Autologous and Heterologous Blood Transfusion in Head and Neck Cancer Surgery

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Objective: To determine if the use of autologous blood ameliorates the increased risk for cancer recurrence that has been associated with perioperative blood transfusion.

Design: Retrospective medical record review.

Setting: Tertiary care hospital.

Patients: One hundred sixty-five consecutive patients with stages II to IV squamous cell carcinoma of the head and neck treated surgically at a university hospital from January 1, 1989, through December 31, 1994.

Main Outcome Measures: We evaluated the impact of perioperative autologous and heterologous blood transfusion and 10 other variables on recurrence. Univariate and multivariate analyses were used.

Results: Heterologous blood recipients had a 59% recurrence rate, whereas those who had received autologous blood or no transfusion had recurrence rates of 33% and 35%, respectively. The following 4 variables had a statistically significant association with recurrence by multivariate analysis: previous treatment of current malignancy ($P < .001$); receipt of heterologous blood ($P = .04$); positive margin ($P = .04$); and nodal disease ($P = .04$). The receipt of heterologous blood was associated with a 40% increased risk for recurrence.

Conclusion: Autologous blood products should be used during head and neck cancer surgery if possible when transfusion is necessary.


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HE IMMUNOSUPPRESSIVE effect of allogeneic blood transfusion was originally described in the transplant literature, when improved renal allograft survival following blood transfusion was recognized. In 1981, Gantt postulated that depression of the immune system associated with blood transfusion may be deleterious in patients with malignant tumors. Since that time, a number of investigators have reported increased recurrence rates in patients with malignant colorectal, lung, renal, and breast disease who received perioperative heterologous blood. This association has been questioned by some reports. Twelve previous, retrospective studies compare the relationship between recurrence rates and heterologous blood transfusion in patients with squamous cell carcinoma of the head and neck (SCCHN). Nine of them, using univariate analysis, show a statistically significant association between blood transfusion and recurrence.

The use of heterologous blood has risks other than immunosuppression, including blood-borne infections and transfusion reactions. For these reasons, preoperative autologous blood donation has gained popularity. The relationship between autologous blood transfusion and cancer recurrence has not been well studied. It has been suggested that even autologous blood transfusion may have immunomodulatory effects, possibly because of changes that occur during the storage and processing of blood products. The effect of autologous blood transfusion in surgically treated patients with SCCHN has not been examined. Our goal was to determine if the use of autologous blood diminishes the risk associated with heterologous blood transfusion in patients with SCCHN.

This article is also available on our Web site: www.ama-assn.org/oto.
PATIENTS AND METHODS

The medical records of all patients treated surgically for SCCHN at Stanford University Medical Center, Stanford, Calif, from January 1, 1989, through December 31, 1994, were reviewed. Patients with salivary gland, thyroid, or other non–squamous cell malignant disease were not included. Patients were excluded from the study for the following reasons: (1) in situ and stage I SCCHN, (2) postoperative death unrelated to recurrent disease, (3) presence of distant metastases at the time of surgery, (4) synchronous primary tumors, (5) insufficient follow-up (<2 years) follow-up or incomplete medical records.

Numerous data were obtained for each patient, including whether they had a postoperative recurrence, the number of units of blood transfused, the time of transfusion, and the type of blood product (autologous blood vs heterologous whole blood, packed red blood cells, or fresh frozen plasma). Patients with recurrent disease at the time of surgery, who had failed previous nonsurgical or surgical treatment were included, and previous treatment of the current malignancy was used as a separate variable in the statistical analysis. Tumor staging was based on the American Joint Committee on Cancer 1989 guidelines. Pathology reports were reviewed for grade, node status, and margins. The site of the malignant neoplasm (oral cavity, oropharynx, nasopharynx, or hypopharynx or larynx) was recorded. Treatment with radiotherapy or chemotherapy in conjunction with surgery was also noted. Other variables included age, sex, preoperative hematocrit value, and estimated surgical blood loss.

A univariate ($\chi^2$) analysis was performed on transfusion status, previous treatment of current malignancy, stage, grade, node status, margin status, site, age, sex, preoperative hematocrit value, and estimated blood loss, with recurrence serving as the dependent variable. A contingency table analysis was used for the nominal variables, and a simple logistic regression was used for continuous variables. Statistically significant variables were incorporated into a multivariate analysis. The multivariate analysis allows for an evaluation of the influence of blood transfusion on recurrence while controlling for variables found to be significant using univariate analysis.

RESULTS

A total of 269 patients with SCCHN treated surgically at Stanford University Medical Center during the study period were identified. Patients excluded from the study included 48 patients with in situ and stage I SCCHN, 15 patients without evidence of recurrent disease who died before 2 years of follow-up, 3 patients with distant metastases at the time of surgery, 2 patients with synchronous primary tumors, 28 patients with insufficient (<2-year) follow-up, and 8 patients with incomplete medical records. One hundred sixty-five patients met the study criteria.

