Survival analysis of intraoperative blood salvage for patients with malignancy disease

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Intraoperative blood salvage as a blood-saving strategy has been widely used in surgery. Considering its theoretic risk of malignant tumor cells being reinfused and the corresponding blood metastases, the safety of intraoperative blood salvage in cancer surgery remains controversial.

Methods: Following the Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA), we searched the Cochrane Library, MEDLINE and EMBASE to November 2017. We included only studies comparing intraoperative blood salvage with allogeneic blood transfusion.

Results: This meta-analysis included 9 studies with 4354 patients with 1346 patients in the intraoperative blood salvage group and 3008 patients in the allogenic blood transfusion group. There were no significant differences in the 5-year overall survival outcome (odds ratio [OR] 1.12; 95% confidence interval [CI], 0.80–1.58), 5-year disease-free survival outcome (OR 1.08; 95% CI 0.86–1.35), or 5-year recurrence rate (OR 0.86; 95% CI 0.71–1.05) between the 2 study groups. Subgroup analysis also showed no significant differences in the 5-year overall survival outcome (OR 0.97; 95% CI 0.57–1.67) of hepatocellular carcinoma patients in liver transplantation.

Conclusions: For patients with malignant disease, intraoperative blood salvage did not increase the tumor recurrence rate and had comparable survival outcomes with allogeneic blood transfusion.

Keywords: allogenic blood transfusion, intraoperative blood salvage, recurrence rate, survival outcomes, tumor

1. Introduction

Intraoperative blood salvage (IBS) is a kind of blood-saving strategy that uses autologous transfusion and is widely used during surgery with massive blood loss to reduce the allogenic blood transfusion volume.\textsuperscript{1,2} Generally, autologous transfusion includes the following 3 modalities: first, preoperative autologous blood donation (ABD), including predonated autologous blood that was stored, retransfused during surgery, and requires patients to donate blood before ≥2 before surgery; second, acute normovolemic hemodilution (ANH), which requires collecting blood preoperatively with subsequently artificial dilute and reinfuse during surgery; third, IBS, an attractive blood management strategy, retrieves and filters blood lost during the operation and then instantly reinfuses it.\textsuperscript{3} In addition, IBS could eliminate many complications associated with storing and processing homologous donor blood.\textsuperscript{4} However, many surgeons still hesitate to embrace IBS for its theoretical risk of increasing the tumor recurrence rate.\textsuperscript{5} These surgeons presume that tumor cells would be reinfused with IBS blood by cell saver, which would result in tumor cell dissemination. Even though this hypothesis is unwarranted, the use of IBS is still restricted by this conjecture. A case report published in 1975 reported that IBS may have cause neoplasm metastasis during the operation of a lung cancer patient.\textsuperscript{6} Since then, IBS is no longer recommended for tumor-related operations.\textsuperscript{7} In view of this conjecture, whether or not tumor cells pass through the cell saver system is the major point of controversy and significantly hampers the clinical utility of IBS. With the development of materials science, the leukocyte depletion filter (LDF) has been suggested to effectively remove a variety of malignant cells in spine tumor surgery and colorectal tumor surgery.\textsuperscript{8} In addition, allogenic transfusion is widely used in clinical practice, but it also has some inherent limitations, such as allergic reaction, infection, hemolysis, perioperative myocardial infarction, postoperative low-output cardiac failure, transfusion-related immunomodulation, transfusion-related acute lung injury, and life-threatening virus infection.\textsuperscript{8–16} Compared with allogeneic blood transfusions, IBS seems to be a better choice regardless of the effect-cost ratio or efficacy in tumor operation.\textsuperscript{17} Even though some doubts and controversies in the IBS still exist, existing evidence has indicated that it was not the major reason for tumor metastasis.\textsuperscript{18}
However, some of the previous studies did not focus on pure intraoperative blood salvage, and they analyzed the other subtype of autologous transfusion methods.\textsuperscript{[19,20]} Therefore, we conducted this meta-analysis with the pretension to evaluate the oncological safety of pure IBS compared with allogeneic blood transfusion (ABT) in operations of malignant disease.

### 2. Methods

Following the Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA),\textsuperscript{[21]} we searched the Cochrane Library (January 1, 2005–November 24, 2017), MEDLINE via PubMed (January 1, 1966–November 24, 2017), and EMBASE (January 1, 1980–November 24, 2017). We combined searching methods with free words and subject terms in searching databases. We searched the terms “Blood Transfusion, Autologous” and “Neoplasms” in PubMed and Cochrane Database of Systematic Reviews and “Blood autotransfusion” in EMBASE as subject terms. The following terms were also utilized: “cell salvage,” “blood salvage,” “autotransfusion,” “autologous transfusion,” “Blood Cell Salvage,” and “retransfusion.”

