Preoperative Autologous Donation Decreases Allogeneic Transfusion but Increases Exposure to All Red Blood Cell Transfusion

Results of a Meta-analysis

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Background: Concern about risks associated with allogeneic red blood cell transfusion has led to interest in methods of decreasing patient exposure to perioperative transfusion.

Objective: To perform a meta-analysis to determine the degree to which predonation of autologous blood reduces patients’ exposure to allogeneic blood and all transfusions of red blood cells (allogeneic or autologous).

Methods: We searched MEDLINE, EMBASE, bibliographies, annual reports, press releases, newsletters from organizations with interests in the blood system, and personal files for randomized studies and concurrent control cohort studies in which the control groups were patients excluded for nonmedical reasons.

Results: Patients who predonated autologous blood were less likely to receive allogeneic blood in the 6 randomized studies (n=933) (odds ratio [OR], 0.17; 95% confidence interval [CI], 0.08-0.32) and in the 9 cohort studies (n=2351) (OR, 0.19; 95% CI, 0.14-0.26). However, autologous donors were more likely to undergo transfusion with allogeneic and/or autologous blood (for randomized studies: OR, 3.03; 95% CI, 1.70-5.39 and for cohort studies: OR, 12.32; 95% CI, 5.90-25.40). Studies that reported use of transfusion protocols found less benefit with preoperative autologous donation, although the difference was not statistically significant.

Conclusions: Preoperative autologous donation of blood decreases exposure to allogeneic blood but increases exposure to any transfusion (allogeneic and/or autologous). There is a direct relationship between the transfusion rate in the control group and the benefit derived from preoperative autologous donation. This suggests that other methods of decreasing blood transfusion, such as surgical technique and transfusion protocols, may be as important as preoperative autologous donation of blood.

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Concern about the transmission of hepatitis and human immunodeficiency virus with allogeneic red blood cell transfusion has led to an increase in the use of measures aimed to reduce perioperative exposure to allogeneic blood. Of the many alternatives available, including cell salvage,\(^1\) intraoperative hemodilution,\(^2\) and medications such as aprotinin,\(^3\) tranexamic acid,\(^4\) and erythropoietin,\(^5\) preoperative autologous donation is one of the most widely used methods.

Numerous articles\(^6\)\(^-\)\(^8\) have encouraged preoperative autologous donation of blood to decrease exposure to allogeneic red blood cell transfusion. However, there is variable use of the technique, as illustrated by the Safe and Good Use of Blood in Surgery (SANGUIS) study.\(^9\) For example, this study found that the proportion of patients undergoing hip arthroplasty who received predonated autologous blood in a number of European hospitals varied from 0% to more than 80%. There is concern that the true efficacy of autologous predonation to decrease exposure to allogeneic blood is still not known. First, most of the information comes from nonrandomized studies, which are known to systematically overestimate the benefit of a treatment.\(^10\) Second, patients in the control groups in the nonrandomized studies were often excluded from donation for medical reasons, making an unbiased comparison between the 2 groups difficult. Third, there have often been no clearly defined transfusion thresholds in the studies, raising the possibility of a different transfusion policy in those who predonated blood and those who did not. To our knowledge, a systematic overview of randomized controlled studies assessing the benefit of preoperative autologous blood donation has not been performed. Therefore, to obtain the best estimate of the efficacy of
preoperative autologous blood donation, we systematically reviewed the literature, selected the most methodologically rigorous studies, and performed a meta-analysis of those studies.

