding factors, a conservative transfusion trigger between 8 and 10 g/dL was associated with improved outcomes (i.e., infection, kidney injury, and respiratory-, thrombotic-, and ischemic outcomes). Like many who studied transfusion-related outcomes before, Pervis et al. recommended that "Prospective studies are needed to more adequately test the relationships among PRBC transfusion, liberal Hb triggers, and clinical outcomes within spine surgery patients". These authors also commented that we lack evidence to consider clinical and economic outcomes associated with transfusion in spine surgery.

Darveau et al. (2021) prospectively considered the impact of transfusion during lumbar stenosis surgery, using a National Surgical Quality Improvement Program (NSQIP, USA) (2012–2018) [35]. Of the 16,329 eligible patients included, 1926 (1.8%) were transfused. These investigators used a propensity-matched cohort study design, including demographic variables and an extensive list of potential confounding factors to consider differences across study groups. Data to consider perioperative changes in haemoglobin and haematocrit and blood loss were unavailable. Despite some limitations, the data were collected across 700 hospitals, did include many patients, and were accurate, reliable and reproducible. The outcomes (i.e., LOS, minor complications, major complications, discharge to facility, readmission, and reoperation) were significantly worse in transfused compared to non-transfused patients. The exact outcomes included as "complications" are unclear.

5. Patient Blood Management (PBM): Reducing ABT Requirement

Measures to conserve allogeneic red cells and reduce perioperative blood loss, now commonly referred to as Patient Blood Management (PBM), are beneficial [36]. Dick et al. confirmed a reduction in the ABT requirement in a paediatric scoliosis surgery program (n = 1039, over 15 years, 2001–2015) that considered facilitating preoperative haemoglobin optimisation, ICS, the use of tranexamic acid, and transfusion criteria awareness. Other beneficial PBM measures include optimisation of iron-deficiency anaemia, management of

perioperative antiplatelet and anticoagulation agents, reducing intraoperative loss through excellent surgical techniques, and reducing postoperative ABT [14].

6. ICS and Outcomes Following Spine Surgery

What did the existing evidence teach us this far? Many clinical outcomes in transfused patients relate to immune competency and the immune consequences of transfusion. ICS is recommended during major spine surgery [37] and may provide immunological benefits (in vitro and clinical) [25,38–40]. The fact that ICS reduces the requirement for ABT is now no longer questioned [2,41]. During spine surgery, a meta-analysis of 18 studies by Cheriyan et al. (n = 2815) demonstrated a reduction in the number of red blood cell (RBC) units transfused intraoperatively when using ICS [42]. In principle, returning blood lost during surgery would conserve a patient's own red cell volume, potentially reduce postoperative anaemia, and subsequently reduce the need to use ABT.

We believe that ICS may play a role in improving DOPR-TRIM (i.e., to change the impact of TRIM) in spine surgery but could not find any relevant research. Investigators interested in the potential benefits of ICS commonly studied postoperative infection, LOS, and mortality rate as outcome measures. DOPR-TRIM, on the other hand, is rarely studied, and the clinical impact is therefore unknown.

A robust comparison of TRIM outcomes between patients who receive (1) cell salvage versus those who do not in spine surgery or (2) are transfused and not transfused (upholding best statistical study design) is challenging and perhaps impossible. A recent Cochrane review by Lloyd et al. (2023) considered patient outcomes following cell salvage (washed and unwashed ICS) for orthopaedic surgery. Within the 106 RCTs (n = 14,528) they included, 6 RCTs (n = 404) were related to ICS in spine surgery [2]. The authors reported with moderate certainty that ICS reduced the requirement for ABT but were unable to (due to the absence of analysable data) assess mortality, reoperation for bleeding, prosthetic joint infection (PJI), thrombosis, deep vein thrombosis (DVT), major adverse cardiovascular events (MACE), myocardial infarction (MI), stroke (CVA), and LOS. In recent decades, many investigators have attempted to apply RCT design to ICS research that considers clinical outcomes but were unable to.

We propose a different concept. ICS cannot replace ABT. A direct comparison is not possible and no longer ethical. We previously asked "Which modality is better, ABT or ICS"? Instead, we should ask "if ICS is available (in addition to, or as an alternative to standard best practise ABT transfusion care), do patients experience a lower incidence and impact from TRIM-related outcomes"?

