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Effect of intra-operative cell salvage in negating the need for allogenic transfusion in patients undergoing primary hip and knee arthroplasty

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Abstract
Introduction: Total joint arthroplasty is the operation of choice and a reliable option for end stage arthritis of the hip and knee. With a growing and aging population, the incidence of total hip and knee arthroplasty is increasing. Total joint arthroplasty surgery carries inherent risks. Anemia due to blood loss remains one of the major complications from joint replacement surgery, and is relatively common. Therefore it is extremely important to improve the safety of this operation and reduce the potential complications to ensure that patients achieve the desired improvement in their quality of life and the costs of care associated with these elective procedures are minimized. This article evaluates the current evidence base for the current strategies employed by orthopedic surgeons to achieve optimal blood transfusion management in total hip and knee arthroplasty.
Aim: The aim of our study was to ascertain if intra-operative cell salvage is effective in negating the need for allogenic transfusion in patients undergoing primary hip and knee arthroplasty.
Methods: The study comprises a retrospective analysis of 371 consecutive patients undergoing primary hip or knee arthroplasty with concomitant use of intra-operative cell salvage. The percentage of patients requiring allogenic transfusion despite cell salvage was the primary outcome. Other factors affecting transfusion risk were analyzed.
Results: The overall transfusion rate was 16%. 24% of hips and 12% of knees received allogenic blood. Despite routinely utilizing cell salvage in all cases, only 59% of hips and 63% of knees received returned red cells. Significantly greater blood loss occurred in the patients who were given returned red cells. Transfused patients had a significantly lower pre-operative hemoglobin, less intra-operative blood loss and were less likely to receive cell salvage blood. Pre-operative hemoglobin less than 120 g/L, female gender, and age greater than 75 was associated with a higher risk of allogenic transfusion. Patients receiving allogeneic transfusion had a longer hospital stay and greater complication rate.
Conclusions: Intra-operative cell salvage reduces but does not eliminate the need for allogeneic blood transfusion in primary hip and knee arthroplasty. The efficacy of cell salvage is related to hematocrit and volume of the blood lost. Intra-operative cell salvage on its own is not effective in patients with a pre-operative haemaglobin less than 120g/L and should be combined with additional strategies such as correcting pre-operative anaemia.

Keywords: Intra-operative cell, primary hip, knee arthroplasty

Introduction
Total hip and knee arthroplasty may result in substantial peri-operative blood loss, leading to post-operative anemia and rendering the patient at risk of requiring an allogenic blood transfusion. Bierbaum *et al.* reported transfusion rates of 57% and 39% for total hip arthroplasty (THA) and total knee arthroplasty (TKA) respectively [1]. Total joint arthroplasty and fracture surgery is responsible for the highest percentage of allogenic transfusions compared with other surgical specialties [2, 3].
Allogenic blood however is associated with risks to the patient, including disease transmission, hemolytic reactions, immunomodulation, hemodynamic overload, acute lung injury, and coagulopathy 4. Previous studies have demonstrated an increased risk of postoperative infection, length of hospital stay and mortality in patients who receive allogenic blood [5, 6, 7]. Consequently, various blood conservation strategies have been employed in THA and TKA to reduce the need for allogenic blood.
Pre-operative autologous donation does reduce allogenic blood requirement [8, 9, 10, 11], however is associated with a high rate of unused blood and is not cost effective [12, 13, 14].

The effectiveness of acute normovolaemic haemodilution in reducing transfusion need is debatable 15. Studies on the use of post-operative reinfusion drains report a risk reduction in allogeneic transfusion [16, 17, 18].

Reinfusion drains however carry the potential for transfusion reactions as unwashed blood contains fibrin degradation products and other potential contaminants [19, 20].

The intra-operative cell salvage technique used at our hospital incorporates washing of blood collected during surgery prior to reinfusion. We favor this method of blood conservation as it causes minimal disruption to surgical workflow and removes biochemical, cellular and non-cellular debri such as activated clotting factors, fatty lipids, and bone [21, 22]. We have routinely used intra-operative cell saver with washed red cells in THA and TKA, in the belief it would eliminate allogenic blood transfusion requirement and improve patient outcomes.

The primary aim of our study was to ascertain if intra-operative cell salvage is effective in negating the need for allogenic transfusion in patients undergoing primary THA and TKA, by determining the percentage of patients requiring allogenic transfusion and comparing this with traditional transfusion rates reported in the literature 1. The secondary aim was to identify risk factors predicting the requirement for allogenic transfusion in patients who underwent cell salvage and establish how to optimize the effectiveness of cell salvage. Whilst previous studies have already reported on the benefits of cell salvage in THA and TKA [23, 24, 25, 26, 27, 28], our study cohort is an updated review reflecting contemporary techniques in arthroplasty surgery including anaesthesia, surgical technique and individualization of transfusion trigger.