The objectives of the meta-analysis of randomized studies were to determine (1) the degree to which preoperative autologous donation of blood reduced patients' exposure to allogeneic red blood cells; (2) if exposure to all transfusions of red blood cells (either allogeneic or autologous) was affected by preoperative autologous blood donation; (3) if the use of a transfusion protocol affected the efficacy of preoperative autologous blood donation; and (4) if the efficacy of preoperative autologous blood donation varied by the type of surgery. Because we anticipated finding few randomized studies, we also conducted a secondary meta-analysis of cohort studies that used appropriate control groups with the same objectives as the meta-analysis of randomized studies.
Table 1. Characteristics of Studies Included in the Meta-analysis*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Study Design</th>
<th>Type of Surgery</th>
<th>No. of Patients (Control/Auto)</th>
<th>Mean Age, y (Control/Auto)</th>
<th>Male-Female (Control/Auto)</th>
<th>Iron Supplementation</th>
<th>Transfusion Protocol Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elawad et al,13 1991</td>
<td>RCT</td>
<td>Hip arthroplasty</td>
<td>15/45 None</td>
<td>71/71</td>
<td>9.6/24.21</td>
<td>Yes†</td>
<td>None</td>
</tr>
<tr>
<td>Lorenz et al,14 1991</td>
<td>RCT</td>
<td>Hip arthroplasty</td>
<td>15/16 None</td>
<td>63/58</td>
<td>5.10/8.8</td>
<td>Yes</td>
<td>Hb &lt; 90 in intensive care unit, or Hb &lt; 100 in ward</td>
</tr>
<tr>
<td>Hoynek van Papendrecht et al,15 1992</td>
<td>RCT</td>
<td>Colon resection</td>
<td>137/245 0/14</td>
<td>67/65</td>
<td>NA</td>
<td>Yes</td>
<td>Hb &lt; 105, &gt; 500 mL EBL</td>
</tr>
<tr>
<td>Heiss et al,16 1993</td>
<td>RCT</td>
<td>Colon resection</td>
<td>62/58 None</td>
<td>61/59</td>
<td>31:31/30:28</td>
<td>Yes</td>
<td>Hb &lt; 100</td>
</tr>
<tr>
<td>Busch et al,17 1993</td>
<td>RCT</td>
<td>Colon resection</td>
<td>236/239 5/26</td>
<td>68/66</td>
<td>132:104/141:98</td>
<td>Yes</td>
<td>&gt; 500 mL of EBL, Hb &lt; 105</td>
</tr>
<tr>
<td>Kajikawa et al,18 1994</td>
<td>RCT</td>
<td>Liver resection</td>
<td>21/10 None</td>
<td>NA/58</td>
<td>NA</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Love et al,19 1987</td>
<td>OP</td>
<td>Cardiac surgery</td>
<td>55/58 None</td>
<td>55/57</td>
<td>44:14/44:14</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Toy and Strauss,4 1987</td>
<td>OP</td>
<td>All types of elective surgery</td>
<td>558/33 0/1</td>
<td>52/47</td>
<td>NA</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Britton et al,20 1989</td>
<td>OP</td>
<td>Cardiac surgery</td>
<td>111/104 1/2</td>
<td>64/59</td>
<td>NA</td>
<td>Yes</td>
<td>Control: Hct &lt; 0.25; Auto: all auto units regardless of Hct</td>
</tr>
<tr>
<td>O’Hara et al,21 1994</td>
<td>OP</td>
<td>Aortic aneurysm resection</td>
<td>72/73 None</td>
<td>68/68</td>
<td>67.5/64.9</td>
<td>No</td>
<td>Hct &lt; 0.30 or Hb &lt; 100</td>
</tr>
<tr>
<td>Giurati et al,22 1995</td>
<td>OP</td>
<td>Radical hysterectomy</td>
<td>29/28 None</td>
<td>50/46</td>
<td>0.29/0.28</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Sandrelli et al,23 1995</td>
<td>OP</td>
<td>Cardiac surgery</td>
<td>344/348 None</td>
<td>53/52</td>
<td>291:53/294:54</td>
<td>Yes</td>
<td>Hb &lt; 80‡</td>
</tr>
<tr>
<td>Toy et al,24 1995</td>
<td>OP</td>
<td>Hip arthroplasty</td>
<td>84/240 None</td>
<td>63</td>
<td>47/53</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Yamada et al,25 1993</td>
<td>OP</td>
<td>Radical prostatectomy</td>
<td>34/37 None</td>
<td>71/64</td>
<td>34.3/37.0</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Clugston et al,26 1995</td>
<td>OP</td>
<td>Mammoplasty</td>
<td>65/81 None</td>
<td>35/34</td>
<td>0.63/0.81</td>
<td>Yes</td>
<td>None</td>
</tr>
</tbody>
</table>

*Auto indicates autologous predonation; RCT, randomized controlled trial; Hb, hemoglobin value; NA, not available; EBL, expected blood loss; Hct, hematocrit value; OP, observational, prospective study; and OR, observational, retrospective study.
†Patients randomized to 4 groups: control, autologous blood predonation with no iron supplementation, autologous blood predonation with iron supplementation, and autologous blood predonation with iron and folate supplementation.
‡Also used guidelines by Goodnough et al.28
§In this study, the mean age is for the entire group and the male-female ratio is a percentage.