7. Statistical and Study Design Challenges

Propensity score matching and logistic regression may, in some instances, provide an alternative method and overcome some limitations of conventional observational studies where an RCT design is not feasible. When it comes to ICS research, even though many tried and failed for decades, the recommendation to develop RCTs remains. It is just not realistic and would be unethical currently (considering existing evidence and accepted international standards) to recruit a patient to a "no ICS" arm within an RCT. Future research should change the direction. Large database data and artificial intelligence (AI) may enable solutions to overcome historical challenges, consider real-life scenarios, and identify valuable research avenues that may ultimately change outcomes in patients. Rather than continuing to try and conduct an RCT to assess whether patients need more ABT with or without ICS, let us consider large data and evaluate the clinical outcomes across many centres, specifically related to outcomes that we know are likely DOPR-TRIM consequences. This is especially important when considering specific patient populations and individualised medicine for unique clinical profiles.

7.1. Confounding Factors

The expectation during ICS research is that all potential confounding factors are included. It is evident that transfusion requirements are complex and altered by many factors. Patient comorbidities, demographic details, and general medical management are commonly considered. In addition, a detailed analysis would include information related to the blood loss volume, time of day, type of surgery, extent of the surgery, duration of surgery, exact surgical procedure considering first surgery compared to repeat procedures, ongoing medication that alters coagulation, trauma, elective or emergency surgery, more than one type of surgical procedure during the same anaesthetic, surgical complications during the procedure, hypothermia, and a patient's age and preoperative Hb [2,3,41].

Beyond the more familiar factors that are commonly considered, other more subtle confounding factors that are even harder to define exist. We agree with Lenet et al., who used a Delphi consensus survey technique to consider the factors influencing transfusion triggers and argued that "Beyond the objective clinical parameters associated with intraoperative transfusion practice, a variety of cognitive, affective, social, and environmental factors also have an effect on transfusion, which may underlie part of the observed inter-clinician variability" [43].

Most factors were previously considered in many studies for decades but are very challenging to include within one trial. Other more subtle confounding factors, including policy differences across facilities and countries and regional expectations, may also have important implications. For example, an anaesthetist who is concerned that blood transfusion may not be timely once a patient arrives in the ward may be inclined to transfuse allogeneic red cells before the patient leaves the theatre. This is one example of a confounding factor with a significant impact on the transfusion incidence that is not considered in studies. Firstly, no existing research considers all these factors. Secondly, even though modern statistical models may overcome some challenges, many unanswered questions remain.

7.2. Should We Continue to Recommend ICS RCTs?

A common theme in manuscripts assessing transfusion in spine surgery relates to the ability of ICS to reduce the requirement for ABT and, therefore, adverse outcomes associated with ABT. This concept is often referred to as "the efficacy" of ICS. In other words, it is referred to as reducing the "incidence and volume of red cell transfusion". The conclusion in many of these studies is that future RCTs are needed. Yet, despite many attempts, it has been impossible to design an **RCT** where the exact same patients during the exact same conditions were receiving either ICS or no ICS.

Other aspects complicate the feasibility of conducting traditional RCTs. ICS in our hospital is booked for elective procedures with major blood loss risk (for example for multilevel posterior spine fusion surgery) and 24 h a day for emergency procedures. Many hospitals in the world, however, do not have such an "in-house" ICS service available. Comparing outcomes between ICS patients in hospitals with different models of care would be difficult. These differences prevent an RCT design. Results across hospitals without the ability to distinguish between elective and emergency procedures are unreliable.

The next challenge relates to data collection and analysis that include sufficiently large numbers of patients to allow for the study of clinical outcomes that are often hidden and occur later during the surgical journey (DOPR-TRIM). Small sample sizes are achieved in these RCTs at best. The alternative study design that includes larger samples is mostly retrospective, with familiar limitations.

A systematic literature review considering outcomes following transfusion in spine surgery by Zhou et al. (2021) found 372 English-language articles with 13 relevant publications; only retrospective non-randomised studies (level IV evidence) were found [44]. Munoz et al. (2006) considered three publications that included 22,000 orthopaedic surgeries and found evidence of increased infection risk following ABT [41]. Despite a large cohort undergoing lumbar spinal fusion (n = 16,329, from more than 700 hospitals, 2012–2018), high-quality data, and propensity-matched study designs, insufficient power to identify

and exclude all potential confounding factors remained a limitation in the study by Darveau et al. (2021) [35].

