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REPORTS OF ORIGINAL INVESTIGATIONS

Allogeneic blood transfusion reduction by risk-based protocol in total joint arthroplasty

Réduction des transfusions sanguines allogènes grâce à un protocole basé sur le risque dans les cas d'arthroplastie avec prothèse totale

Saifudin Rashiq, MB · Kathryn Jamieson-Lega, BSc · Carolyn Komarinski, RN · Susan Nahirniak, MD · Lisa Zinyk, RN · Barry Finegan, MB

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Abstract

Purpose *To evaluate the effect of a preoperative protocol that triages patients awaiting total joint arthroplasty to one of four strategies designed to mitigate the risk of allogeneic blood transfusion (ABT) based on a priori transfusion risk on perioperative exposure to allogeneic blood.*

Methods *We compared the transfusion experiences of a historical control series of 160 subjects with a study group of 160 subjects treated by protocol. Protocol subjects with hemoglobin (Hb) 100-129 $g{\cdot}L^{-1}$ were given erythropoietin, dosed by weight. Subjects with Hb 130-139 $g{\cdot}L^{-1}$ underwent preoperative autologous blood harvest and perioperative re-infusion as deemed clinically necessary. Subjects with Hb >139 $g{\cdot}L^{-1}$ received no special intervention, unless they were aged >70 yr and weighed < 70 kg, in which case they received oral iron and folate supplementation.*

Results *The relative risk of ABT in the Study group was 0.68 (95% confidence interval 0.54-0.85). The Control group received 104 units of allogeneic blood and the Study group received 35 units ($P = 0.0007$). These differences cannot be explained by differences in transfusion risk or autologous units transfused. There was no worsening of anemia or its consequences in the Study group.*

Conclusion *A simple protocol based on easily obtained preoperative clinical indices effectively targets interventions that mitigate the risk of ABT.*

Résumé

Objectif *Nous avons voulu évaluer l'effet d'un protocole préopératoire répartissant les patients devant subir une arthroplastie totale afin qu'ils suivent l'une de quatre stratégies dans le but de diminuer le risque de transfusion de sang allogène (TSA) selon leur risque a priori de transfusion sur l'exposition périopératoire à du sang allogène.*

Méthode *Nous avons comparé les expériences de transfusion d'une série historique de cas témoins composée de 160 patients à un groupe d'étude de 160 patients traités sur la base de notre protocole. Les patients de notre protocole présentant un taux d'hémoglobine (Hb) de 100-129 $g{\cdot}L^{-1}$ ont reçu de l'érythropoïétine, dosée en fonction de leur poids. Les patients ayant une Hb de 130-139 $g{\cdot}L^{-1}$ ont subi une récolte préopératoire et une re-perfusion périopératoire de sang autologue lorsque cela a été jugé nécessaire d'un point de vue clinique. Les patients ayant une Hb >139 $g{\cdot}L^{-1}$ n'ont pas fait l'objet d'une intervention spéciale, sauf s'ils étaient âgés de > 70 ans et pesaient < 70 kg; dans ce cas, ils ont reçu des suppléments de fer et d'acide folique par voie orale.*

Résultats *Le risque relatif de TSA dans le groupe à l'étude était de 0,68 (intervalle de confiance 95 %, 0,54-0,85). Le groupe témoin a reçu 104 unités de sang allogène, contre 35 dans le groupe à l'étude ($P = 0,0007$). Ces différences ne peuvent s'expliquer par des différences au niveau du risque*

S. Rashiq, MB (✉) · K. Jamieson-Lega, BSc · S. Nahirniak, MD · B. Finegan, MB
Department of Anesthesiology and Pain Medicine, University of Alberta Hospital, University of Alberta, 8-120 Clinical Sciences Building, T6G 2G3 Edmonton, AB, Canada
e-mail: srashiq@ualberta.ca

S. Rashiq, MB · C. Komarinski, RN · S. Nahirniak, MD · L. Zinyk, RN · B. Finegan, MB
Perioperative Blood Conservation Program, University of Alberta Hospital, University of Alberta, Edmonton, AB, Canada

de transfusion ou des unités de sang autologue transfusées. Il n'y a pas eu de détérioration de l'anémie ou de conséquences de l'anémie dans le groupe à l'étude.