STUDY LOCATION, SELECTION, AND EVALUATION

Of the 61 studies, 21 were rejected because there was no control group, which left 6 randomized controlled studies and 34 cohort studies. Of the concurrent control cohort studies, 25 were rejected because the control group was not appropriate (the control group was not described in 12 studies; patients had been excluded from autologous blood donation for medical reasons in 11 studies; and allogeneic blood use in the 2 groups was not described 2). Six randomized controlled studies13-18 and 9 concurrent control cohort studies8,19-26 (7 prospective, 2 retrospective) were included in the analysis. A list of the excluded studies is available from the authors upon request. One randomized study was published as 2 separate articles16,27 in an overlapping population. The article16 with the greatest number of patients was used for our analysis. Disagreement among the reviewers occurred on 3 occasions regarding the eligibility of the observational studies only (κ=0.86). All 6 randomized studies scored 2 on the quality scale by Jadad et al.11 Since it is ethically inappropriate to blind autologous blood donors to the treatment they received, the maximum possible score for quality in these studies was 3. There was no disagreement on the quality of the articles.

STUDIES INCLUDED IN THE META-ANALYSIS

Summary data from the 6 randomized and 9 concurrent control cohort studies used in the final analysis are presented in Table 1 and Table 2. The sample size in the randomized studies varied from 31 to 423 with a total of 933 patients included in the meta-analysis. The sample size in the cohort studies varied from 57 to 692 with a total of 2351 patients included in the meta-analysis.

EFFICACY IN RANDOMIZED STUDIES

The 6 randomized studies16-20 were conducted in patients who underwent the following types of procedures: colorectal surgery for bowel cancer (3), hip arthroplasty (2), and liver resection (1). All 6 studies demonstrated a statistically significant decrease in exposure to allogeneic blood in patients who predeposited autologous blood compared with those who did not. The OR when all these studies were combined was 0.17 (95% confidence interval [CI], 0.08-0.32), demonstrating that preoperative autologous blood donation decreased the exposure to allogeneic blood. The OR for colorectal surgery was 0.26 (95% CI, 0.19-0.37) compared with 0.20 (95% CI, 0.00-0.28) in patients who underwent hip arthroplasty. The OR in studies in which a transfusion protocol was reported was 0.25 (95% CI, 0.17-0.37) compared with 0.02 (95% CI, 0.00-0.24) in those that
did not report a transfusion protocol. Five randomized studies reported the total number of units transfused (allogeneic and autologous blood). Autologous blood donors were more likely to receive any transfusion (allogeneic and/or autologous red blood cells) with an OR of 3.03 (95% CI, 1.4-5.39). These results were minimally affected when the analysis was restricted to the 4 studies that reported a transfusion protocol, but one of these had a different transfusion protocol for patients donating autologous blood than for patients who did not donate autologous blood. Six studies reported the total number of units transfused (allogeneic and/or autologous). Similar to the randomized studies, autologous donors were more likely to receive any transfusion (allogeneic and/or autologous red blood cells) with a common OR of 12.32 (95% CI, 5.90-25.40).

HEMATOCRIT VALUES

Preoperative hematocrit values were an average of 3.5 units lower in patients who donated autologous blood than in patients in the control group. The last hematocrit values before patient discharge were similar in both patient groups in the 8 studies in which this was recorded, and these values were not affected by the use of a transfusion protocol. They ranged from 0.30 to 0.38 in the 7 studies reporting this outcome.