Table 1. Distribution of Variables by Transfusion Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Autologous</th>
<th>Heterologous</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>18</td>
<td>42</td>
<td>105</td>
<td>165</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>54 (66.7)</td>
<td>61 (73.3)</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (66.7)</td>
<td>30 (71.4)</td>
<td>73</td>
<td>115</td>
</tr>
<tr>
<td>Female</td>
<td>6 (33.3)</td>
<td>12 (28.6)</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>Previous treatment of malignant neoplasm, No. (%)</td>
<td>8 (44.4)</td>
<td>20 (47.6)</td>
<td>25 (23.8)</td>
<td>53 (32.1)</td>
</tr>
<tr>
<td>Site, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>2 (11.1)</td>
<td>12 (28.6)</td>
<td>37</td>
<td>51</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>6 (33.3)</td>
<td>14 (33.3)</td>
<td>29</td>
<td>49</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>5 (27.8)</td>
<td>3 (7.1)</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Hypopharynx or larynx</td>
<td>5 (27.8)</td>
<td>13 (31.0)</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td>Stage, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (13.3)</td>
<td>6 (16.7)</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>III</td>
<td>2 (13.3)</td>
<td>7 (19.4)</td>
<td>25</td>
<td>34</td>
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<tr>
<td>IV</td>
<td>11 (73.3)</td>
<td>23 (63.9)</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td>Grade, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>2 (11.8)</td>
<td>3 (7.1)</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (52.9)</td>
<td>24 (57.1)</td>
<td>59</td>
<td>72</td>
</tr>
<tr>
<td>Poor</td>
<td>6 (35.3)</td>
<td>15 (35.7)</td>
<td>26</td>
<td>47</td>
</tr>
<tr>
<td>Positive margins, No. (%)</td>
<td>3 (17.6)</td>
<td>10 (25.6)</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>Positive nodes, No. (%)</td>
<td>6 (33.3)</td>
<td>20 (47.6)</td>
<td>34</td>
<td>60</td>
</tr>
<tr>
<td>Mean hematocrit, mL</td>
<td>0.38</td>
<td>0.36</td>
<td>0.41</td>
<td>0.39</td>
</tr>
<tr>
<td>Mean blood loss, mL</td>
<td>712</td>
<td>803</td>
<td>305</td>
<td>481</td>
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</tbody>
</table>

Of these, 60 patients received blood products. A total of 28 autologous blood recipients were identified; 10 of these patients received both autologous and heterologous blood and therefore were placed in the heterologous transfusion group. The mean patient age was 59.3 years, and 70% of the patients were men. Thirty-five patients had stage II SCCHN; 34 had stage III; 77 had stage IV; and the stage for 19 patients was unavailable.

The incidence of transfusion with respect to the variables studied is shown in Table 1. The autologous and heterologous transfusion groups had a higher percentage of patients with previous treatment of the current malignancy ($P = .01$), higher volume of surgical blood loss ($P < .001$), and lower preoperative hematocrit values ($P < .001$) than those not undergoing transfusion; there were no statistically significant differences between the autologous and heterologous transfusion groups, although there was a trend toward a higher rate of lymph node metastases ($P = .22$) and positive margins ($P = .33$) in the heterologous group.

The results of the univariate analysis of nominal variables is summarized in Table 2. Previous treatment of the current malignancy ($P < .001$), heterologous blood transfusion ($P = .006$), margin status ($P = .01$), and the presence of nodal metastases ($P = .02$) were significantly associated with recurrence. Receipt of autologous blood was not associated with an increased recurrence rate. Univariate analysis of the continuous variables included preoperative hematocrit value ($P = .19$) and age...
Patients in the autologous group received a mean of 1.2 U of blood, whereas those in the heterologous group received a mean of 2.9 U. In the heterologous group, 2 patients received 2 U of fresh frozen plasma; otherwise, all blood products were packed red blood cells or whole blood. As heterologous blood transfusion was associated with an increased risk for recurrence, the effect of the quantity of heterologous blood received was examined. The recurrence rates of patients who received different amounts of heterologous blood is summarized in Table 3. The number of units of heterologous blood received was not significantly associated with risk for recurrence by univariate analysis ($P = .58$).

Multivariate analysis with the Cox semiparametric regression model was initially constructed using the 3 transfusion groups. The $\beta$ coefficient, a measure of the correlation between the variable of interest and recurrence, was used to calculate an adjusted odds ratio. The adjusted odds ratio associated with receipt of heterologous blood was 1.40 (40% increase in relative risk). Statistically significant variables were then added to the model, and the results are summarized in Table 4. In this model, the risk associated with previous treatment of the current malignancy, nodal disease, positive margin, and receipt of heterologous blood remained statistically significant.