Conclusion *Un protocole simple se fondant sur des indices cliniques préopératoires faciles à obtenir cible efficacement les procédures qui atténuent le risque de TSA.*

There are many well-known reasons to wish to reduce the number of patients undergoing allogeneic (banked) blood transfusion (ABT).[1] In 2008, one-third of the 779,697 units of allogeneic blood transfused in Canada (excluding Quebec) were utilized for elective surgical procedures.[A] In 2004, 10% of ABT in our health region was attributed to non-trauma orthopedic patients. Total joint arthroplasty (TJA) significantly enhances quality of life,[2] and likely will be performed in increasing numbers as more of our population moves into the age range that is at greatest risk for degenerative joint disease. The published risk of ABT in TJA varies widely, but in the year 2000, it was 27% in our region.[3] Therefore, TJA is a logical area in which to apply strategies designed to reduce ABT.

Several therapeutic interventions reduce the need for ABT in TJA, for example, measures to increase available red cell mass prior to surgery, either by the administration of iron[4] or erythropoietin[5] or by preoperative autologous blood donation;[6] measures to reduce surgical blood loss by hemodilution,[7] induced hypotension[8] or the use of antifibrinolytic agents;[9] and measures to make shed blood available for re-transfusion.[10] All of these measures have advantages and disadvantages in effectiveness, cost, risk, and convenience, and none has been proven to be completely superior to any other in every respect. It makes sense to target such interventions preferentially towards those patients who are at greatest risk for ABT.

We previously published a clinical prediction rule[3] that delivered a valid preoperative estimate of ABT risk in TJA using six easily obtained clinical data points: age, gender, hemoglobin, weight, American Society of Anesthesiologists (ASA) classification, and whether the proposed operation was a primary or revision procedure. In this study, we evaluate the effectiveness of a strategy designed to reduce the need for ABT based on this prediction rule.

Methods

Edmonton's Perioperative Blood Conservation Program (PBCP) is a publicly funded clinic to which any patient contemplating surgery in Northern Alberta may be referred. Patients are assessed by anesthesiologists and nurse specialists, and preoperative interventions to mitigate the risk of allogeneic transfusion are prescribed as appropriate. At the time of this investigation, available interventions consisted of oral iron and folic acid supplementation, erythropoietin, and autologous blood harvest and storage. The prescription of intraoperative strategies for blood conservation, such as hemodilution and cell salvage, was not part of PBCP's mandate and was not used in either the historical control or the prospective study groups. The costs of autologous donation were covered by Canadian Blood Services, but patients had to pay for prescribed iron/folate tablets and erythropoietin. Patients were referred to PBCP at the surgeon's discretion, and apart from general information about the existence of the service, no special effort was made to solicit referrals. Prior to the initiation of the protocol, autologous blood harvesting, while possible, was not readily and systematically available.

In May 2002, PBCP began using a treatment algorithm based on our prediction rule to target its interventions in TJA. The general objectives were to avoid the unnecessary waste and risk associated with over-treatment of those at low absolute risk of transfusion and to provide those at highest risk with the most effective measures. The algorithm (Figure 1) places patients in one of four treatment arms based on his/her *a priori* risk of allogeneic transfusion. PBCP clinicians determined by consensus which treatment the algorithm would prescribe in each arm. Not all risk factors identified in the prediction rule were used in the algorithm; gender, ASA classification, and revision surgery status were omitted. This decision was made in order to simplify the process in view of the relatively small influence of these three variables on transfusion risk calculation.

We sought to assess the effectiveness of this development by comparing ABT in two samples of TJA patients, one sampling from before this change (Group C [Control group] from 2001-2) and one sampling from after this change (Study group [Group S] from 2002-7, data collected prospectively). Eighty-nine of the 160 subjects in the Study group were recruited in 2002 or 2003, 3 in 2004, 11 in 2005, 26 in 2006, and 30 in 2007. Our null hypothesis was that the application of the treatment algorithm followed by routine perioperative clinical care would not result in any difference in the number of allogeneic red cell unit exposures per group.

During both phases of data collection, TJA were performed by a number of different surgeons in more than one facility. Since we could not control which TJA patients were referred to PBCP, both groups were convenience samples. We assumed that the number of TJA candidates referred for PBCP assessment by surgeons would be biased towards those with the greatest perceived transfusion risk.

[A] Personal communication with David Howe, Canadian Blood Services.