ABSOLUTE EFFICACY OF PREDONATION

There was a direct relationship between the proportion of patients who underwent transfusion with allogeneic blood in the control group and the absolute benefit of preoperative autologous donation (Figure).
or hematocrit values, \(^{20}25\%\) to \(46\%\) of units were not used. In 2 other studies, \(^{16,17}9\%\) and \(26\%\) of the autologous blood donor patients had none of their units returned, but data about the proportion of autologous units not used were not provided. In one study, \(^{20}\) of patients undergoing mammoplasty, the transfusion rate in the control group was only \(3\%\).

**CLINICAL COMPLICATIONS**

Only 1 of the randomized studies, \(^{17}\) provided data on the recurrence of cancer and overall survival. It demonstrated a statistically significant increase in 4-year disease-free survival in patients with colorectal cancer who did not undergo transfusion with any blood compared with patients who underwent transfusion with either autologous or allogeneic blood (73% vs 59%, respectively; \(P<.001\)). Of the randomized studies in colorectal cancer, 2 studies, \(^{16,17}\) provided data on the incidence of postoperative infection. There was no statistically significant increase in the risk of postoperative infection (OR, 1.44; 95% CI, 0.49-4.26). The studies included in our meta-analyses did not provide sufficient information to determine if medical complications, such as myocardial infarction, angina, prolonged hospital admission, and venous thrombosis, differed between the groups who pre-donated blood and those who did not.

This meta-analysis of 6 randomized studies suggests that preoperative donation of autologous blood reduces exposure to allogeneic blood (OR, 0.17; 95% CI, 0.08-0.32). These studies were performed in patients undergoing colorectal resection, hip arthroplasty, and liver resection. Patients undergoing cardiac, urologic, vascular, gynecological, and mammoplasty surgery were assessed in 9 cohort studies that met our inclusion criteria. The OR for the cohort studies was similar to that of the randomized controlled studies (OR, 0.19). Thus, it is likely that preoperative autologous donation of blood reduces exposure to allogeneic red blood cells in most types of surgery with considerable blood loss.

One of the striking results of this meta-analysis is that patients who predonated autologous blood were considerably more likely to receive any blood transfusion (autologous and/or allogeneic) than patients in the control group. This may be partly due to the lower mean preoperative hematocrit values in patients undergoing preoperative autologous donation of blood; however, it is almost certainly also due to a more liberal transfusion policy with autologous blood. \(^{29}\) Although some \(^{30}\) argue that the safety of autologous blood justifies a more liberal transfusion policy in autologous donors, most \(^{31}\) believe that the criteria for transfusion should be the same in those who predonate autologous blood and those who do not.

Autologous blood is associated with a smaller chance of transmitting viral infections than allogeneic blood. However, the likelihood of becoming infected with hepatitis or the human immunodeficiency virus with allogeneic blood is now very low. The most recent published estimate \(^{31}\) from the United States is 1 in 493,000 transfusions for human immunodeficiency virus, 1 in 103,000 for hepatitis C, and 1 in 63,000 for hepatitis B. In addition, an infectious agent that we are currently unaware of may be transmitted by allogeneic blood. However, noninfectious complications, such as transfusion of the wrong unit of blood because of laboratory, clerical, or ward error, bacterial contamination, and fluid overload because of excess transfusion, occur at least as frequently in recipients of autologous blood as in patients who receive allogeneic blood. The reported frequency of these complications varies, \(^{31}\) but a recent review \(^{31}\) from New York State found a 1 in 33,000 chance of ABO incompatibility and a 1 in 600,000 chance of a fatal acute hemolytic transfusion reaction. Thus, it is possible that autologous blood donors, if they are more likely to receive transfusion of any kind, are ultimately placed at higher risk than nondonors. The donation procedure itself is also not completely free of risk because older patients with cardiac disease are more likely to have a reaction associated with donation than younger, healthier patients; \(^{25}\) in one study, \(^{29}\) autologous blood donors were 12 times more likely to have a reaction requiring hospitalization than donors of blood intended for allogeneic use (the actual incidence was low in both groups: 1 of 198,000 allogeneic donations and 1 of 17,000 autologous donations). For patients to derive the full benefits of preoperative autologous blood donation, it is important that clinicians recognize that collection and transfusion of autologous blood is not entirely without risk and they should not alter the transfusion threshold.