Aim: The aim of our study was to ascertain if intra-operative cell salvage is effective in negating the need for allogenic transfusion in patients undergoing primary hip and knee arthroplasty.

Materials and Methods

The study comprises a retrospective analysis of 371 consecutive patients undergoing primary THA and TKA with concomitant use of intra-operative cell salvage from January 2014 to December 2016. From the currently available literature, similar studies have reported the proportion of patients requiring transfusion to be approximately 20%. Therefore, in order to obtain a 95% confidence interval, we calculated 246 patients would be required for sufficient power for the study. Ethics approval was obtained from the Hospitals Regional Ethics Committee.

One surgeon performed all surgeries, using the same prosthesis, surgical technique and identical post-operative protocol in all patients. The hips were performed through an antero-lateral approach with the patient in the lateral position. Uncemented acetabular and femoral components were inserted in all patients, without use of a drain. The knees were performed through a standard medial para-patellar approach without tourniquet. Computer navigation was utilized for alignment and preparation, and cemented femoral, tibial and patella components were used in all patients. An intra-articular drain on low suction was removed day 1 post operatively for the knees. All patients received enoxaparin 40mg daily for venous thromboembolic prophylaxis, commencing 4 hours post-operatively and continued for 14 days for TKA and 28 days for THA. Aspirin was continued through the peri-operative period if the patient was already on the medication prior to surgery. Intraoperative cell salvage was performed in each case with the Haemonetics Cell Saver 5+ machine. The salvaged blood was washed and concentrated prior to reinfusion. Reinfusion was commenced in the recovery room and completed on return to the ward. Hemoglobin levels were checked day 1 post-operatively. Haemoglobin of less 80g/L was an absolute trigger and less than 100g/L with symptomatic anemia and significant co-morbidities a relative indication for transfusion. The relative indication for transfusion was based on the surgeon's best judgment according to the patient's symptoms and risk of complication such as myocardial events.

Our primary objective was to ascertain if intra-operative cell salvage is effective in negating the need for allogenic transfusion in patients undergoing primary hip and knee arthroplasty, by determining the percentage of patients requiring allogenic transfusion despite cell salvage. Additional data collection included demographics, complications, days until discharge, and hemoglobin change from pre-operatively to day 1 post-operative. Blood loss was measured and calculated using three methods of cell salvage volume, post-operative drain volume in TKA patients, and the difference between pre-operative and post-operative hemoglobin.

Results were described using proportions for binary variables, means and standard deviations for normally distributed variables and medians and inter-quartile ranges for variables not normally distributed. We analysed using simple and multivariable logistic regression to determine predictors of need for transfusion.

Results

Demographics of the study cohort are summarized in table 1. Including the proportion of patients in each category of pre-operative hemoglobin level. Eight percent of patients started with pre-operative hemoglobin less than 120g/dL, with the rate being 3 times higher in THA patients.

The overall transfusion rate was 16%, with 24% of THA patients and 12% of TKA patients requiring allogenic blood despite intra-operative cell salvage. Our results demonstrate a statistically significant decrease in allogenic transfusion rates compared to the historical non-cell salvage population of Bierbaum. A summary of transfusion rate of the current study compared with previously published literature is presented in tables 2 and 3 for THA and TKA respectively.

Blood loss outcomes for the 371 patients are shown in table 4. A pertinent finding is only 63% of knees and 59% of hips actually received returned red cells. Comparison of patients who received returned red cells with those who didn't is displayed in table 5. Significantly greater intra-operative blood loss occurred in the cell salvage group, with a mean of 362.48mls compared to 156.15mls. Intra-operative blood loss ranged from 200mls to 1200mls in the salvage group, in contrast to 50mls to 350mls in the non-salvage patients. Only 9 patients, in whom salvaged blood could not be obtained, had intra-operative blood loss greater than 200mls. From our data, a minimum of 200mls intra-operative blood loss is required to have sufficient volume to cell salvage.