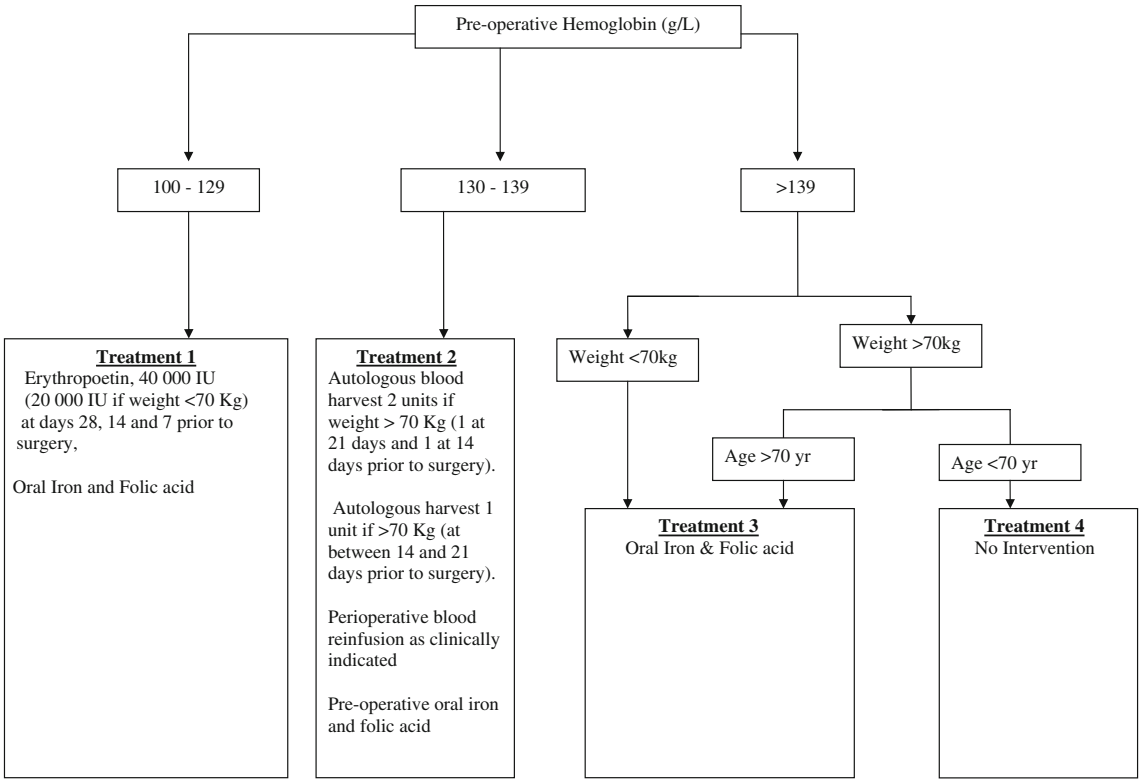

Fig. 1 Treatment allocation

Accordingly, we stratified recruitment into both groups according to the treatment algorithm itself, enrolling 40 subjects into each of the four treatment arms in each of the two study phases. These sample sizes were chosen arbitrarily.

We compiled the Control group from hospital databases by identifying sequential TJA patients who had undergone TJA without PBCP involvement. The information was gathered in reverse chronological order from the date on which the algorithm was introduced until we had data on 160 subjects, 40 of whom would have been placed into each of the four treatment arms had it been in use. Demographic data, operative reports, recorded complications, and length of stay were obtained from the hospital chart. Anesthesia data, including the types and quantities of intraoperative fluids administered were obtained from the anesthetic record. We corroborated the use of allogeneic and autologous blood units recorded in the charts by crosschecking the blood bank's computerized inventory. For the Study group, we recruited consecutive consenting TJA patients referred to PBCP until we had accumulated data for 40 subjects in each treatment arm, and we collected their data retrospectively. For both groups, we restricted recruitment to those presenting for primary, complete, unilateral TJA. We excluded subjects under 18 yr of age, those with hemoglobin $\leq$ 100 g·L^{-1}, those with a bleeding diathesis or taking anticoagulant treatment (other than low-dose aspirin), anyone stating that they would inevitably decline a blood transfusion even if it was thought to be medically necessary, anyone who insisted on a particular blood conservation strategy outside the protocol (most often, subjects who insisted on banking autologous blood despite a low *a priori* ABT risk), and anyone who did not have sufficient money or insurance coverage to pay for the allocated treatment**.** This latter factor was predominantly relevant to erythropoietin treatment, which cost $401.85 for 40,000 IU in 2007 (oral iron and folic acid cost $0.25/day and autologous blood was harvested without charge). We did not influence subjects' other treatment in any way. Anesthesiologists and surgeons administered blood transfusions, other infusions, and all other interventions in accordance with clinical judgment and patient preference.