**COMMENT**

Although it is generally accepted that heterologous blood transfusion causes immunosuppression, it is not clear whether perioperative blood transfusion in patients with cancer causes increased recurrence rates. The otolaryngology literature is divided as to whether heterologous blood exerts an independent effect on recurrence. One problem with some of the earlier studies in this field was that patient variables that could effect recurrence were not controlled. Nine studies included a multivariate analysis; 4 found heterologous blood transfusion...
to be a significant risk factor independent of other variables. Woolley et al.11 in addition to reviewing their own experience, performed a meta-analysis of 5 of the published studies and found that transfusion was significantly associated with recurrence. In our study, heterologous transfusion incurred a statistically significant increased relative risk using multivariate analysis compared with autologous or no transfusion.

The data analysis of our 165 patients also revealed that previous treatment of the current malignancy, positive margins, and presence of nodal metastases were significantly associated with recurrence using multivariate analysis. Of our 165 patients, 32% had a history of failed initial treatment, which in most cases was radiotherapy but also included surgery, chemotherapy, or both. This failure of previous treatment may indicate that the patient has a phenotypically more aggressive tumor or has a weakened immune system. The patients with positive margins fared the worst, with a recurrence rate of 65%, whereas nodal metastases were associated with a 53% recurrence rate. When these 3 powerful variables were controlled, the increased relative risk associated with heterologous blood transfusion remained statistically significant.

Our results suggest that a number of variables tend to be associated with the need for blood transfusion. Patients undergoing transfusion had a higher percentage of the following variables: previous treatment of the current malignancy, higher volume of surgical blood loss, and lower preoperative hematocrit values. Despite this distribution of variables, the rate of recurrence was almost identical between patients who received autologous transfusions and those who received no transfusion.

Patients in the heterologous transfusion group differed from patients in the autologous transfusion group in that they had a higher incidence of positive margins and lymph node metastases. The higher frequency of these variables in patients who require heterologous blood transfusions may denote the presence of more advanced tumors, which sometimes resulted in the inability of patients to donate their own blood. Controlling for margins and node status, the receipt of heterologous blood still incurred a significant independent risk.

Patients with recurrent nasopharyngeal carcinoma treated with a transpalatal nasopharyngectomy were included in our study. This subgroup of 13 patients accounted for a relatively high percentage (28%) of the autologous blood transfusions (Table 1). This may reflect a group of patients in whom blood loss was successfully anticipated (62% of patients required a blood transfusion), and, therefore, autologous blood was more consistently obtained. The recurrence rate in the group of patients with nasopharyngeal carcinoma was 46%, the second highest recurrence rate by location (Table 2). Despite having a larger proportion of patients with nasopharyngeal carcinoma, the recurrence rates of patients receiving autologous blood were nearly identical to those who did not receive a transfusion.

Although a number of studies have reviewed outcome following heterologous transfusion in head and neck cancer surgery, none have examined the influence of autologous blood products. There are few data in other surgical disciplines examining the relationship of recurrence with heterologous and autologous blood transfusion. Ness et al.19 performed a prospective study of 309 patients treated with radical surgery for prostate cancer and found that recurrence rates did not differ significantly between patients who received heterologous blood compared with those who received autologous blood or no transfusion. Busch et al.20 prospectively evaluated 475 cases of colorectal cancer and found no significant difference in recurrence rates of patients who had autologous or heterologous perioperative blood transfusions; however, transfusion with either blood product carried a much higher risk than no transfusion.

Autologous blood transfusion traditionally has been assumed to be free of most risks associated with heterologous transfusion. Recently, several investigators have cautioned against this assumption, hypothesizing that autologous blood may have an impact on cancer recurrence via immunosuppressive actions.17,18 Vliet et al.21 reported that blood processing and storage resulted in changes that inhibited the proliferation response of lymphocytes. Whether such changes effect cancer recurrence rates is not known. In animals, syngeneic transfusions have not been shown to have the adverse effects on malignant disease seen with allogeneic transfusion.22,23 The results of our study suggest that perioperative autologous blood transfusion is not associated with increased recurrence rates.

Evidence that heterologous blood has immunosuppressive properties is much stronger than that described for autologous blood, yet the mechanism remains poorly understood. A number of changes in immune profile have been reported in patients who received allogeneic blood transfusions, including an increased level of CD8 suppressor cells,24 decreased levels of CD4 helper cells and interleukin 2 receptor–positive helper cells,25 and a decreased level of natural killer cells.26 It had been presumed that the cellular components of transfused blood were responsible for these immune modifications. More recently, however, transfusion of plasma has also been found to be associated with immunosuppression.27,28 The details of transfusion-induced immunosuppression remain to be better elucidated.

Our results demonstrate an independent risk associated with heterologous transfusion that was statistically significant using multivariate analysis. The increased relative risk is worrisome and warrants judicious use of heterologous blood products. Transfusion with autologous blood not only protects patients from the risk for blood-borne infection and transfusion reaction, but it may also diminish the risk for increased recurrence frequently associated with heterologous blood transfusion. Our results suggest that autologous blood transfusion carries the same risk as no transfusion. Preoperative autologous blood collection for head and neck surgery is therefore justified, and autologous blood products should be used if possible when transfusion is necessary.

CONCLUSIONS
REFERENCES