Table 6 compares patients who received allogenic blood transfusion versus patients who did not. Significantly, transfusion risk was reduced with greater intra-operative blood volume loss, higher pre-operative haemaglobin and if the patient received salvaged blood. Our philosophy was to use an individualized variable transfusion trigger. Mean post-operative haemoglobin in the transfused patients was 103.46g/L compared to 121.65g/L in the non-transfused patients. The difference was statistically significant. The post-operative haemaglobin in patients who required allogenic blood ranged from 71g/L to

110g/L. Allogenic transfusion requirement significantly increased length of hospital stay and incidence of peri-operative complications.

Using multivariable regression analysis, female gender, pre-operative haemaglobin less than 120 g/L, and age greater than 75 years proved to be significant risk factors for requiring allogenic blood, despite the use of intra-operative red cell salvage. Results of the univariable and multivariable analyses are shown in table 7. Four patients in the study group had a BMI less than 20. All 4 of these patients required allogenic transfusion, however the numbers were too small to allow statistical analysis.

Discussion

An effective blood management strategy is one of a number of critical components required for the successful care of joint arthroplasty patients. Significant blood loss may occur following THA and TKA, resulting in post-operative anemia, hindering patient recovery or leading to the need for allogenic blood transfusion. Allogenic transfusion has been shown to be detrimental to patient outcome and recovery following joint arthroplasty surgery [30, 31, 32].

Intra-operative red cell salvage re-infuses fresh blood and avoids problems with storage of red blood cells seen with autologous pre-donation and allogeneic red blood cells. This translates to more efficacious oxygen carrying red blood cells with a higher mean erythrocyte viability 33 and increased preservation of 2-3 diphosphoglycerate [34]. The technique also incorporates washing the blood loss volume, thereby removing contaminants and concentrating the reinfusion volume.

Our study has shown intra-operative cell salvage does significantly reduce transfusion requirements in primary THA and TKA compared to traditional rates reported in the literature. However we observed a substantial number of patients still required allogenic blood despite the use of red cell salvage. Patients undergoing THA were more likely to require allogenic blood. This appears to be a consequence of an increased proportion of THA patients with pre-operative hemoglobin less than 120g/L and potential for greater hidden blood loss into the thigh and buttock following THA.

One noteworthy finding of our study is only about 60% of patients actually received returned red cells. Nearly half the patients did not receive back any of their own blood lost during surgery. It appears for cell salvage to be effective, a critical amount of blood loss is necessary. Processing returned red cells is an interaction of volume loss and haematocrit of the blood salvaged. From our data, average blood loss in the patients receiving returned red cells was 362mls, range 200mls to 1200mls, compared to average 156mls, range 50mls to 350mls in the group with insufficient loss to salvage. A minimum of 200mls intra-operative blood loss is required to cell salvage, dependent also on the haemaglobin of the blood lost. Paradoxically, anemic patients require greater blood loss intra-operatively to be able to utilize cell salvage effectively. This further emphasizes the importance of correcting pre-operative hemoglobin, in our results to a minimum of 120g/L.

Reflecting the above observations, in our cell salvage cohort a greater intra-operative blood loss and higher pre-operative haemaglobin resulted in a significantly reduced risk of allogenic transfusion. Patients who received returned red cell were less likely to require allogenic blood, confirming its protective effect. In keeping with previous literature, receiving allogeneic blood was detrimental to our patients' recovery, culminating in a longer hospital stay and higher incidence of complications.

We demonstrated patients with low hemoglobin pre-operatively were at higher risk of requiring allogenic blood despite the use of cell salvage, emphasizing the need to identify and correct pre-operative anemia prior to surgery [15, 35]. In our cohort, the critical haemaglobin level was 120g/L, which increased the transfusion risk by 30 times compared to patients with haemaglobin above 150g/L. There were several non-modifiable factors, such as age and gender, which increased transfusion risk, highlighting the need to be diligent and proactive in these patient groups in correcting or optimizing other factors.

Our study does have several limitations and weaknesses. Being a retrospective study predisposes the data to recall and selection bias. We did not have a control or comparison group. Instead we chose to compare our results with transfusion rates reported in the literature. We cannot therefore be sure our results are purely due to the use of cell salvage technique alone and not other factors. Care should be taken when comparing our study with other cell salvage studies, which may have different patient populations, cell salvage devices, transfusion triggers, anesthetic practices and surgical technique. We did not use a tourniquet when performing TKA, which increases intra-operative blood loss. However increasing intra-operative blood loss during TKA should increase the benefits of intra-operative cell salvage. We also concede the use of intra-articular drains has now been shown to increase transfusion risk and a drain in TKA is often no longer routinely used. Recent studies have focused on hemostatic agents such as tranexamic acid, showing excellent effectiveness in reducing blood requirements following both THA and TKA [36, 37, 38].