The Health Research Ethics Board of the University of Alberta approved the study, and informed consent was obtained, both for access to patients' medical records retrospectively, and for prospective treatment.

Statistical analyses were performed using SAS for Windows Version 9.1 (SAS Institute, Cary, NC, USA). We considered continuous variables with kurtosis of < 1.5 and skew -1.0 to 1.0 in both groups to be distributed normally. We compared the groups using two-tailed t tests for

normally distributed continuous variables, the Wilcoxon Rank-Sum test for other continuous variables, and χ^2 tests for the categorical variables gender, ASA Class, type of TJA performed, and type of anesthesia. In order to detect as many potential confounders as possible, we did not correct for multiple comparisons when comparing the baseline characteristics of the two groups. Statistical significance was inferred at $P < 0.05$.

Results

The subjects are described in Table 1. The variable surgery time was found to have a non-normal distribution and, therefore, was analyzed non-parametrically. Group S had a lower mean body mass, underwent operations of shorter duration, comprised more female subjects, consisted of fewer subjects with ASA Classifications of III or greater, and received more spinal anesthesia *vs* general anesthesia.

Table 2 gives outcome data. Donor unit exposure was reduced by 62% in Group S. The number of subjects in Group S exposed to allogeneic blood was more than halved. The 27 units of autologous blood transfused in Group S (compared with zero in Group C) were associated with a complete elimination of ABT in that sub-group. The overall reduction in ABT was not obtained merely by tolerating more perioperative anemia; neither the lowest nor the discharge hemoglobin was different between groups. There was no difference in the amount of crystalloid infused, although about 250 mL more colloid was administered in Group S. The lowest hemoglobin recorded in subjects receiving transfusion of any kind (allogeneic or autologous) was 78 ± 10 $g{\cdot}L^{-1}$ in Group C and 80 ± 6 $g{\cdot}L^{-1}$ in Group S.

Twenty-eight units of autologous blood were collected but not administered in Group S, a wastage rate of 51%. This was due to either unexpected delay in surgery resulting in out-dating of the harvest or the determination that the transfusion was unnecessary.

In Table 3, allogeneic transfusions are broken down by treatment allocation. Erythropoietin and autologous blood treatment were associated with a reduction in ABT, but the 95% confidence intervals for the effect of oral iron/folic acid crossed zero.

Complications are tabulated in Table 4. There were no in-hospital deaths. While the diversity and small number of complications preclude quantitative analysis, the data do not suggest that events potentially attributable to acute anemia or its complications were more common in the study group.

Discussion

We have shown that the preoperative application of a simple treatment algorithm based on easily obtained clinical measurements significantly reduces the requirement for ABT in TJA without increasing perioperative anemia. Our null hypothesis is rejected.

The demonstrated reductions in allogeneic transfusion resulted from the comparison of two groups with equal numbers in each treatment arm. We designed this artificial environment to obtain as much information as possible about the effect of each arm. Nonetheless, if we project these reductions in transfusion resulting from each treatment onto our entire TJA joint population from the year 2000, even then, the weighted mean reduction in ABT would be 54%. The majority of this transfusion sparing (52% of the reduction, not of transfusions) would have occurred in subjects with Hb 130-139 $g{\cdot}L^{-1}$ undertaking autologous blood banking, and the next highest yield (28%) would have been from those with Hb 100-129 $g{\cdot}L^{-1}$ receiving erythropoietin.