Many of these challenges are now clear after decades of studying the clinical outcomes following ABT. It should be anticipated that the same challenges, confounding factors, and hidden outcomes may apply during the study of ICS when designing future trials. It is important to remember that a small subset of those who receive ABT currently receive ICS. The sample sizes for ICS trials will therefore be even smaller than those that were previously inadequate to achieve satisfactory results when considering ABT. If it is not feasible to achieve adequate sample sizes to confirm the same outcomes for ABT, it will likely never be possible for ICS. ICS RCTs are commonly deemed to not be of high quality and are not blinded, with investigator bias [2]. A robust assessment of the potential benefits of ICS related to immune consequences will include a large prospective observational study design.

8. It Is Often Difficult to Predict Expected Blood Loss During Spine Surgery

The need for transfusion is often expected during posterior multilevel spine surgery. Blood loss may be harder to predict during other spine surgery procedures. The booking of ICS within our hospital's ICS service relies on this ability. Even though we can provide ICS on an urgent basis on site, a staff member still needs to be rostered and available. Certain key factors are associated with major blood loss during spine and spinal tumour surgery [7,44–46]. The ability to define these factors, and therefore to predict the need for ICS, would be beneficial to our ICS booking process. Future research aiming to inform this requirement will ensure feasibility and enable hospital services to plan and provide ICS facilities for relevant cases. Predictive tools would improve the value of this research.

9. Cancer Surgery

Intraoperative blood loss during spine surgery for primary and metastatic tumours is often unpredictable, but potentially significant. Risk factors associated with major blood loss include tumour localization (thoracic tumours) [47], tumour histology, operative procedure length, epidural spinal cord compression (ESCC) score, BMI, and surgical strategy [44].

The use of ICS in the presence of cancer is, however, still controversial, and clinical evidence related to outcomes (i.e., cancer recurrence risk) exists only in small sample sizes and for specific types of cancer. Even though the presence of a leucodepletion filter (increasingly used in this context) may reduce the risk of systemic dissemination of cancer cells, a concern remains during primary spine cancers, for example during those for chordoma/sarcoma surgery [48]. To assess the removal of cancer cells during metastatic spinal tumour surgery, Zong et al. (2022) compared a modified leucocyte depletion filter (MLDF, Separator Haemo-Technology Beijing Co Ltd., Beijing, China (bore diameter of 18 μm)) with a regular leucocyte depletion filter (RLDF, SB; Haemonetics Corporation (bore diameter of 40 μm)) in combination with ICS (Cell Saver 5+; Haemonetics Corporation, Braintree, MA, USA) [49]. Even though tumour cells were removed (RLDF > MLDF), residual tumour cells remained.

Kumar et al., in 2023 (n = 73, 2014–2017), compared the use of ICS (n = 26), ABT (n = 27), and no transfusion (n = 20) during metastatic spine surgery [50]. The risk of developing an infection was higher in the ABT group (vs. other groups). The authors identified the "non-randomised nature of this study" mandated by department treatment protocols as a limitation. The types of cancer metastasis were noted as lung, prostate, colon, etc. This, however, does not define the cell type and, therefore, the technical ability of an LDF to remove cells or the risk of dissemination and recurrence. Without these considerations and within this small sample size, it is unclear how definitive these results are. Furthermore, a multimodal treatment approach with chemotherapy and radiation often accompanies metastatic spine surgery. These factors add to the previously mentioned confounding factors encountered during ICS research [45,51].

10. Other Immune-Related Consequences

While this manuscript focusses on TRIM, it is important to recognise that many other knowledge gaps related to potentially hidden immune consequences may face similar challenges. The overarching goal is to shed light on the fundamental obstacles in transfusion medicine research that impede progress and to provide insights that could apply to a wider range of immune-related consequences beyond TRIM, such as TRALI; microchimerism; and allergic, anaphylactic, and haemolytic reactions. Various mechanisms for transfusion-related acute lung injury (TRALI) have been proposed. The current expert opinion commonly considers passive transfer of human leucocyte antigen (HLA) or human neutrophil antigen (HNA) antibodies or biological response modifiers (BRMs) in the donor's plasma and subsequent damage to blood vessels (leading to permeability) as potential causes of TRALI [52]. The incidence of mortality following TRALI seems low (i.e., 0.0494 per 100,000 transfused blood components) [53]. This low reported incidence may reflect issues with under-diagnosis and under-reporting. Similar challenges are evident in research on TRIM, where outcomes can be obscured within the broader context of the surgical journey and may not be readily recognised as immune-related consequences. Gajewsk et al. reported the potential for microchimerism during blood transfusion in immune-suppressed patients. Donor lymphocytes may be detected in recipients' circulation years after blood transfusion and potentially cause transfusion-associated graft-versus-host disease (TA-GVHD) [54].