Our study cohort did not receive any form of tranexamic acid, which has now become common practice in joint arthroplasty. Additionally, our patients continued aspirin during the peri-operative period in the belief this would be cardio-protective. However a recent large randomized controlled trial of 10010 patients of which 39% underwent orthopaedic procedures, comparing aspirin versus placebo with 30 days follow up after surgery, found contradictory results [39]. There was no difference in the primary outcome of death or myocardial infarction between the 2 groups, regardless of whether the patient was taking aspirin prior to surgery or not. Aspirin increased the risk of major bleeding compared with placebo. The authors concluded aspirin administration before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding. We no longer routinely continue aspirin unless absolutely necessary.

Nevertheless, we believe our study retains relevance as cell salvage remains one of a number of options available in a blood management strategy and is still commonly used. It is relatively simple to implement into the surgical algorithm and can be combined with other modalities. Our study was a consecutive series with sufficient numbers to be able to deduce several important conclusions.

Avoiding allogenic blood following THA and TKA has taken on increased significance due to the escalating cost of blood banking and stored blood. Therefore, intra-operative cell salvage should be incorporated in a comprehensive blood management strategy. Whilst cell salvage is effective in reducing allogenic blood requirements, other strategies should be used in combination, including maximizing pre-operative hemoglobin, using appropriate anti fibrinolytic agents such as tranexamic acid and individualizing the transfusion trigger. The ultimate aim is allogenic blood requirement in elective THA and TKA should be zero.

Conclusion

Intra-operative cell salvage reduces but does not eliminate the need for allogenic blood transfusion following primary THA and TKA. A critical amount of intra-operative blood volume loss of 200mls and pre-operative hemoglobin above 120g/L is required for cell salvage to be effective. Future studies are required to define the ideal and most cost effective blood management program in THA and TKA.

Table 1: Demographics of the study population

Characteristic	THA (n=135)	TKA (n=236)	Total (n=371)
Female gender	86 (63%)	130 (55%)	216 (58%)
Age > 75	39 (29%)	62 (26%)	101 (27%)
Age years (mean, range)	70 (17- 91)	70 (47 – 95)	70 (17 – 95)
BMI kg/m2 (mean, range)	27.4 (15.7-43.8)	30.3 (18.5-52.2)	29.2 (15.7-52.2)
BMI category <20	3 (2%)	1 (<1%)	4 (1%)
20 – 25	47 (35%)	30 (13%)	77 (21%)
>25 – 30	45 (33%)	98 (42%)	143 (39%)
>30	40 (30%)	107 (45%)	147 (40%)
Diagnosis	119 (88%)	230 (97%)	349 (94%)
Osteoarthritis	2 (1%)	4 (2%)	6 (2%)
Inflammatory Other	14 (10%)	2 (1%)	16 (4%)
Pre-op Hb g/L (mean, range)	134 (72 – 170)	138 (103 – 177)	137 (72 – 177)
Pre-op Hb category >= 150g/L	20 (15%)	63 (27%)	83 (22%)
>=120 – 150 g/L	95 (70%)	162 (69%)	257 (69%)
<120 g/L	20 (15%)	11 (5%)	31 (8%)

Table 2: Effects on Allogenic Transfusion Rates of autologous re-transfusion of salvaged blood cells in randomized controlled trials and cohort studies for THA compared to historical rate reported by Bierbaum without intervention

Study	Bierbaum 1	del Trujilo 24	Smith 25	Moonen 26	Our Data
Allogenic Transfusion Rate	57%	15%	8%	6%	23.7%

Table 3: Effects on Allogenic Transfusion Rates of autologous re-transfusion of salvaged blood cells in randomized controlled trials and cohort studies for TKA compared to historical rate reported by Bierbaum without intervention

Study	Bierbaum 1	Shenolikar 27	Thomas 28	Munoz 40	Our Data
Allogenic Transfusion Rate	39%	16%	7%	11%	11.9%

Table 4: Transfusion, blood loss and outcomes for THA, TKA and combined cohort of patients

Outcome	THA (n=135)	TKA (n=236)	Total (n=371)
Transfused	32 (24%)	29 (12%)	61 (16%)
Whole blood loss mL (mean, range)	271 (50 – 1200)	290 (100 – 950)	283 (50 – 1200)
Red cells returned	79 (59%)	149 (63%)	228 (61%)
Volume cell salvaged (mL)‡	205 (40 – 890)	193 (10 – 650)	197 (10 – 890)
Hb loss to day 0* g/L (mean, range)	17.7 (-34 – 40)	18.7 (-12 – 47)	18.3 (-34 – 47)
Hb loss to day 1** g/L (mean, range)	27.3 (-29 – 53)	29.1 (6 – 56)	28.4 (-29 – 56)
Knee drain volume mL (mean, range)	---	209 (0 – 800)	---
Any surgical complication	29 (21%)	45 (19%)	74 (20%)
Days to discharge (mean, range)	6 (3 – 16)	6 (3 – 30)	6 (3 – 30)