Our choice of treatment for each risk category was based on simple premises: 1) Patients with relatively low Hb (< 130 $g{\cdot}L^{-1}$) are better served by enhancing red cell mass by forced erythropoesis than by banking their already erythrocyte-poor blood; 2) Patients in the middle ground

Table 1 Demographic and surgical characteristics by group

	Group C ($n = 160$) (Historical controls)	Group S ($n = 160$) (Study group)	P value
Age (yr) mean ± SD	68.2 ± 10.8	66.1 ± 10.6	0.076
Weight (kg) mean ± SD	86.8 ±1 8.6	82.2 ± 18.2	**0.025**
BMI ($kg{\cdot}m^{-2}$) mean ± SD	30.7 ± 5.9	30.0 ± 6.2	0.28
Initial Hb ($g{\cdot}L^{-1}$) mean ± SD	139 ± 12	138 ± 14	0.42
Surgery time (min) median ± IQR	65 ± 32	60 ± 27	**0.015**
Female (n)	81 (51%)	101 (63%)	**0.024**
ASA Class > II (n)	58 (36%)	38 (23%)	**0.015**
Hip : knee arthroplasty (n)	75:85 (47:53%)	73:87 (46:54%)	0.82
Spinal: general anesthesia (n)	96:63 (60:40%)	117:42 (74:26%)	**0.0012**

Bold = $P < 0.05$; BMI = body mass index; Hb = hemoglobin; IQR = interquartile range; SD = standard deviation

Table 2 Outcomes by group

		Group C (Historical controls) $n = 160$	Group S (Study group) $n = 160$	Relative risk to study group	95% CI
Subjects receiving allogeneic blood		40 (25%)	19 (12%)	**0.68**	**0.54-0.85**
				P	
Allogeneic units transfused	Per group	104	35	**0.0007**	
	Mean unit exposure per subject	0.65	0.22		
Intraoperative crystalloid infused per subject (mL) mean ± SD		1610 ± 890	1800 ± 1060	0.84	
Intraoperative colloid infused per subject (mL) mean ± SD		550 ± 200	270 ± 300	**0.001**	
Estimated intraoperative blood loss (mL) median ± IQR		300 ± 250	300 ± 300	0.30	
Lowest Hb ($g \cdot L^{-1}$) mean ± SD		94 ± 14	96 ± 14	0.20	
Discharge Hb ($g \cdot L^{-1}$) mean ± SD		101 ± 12	102 ± 12	0.42	
Autologous units transfused		0	27	**<0.0001**	
Length of hospital stay (days) median ± IQR		6 ± 2	5 ± 3	0.53	

Bold = $P < 0.05$; BMI = body mass index; Hb = hemoglobin; IQR = interquartile range; SD = standard deviation

Table 3 ABT by treatment allocation and group

Treatment Arm	Subject Characteristics	Treatment allocation	Allogeneic units transfused		Reduction in units transfused (95% CI)
			Group C	Group S	
1	Hb 100-129 $g \cdot L^{-1}$	Erythropoetin, 40,000 IU (20,000 IU if weight < 70 kg) at days 28, 14, and 7 before surgery, plus oral iron and folic acid	51	23	28 (2,54)
2	Hb 130-139 $g \cdot L^{-1}$	Autologous blood harvest 2 units (1 unit if >70 kg) plus oral iron and folic acid	23	0	23 (11,35)
3	Hb > 139 $g \cdot L^{-1}$ and weight < 70 kg Or Hb > 139 $g \cdot L^{-1}$, weight > 70 kg, and age > 70 yr	Oral iron and folic acid	25	8	17 (-8,42)
4	Hb > 139 $g \cdot L^{-1}$, weight > 70 kg	No intervention	5	4	1 (-8,8)

CI = confidence interval; Hb = hemoglobin

Table 4 In-hospital complications by group

	Group C ($n = 160$) (Historical controls)	Group S ($n = 160$) (Study group)
Myocardial infarction	2	0
New arrhythmia	1	1
Deep vein thrombosis	1	1
Delirium	4	2
Respiratory event	1	2
Pruritus/erythema	1	1
Local/incisional	3	1
Other	3	2

(130-139 $g \cdot L^{-1}$) have enough red cell mass to make autologous donation worthwhile and are at sufficient risk of requiring transfusion to make it worthwhile; and 3) Special measures are wasted on those with the highest Hb. Others might make valid arguments for differing cut-points or treatment allocations. In retrospect, a more aggressive strategy for the < 130 $g \cdot L^{-1}$ group and a higher upper hemoglobin cut-off for the use of autologous transfusion might have been worthwhile. We also acknowledge that our protocol cannot be considered as being truly comprehensive, inasmuch as it does not incorporate intraoperative blood sparing measures or any attempt to inform or influence the decision to transfuse as it is being made.