11. Other Challenging Topics

Another important area where these challenges have significant consequences is preoperative iron-deficiency anaemia (IDA). The challenges highlighted in this manuscript also impact the ability to evaluate clinical outcomes and develop effective therapies to manage IDA. Transfusion thresholds play a crucial role when studying outcomes related to IDA, which is prevalent among chronically ill patients undergoing major surgery. IDA is multifactorial and complicated by numerous confounding factors within the surgical journey. Over the past 15 years, many studies and guidelines addressing IDA have been published, often providing conflicting advice. Munoz et al. published "The International consensus statement on the perioperative management of anaemia and iron deficiency" in *Anaesthesia* in 2016 [55]. These investigators noted that "Despite the lack of level-one evidence for improved outcomes, it is still recommended as good clinical practice to treat all surgical patients with preoperative iron-deficiency anaemia, but with a particular emphasis on treating those undergoing major surgery". Richards et al. reported at the conclusion of the "Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT)" study in the *Lancet* in 2020 that "Preoperative intravenous iron was not superior to placebo to reduce need for blood transfusion when administered to patients with anaemia 10–42 days before elective major abdominal surgery" [56]. The challenges in designing studies within transfusion medicine, due to limitations of traditional methods, hinder our ability to address key research questions effectively.

Another relevant field is perioperative coagulation testing. Viscoelastic testing is now widely adopted across the world to identify the amount and type of blood products that are required to ensure adequate clot formation during surgery. The ease of interpretation is aided by algorithms and technological advances such as "3D animated blood clot: the Visual Clot" [57]. Further advances include a new ultrasound technology called SEER (Sonic Estimation of Elasticity via Resonance) or Sonorheometry (Quantra® Hemostasis Analyzer, HemoSonics). Sonorheometry promises improved design, simplicity, and ease of use [58]. However, evaluating the clinical value of coagulation-testing technologies presents similar challenges to those mentioned earlier in this manuscript. Heterogeneity in study designs and inherent biases can significantly impair the validity of clinical research and hinder our ability to confirm the benefits of these technologies [59]. Baksaas-Aasen et al., in 2021, published "Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial" in *Intensive Care Medicine*

and concluded that "There was no difference in overall outcomes between VHA- and CCT-augmented-major haemorrhage protocols" [60]. It is possible that these technologies are of benefit, but that in the larger patient journey, the clinical outcome measures are difficult to study, hidden and under-reported due to the challenges mentioned in this manuscript.

12. Future

The impact of ICS on immune-related consequences following spine surgery remains unclear. The cumulative effect of challenges, requirement for large sample sizes, likelihood of missing values, and confounding factors reduces the value of retrospective study designs in this context. Alternatively, the gold standard, RCT, has proven to not be feasible. Future research should focus on the prospective collection of relevant immune-related outcomes (DOPR-TRIM) in large sample sizes and consider all possible confounding factors.

Laboratory analysis can provide additional insights. In addition to clinical outcomes, the use of immune cell numbers or function to assess immune modulation may potentially create another avenue to inform knowledge gaps [61]. Neutrophil numbers and immune cell ratios were previously used to stratify the risk of heart failure and mortality after myocardial infarction [62,63]. Immune cell numbers may be associated with postoperative outcomes [33]. We identified differentially altered immune cell numbers that may potentially be associated with specific immune competencies [38]. Further research considering these cells and biomarkers may provide valuable insights into the mechanism of TRIM and the benefits of ICS.

The study design is often complicated by confounding factors and controversies, and the causation of TRIM is yet unclear. For decades, many attempted to consider all confounding factors and many attempted RCTs, but none were successful. Furthermore, an assessment of detailed DOPR-TRIM outcomes is often not feasible within traditional study design. Yet, no one denies that ABT is associated with these typical adverse outcomes. It is perhaps time to consider a different route and more relevant clinical outcome measures and develop solutions to overcome them.

13. Conclusions

Recommendations for the implementation of cell salvage in spine surgery practise include the following:

- The implementation of ICS is recommended.
- Further research to specifically assess immune-related outcomes is required.
- Seeing that many investigators were unable to produce a relevant RCT, future work should focus on more feasible research study designs.
- Developing large database study designs with the ability to include many confounding factors will enable the identification of further relevant clinical evidence.
- The development of predictive tools to consider risk factors for transfusion and confounding factors during surgeries that require ICS is recommended.
- Laboratory studies to evaluate the safety of ICS in cancer surgery are recommended.

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