* Pre op Hb minus day 0 post op Hb

** Pre op Hb minus day 1 post op Hb

‡ In those with cell salvage only (n = 228)

Table 5: Comparison of pre-operative haemaglobin and intra-operative blood volume loss according to patient cell salvage status

Characteristic	Cell Salvage Status		Mean Difference (95% CI)	p-value
Outcome	Yes		No	
Pre-operative Hb [g/L; mean (SD)]	137.40 (14.03)	135.85 (12.76)	1.6 (-1.4- 4.5)	0.30
Blood Loss [mL; mean (SD)]	362.48 (136.69)	156.15 (52.06)	206.3 (182.8- 229.8)	<0.001

Table 6: Comparison of blood loss and outcomes for patients who received alldogenic blood transfusion and patients who were not transfused

Outcome	Transfused (n=61)	Not Transfused (n=310)	Total (n=371)	Difference (95% CI)§	p-value§
Pre-operative Hb. [g/L; mean (SD)]	122.76 (14.26)	139.61 (11.54)	136.80 (13.56)	-16.9 (-13.5- -20.2)	<0.001
Whole blood loss [mL; mean (SD)]	245 (156)	290 (148)	283 (150)	-45.6 (-4.4- -86.8)	0.03
Red cells returned [count (%)]	29 (48%)	199 (64%)	228 (61%)	-16% (-3%- -30%)	0.02
Volume cell salvaged [mL; median (IQR)]	156 (130 - 270)	150 (135 - 250)	150 (135 – 250)	6 (N/A)	0.40
Hb loss to day 0* [g/L; mean (SD)]	19.3 (13.2)	18.1 (8.2)	18.3 (9.3)	1.2 ()	0.38
Hb loss to day 1** [g/L; mean (SD)]	28.4 (16.2)	28.5 (8.4)	28.4 (10.1)	-0.1 (-3.0- 2.8)	0.95
Post-op Hb Day 1 [g/L; mean (SD)]	103.46 (11.04)	121.65 (12.60)	118.46 (14.14)		
Knee drain volume [mL; mean (SD)***]	205 (162)	210 (170)	209 (169)	-4.8 (-73.4 - 63.7)	0.89
Time to discharge [days; median (IQR)]	6 (5 - 8)	5 (5 - 7)	5 (5 - 7)	1 (N/A)	0.01
Any surgical complication [count (%)]	29 (48%)	45 (15%)	74 (20%)	33% (20% – 46%)	<0.001

§ 95% confidence intervals and p-values are for the difference between transfused and not transfused groups *** in 27 transfused patients and 197 non-transfused patients with knee surgery

Table 7: Univariable and multivariable analysis of risk factors for allogenic blood transfusion with the use of intra-operative red cell salvage

Univariable analysis			
Risk factor	**Odds ratio**	**95% C.I.**	**P-Value**
Female gender	3.5	1.8 – 6.8	<0.001
Age >75	5.2	2.9 – 9.2	<0.001
Procedure - hip*	2.3	1.3 – 4.0	0.004
Diagnosis inflammatory**	1.2	0.1 – 10.1	0.75
Diagnosis other**	4.62	1.74 – 12.28	0.002
Hb <120 g/L***	44.4	12.8 – 154.3	<0.001
Hb >=120 <150 g/L***	2.5	0.8 – 7.3	0.21
BMI < 20 ****	NA	NA	NA
BMI >25 – 30 ****	0.34	0.17 – 0.67	0.002
BMI >30 ****	0.23	0.11 – 0.48	<0.001
Multivariable analysis			
Risk factor	**Odds ratio**	**95% C.I.**	**P-Value**
Female gender	2.8	1.2 – 6.6	0.02
Age >75	5.9	2.9 – 12.1	<0.001
Hb <120***	30.1	7.5 – 121.6	<0.001
Hb >120 <150 g/L***	1.3	0.4 – 4.1	0.32

* Compared with knee replacement
** Compared with diagnosis = osteoarthritis
*** Compared with Hb >150g/L group.
**** Compared to 'normal' BMI category of 20 – 25

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