We recognize that a purely prospective design with random allocation of subjects to the two treatment arms and standardization of all subsequent aspects of care would have been a superior test of the intervention, but such a design was simply beyond our reach. Our use of a less rigorous design made it vital to ensure that, as far as possible, the two groups were at equal *a priori* risk of the

major outcome of interest, i.e., ABT. The study's treatment algorithm itself served as the basis for subject selection. It was derived from the multivariate analysis of 1,875 TJAs performed in our region in 2000,[3] from which we determined that the three strongest determinants of allogeneic transfusion risk were hemoglobin concentration, body mass, and age. Neither the prediction rule nor the treatment algorithm allocated exactly equal weight to each of these three criteria, so we were not surprised to discover that our two groups differed in one of these three factors as well as in other respects. Group S had lower body mass and mean ASA grade than Group C; it also included more women, received more spinal anesthetics, and had shorter operations. The net effect of these differences on transfusion risk can be estimated using data from another analysis of the 2000 TJA database.[11] We found that female gender increases the point odds of transfusion by 1.418; ASA III classification or greater increases it by 1.483; increasing body mass decreases it by $0.972 \cdot kg^{-1}$; duration of surgery increases it by $1.017 \cdot min^{-1}$; and regional anesthesia reduces it by 0.729. Multiplying these effect sizes by the differences found between groups indicates that the net effect was to place Group S at higher risk, not lower risk, of transfusion. We therefore believe that selection bias is an unlikely explanation for our principal finding.

Since we did not control subjects' surgical or anesthetic treatment, the possibility of a secular confounding factor(s) providing a better explanation for Group S's lower transfusion rate ought to be considered, but there does not appear to be any evidence supporting it. Blood loss estimates and perioperative hemoglobin measurements were the same between groups.

We know that erythropoietin and autologous blood harvest took place as prescribed, but we could not verify that patients prescribed oral iron and folic acid took it according to instructions for the desired duration. We cannot be sure that patients allocated to no intervention did not take iron supplements on their own initiative. Furthermore, we did not collect data about the direct or indirect cost of these interventions, which is clearly important in deciding whether to offer them. We must also acknowledge the possibility that each of these blood conservation interventions can cause harm. While we did not document any increased incidence of in-patient adverse events in Group S, the risk of a thrombotic event from erythropoietin or the risk of an ischemic episode following autologous blood harvest must be borne in mind as these therapies are offered.

Our findings are broadly in agreement with those of other groups. A comprehensive perioperative blood management strategy based on body weight and hematocrit incorporating more complex treatment options than ours was associated with a reduction in mean allogeneic donor unit exposure from 0.61 to 0.31 in 475 French subjects undergoing primary TJA.[12] Our 51% wastage rate of autologous units is in line with other TJA studies.[13] A study from another French group highlighted the need for selectivity in the administration of blood sparing strategies by recording large reductions in transfusion requirements merely by excluding subjects with adequate red cell mass from their autologous donation program.[14] A conceptually simpler strategy (administration of erythropoietin in anyone expected to be rendered to a Hb of $< 7.0\ g \cdot L^{-1}$ by subtracting a standardized procedure-specific predicted blood loss from his or her pre-operative hemoglobin) still yielded almost sixfold reductions in allogeneic transfusions.[15] Although the control group's transfusion rates in that investigation were very low to begin with, their decision to use protocol non-compliers as the control group will not find universal approval. Other strategies have reduced allogeneic transfusion rates in TJA successfully. These approaches range from the simple dissemination of a one-page flow sheet to guide clinicians contemplating administering a transfusion,[16] to bedside confirmation of hematocrit immediately prior to administering transfusions.[17]

There is no consensus about how best to use the various available strategies to reduce TJA-associated transfusion.[18] Our approach is a simple scheme that has yielded significant results in our population. Our intention is to refine it further in order to take advantage of emerging modalities, such as parenteral iron therapy, to simplify the algorithm, if possible, and to evaluate the potential additional utility of measures that currently are not included. In addition, we would like to be able to derive estimates of whether, in the aggregate, health care resources are saved by our efforts. While there may be no strategy that can completely prevent allogeneic exposure in every TJA, our patients are well served by our efforts towards that goal.

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Conflicts of interest None declared.

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