There are a number of limitations of this meta-analysis. First, there were only 6 randomized studies with a total of 933 patients. The largest study included 475 patients, but 3 studies included fewer than 100 patients. Previous meta-analyses that included a similar number of patients were subsequently shown to have overestimated the benefit of therapy compared with large, definitive, randomized studies. \(^{37}\) Second, the results of the eligible studies were statistically and clinically heterogeneous. Since all the randomized studies found a decrease in exposure to allogeneic red blood cells with preoperative autologous donation of blood, the heterogeneity concerns the degree of benefit from autologous donation of blood, rather than whether the

![Correlation between the absolute risk reduction in exposure to allogeneic blood associated with autologous predonation and the frequency of receiving allogeneic blood in the control group.](image-url)
technique was efficacious. In addition, much of the heterogeneity seemed to be explained by the type of surgery and the presence of a transfusion threshold. Nonetheless, the presence of heterogeneity in a meta-analysis decreases the strength of any inferences or statistical conclusions. We used a random effects model, which leads to wider confidence limits around the estimate of treatment effect than a fixed effects model. Third, the hemoglobin value used as a transfusion threshold for asymptomatic postoperative patients was quite high in some studies (often 100 g/L), suggesting a liberal use of perioperative transfusion. Since the absolute benefit derived from preoperative autologous donation of blood was proportional to the use of allogeneic blood in the control group (Figure), it is likely that the effect of preoperative autologous donation of blood on the frequency of allogeneic blood transfusion would have been less had allogeneic blood been used more conservatively in the control group. However, it must be recognized that the lowest safe postoperative hemoglobin value has not been established, and a recent study suggests that some patients with a history of cardiac disease may develop symptomatic anemia. Fourth, because the studies were unblinded, the decision to transfuse allogeneic blood may have been different in the 2 groups. It is also impossible to know whether the clinical characteristics of patients in the control groups in the cohort studies were actually similar to those in the autologous predonation group. Finally, it is unclear if current transfusion practice is the same now as it was when the studies used in the analysis were performed.

Despite these limitations, preoperative autologous donation of blood decreased the exposure to allogeneic red blood cells. Important unanswered issues about autologous predonation of blood include the indications for the procedure and how the procedure compares with other approaches to minimizing exposure to perioperative allogeneic blood transfusion. Recent economic evaluations have suggested that for most surgical procedures, preoperative autologous donation of blood does not meet conventional criteria for cost-effectiveness. This is largely due to the low frequency of viral infections with current allogeneic blood, the higher costs of collecting autologous blood, and the fact that autologous blood that is not required by the donor is discarded. Therefore, it would seem appropriate to use only preoperative autologous donation of blood in patients who have a high risk of needing allogeneic blood, although the definition of high risk has not been established.

Preoperative autologous donation of blood has both advantages and disadvantages when compared with other modalities used to decrease exposure to allogeneic blood. Advantages include patients' sense of control over their care, the decrease in the risk of transmission of known viral infections, the possibility of avoiding unknown infections, avoidance of alloimmunization to donor blood components and other immunomodulatory effects related to allogeneic blood transfusion, and the lack of adverse effects from the use of medications. Disadvantages include the inconvenience of predonation to the patient, medical contraindications to preoperative autologous donation of blood for some patients, a strain on the blood collection system because of the extra organizational requirements of preoperative autologous donation of blood, and difficulties with scheduling surgery. Also, in the manner the technique was used in these studies, patients who predonate autologous blood are more likely to receive any transfusion of blood (allogeneic and/or autologous) than patients who do not donate their own blood preoperatively.

Recently completed meta-analyses of randomized studies (also A.L. and D.F., unpublished data, 1997) of the efficacy of aprotinin, tranexamic acid, and erythropoetin found all to be effective with ORs varying from 0.32 to 0.55. Thus, to determine which blood conservation technology is most appropriate, large direct comparisons of preoperative autologous donation of blood with the other modalities are needed. These studies will require strict transfusion policies and should incorporate economic evaluations to determine the relative advantages and disadvantages of the various options available to decrease perioperative exposure to allogeneic blood.

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REFERENCES