Because studies included in this meta-analysis have been published, it is not needed for the ethical approval from ethics committees. After searching the databases, 2 researchers screened and excluded the articles through title and abstract according to inclusion criteria. We included only English studies that compared IBS and ABT during the operation, regardless of what research type or publication status. The intervention group was strictly confined to the IBS method. Those studies with the autotransfusion method of ABD or ANH were excluded. Therefore, the intervention group comprises patients who accepted pure IBS therapy, and the control group comprises patients with the same type of malignant tumor who used ABT in their operations. The studies that passed the first-round selection were further filtered by reading the full-text and removed from this study based on exclusion criteria by 2 researchers.

The data analyzed in this study were extracted from the full-text article and include the following parameters: name of the first author, periodical titles, publication year, type of tumor, IBS group characteristics, control group characteristics (allogeneic blood transfusion group), exclusion criteria, sample size, length of follow-up, and mean patient age (Table 1). One author extracted data, and another author checked this process. We also strived to search for any relevant information from the references of every included report.

The quality assessment of all of the included studies were determined by 2 authors based on the Newcastle-Ottawa Scale (NOS), and those studies had at least a score of 5.\textsuperscript{[22]} Therefore, we deemed that the included studies were reliable for this meta-analysis. Articles were evaluated and discussed with a third person when any divergence existed.

### 3. Results

We retrieved 3169 records within 255 duplicates. After reading the titles and abstracts, 74 articles remained for reassessing according to their full-text. After reading the full-text of these articles, we included 17 studies in which blood salvage was performed intraoperatively. However, 8 of these studies were excluded due to a lack of outcome indicators.
In total, only 9 studies were available to pool into this meta-analysis (1,2,30–36) (PRISMA Flow Diagram). Except for the study from Engel et al.,[32] which was a prospective study, all of the other included studies were retrospective studies. We also evaluated the quality of all included studies with the NOS scale, and the results showed that all studies had a score >5. Five studies reported a follow-up period as follows: 25.8 ± 15.1 months in the IBS group and 17.9 ± 12.8 months in the ABT group.

For all included studies performed in statistics, there were no significant differences in overall survival (Fig. 1), disease-free survival (Fig. 2), or recurrence rate (Fig. 3) between patients in the IBS group or patients in the ABT group. In subgroup analyses, there were no significant differences in the postoperative 1-year recurrence rate (95% CI, 0.61–1.28; P = .32, Fig. 3A), 3-year recurrence rate (95% CI, 0.72–1.21; P = .66, Fig. 3B) or 5-year recurrence rate (95% CI, 0.71–1.05; P = .37, Fig. 3C) between the IBS and ABT groups. In addition, we noticed that patients in the IBS group showed a lower recurrence rate than the ABT group in 2 studies. However, these 2 studies showed similar overall survival outcomes and disease-free outcomes between the 2 transfusion methods. (2,34) Publication biases were not observed in this meta-analysis, with the P value for the Egger linear test of 0.245 (t = –1.44).

All stage of grade of tumor of included studies have not reported to be difference significantly. Only 2 of them reported postoperative complications. (2,31) Kim et al[2] reported non-IBS group has higher renal dysfunction (P = .028), bleeding (P = .046), bacterial infection (P = .012), and urinary tract infection (P < .001) morbidity.

There was no noticeable heterogeneity between the IBS and ABT groups in overall survival (I² = 0%, P = .99), disease-free survival (I² = 0%, P = .68), or recurrence rate (I² = 0%, P = .64).

In addition, we considered the potential bias associated with different diseases and operations. A subgroup analysis was performed on 5 studies, which focused on liver transplantation surgery. (1,2,34–36) and the results showed that there were also no significant differences in the 5-year overall survival outcomes (95% CI 0.57–1.67, P = .92, Fig. 4A) between the IBS and ABT groups. Remarkably, the IBS group showed a lower 5-year overall recurrence rate than the ABT group (95% CI, 0.46–0.92, P = .02, Fig. 4B). Both of these studies presented low heterogeneity (I² = 0%) in the overall survival and recurrence rate.
4. Discussion

In the present study, we used the recurrence rate as the primary outcome, and the overall survival and disease-free survival was used as the secondary outcomes. In total, 6 included studies performed overall survival as the primary outcome, and 4 included studies performed disease-free survival as the primary outcome. There were no significant differences between the IBS and ABT groups in the 1-year, 3-year, or 5-year overall survival or disease-free survival outcomes. Meanwhile, for the 6 included studies, patients in the IBS group had a similar recurrence rate as patients in the ABT group.

A study reported that the average intraoperative blood loss in open radical retropubic prostatectomy is over 1000mL.[17] In addition, a report based on 984 living donors presented that the mean intraoperative blood loss in hepatic resection was 691.3 ± 365.5mL.[18] Given these results and considering the potential intraoperative blood loss in surgery, surgeons should always be prepared for preoperative transfusion. However, allogenic blood transfusions were associated with various complications that threatened patient recovery and prolonged hospital stays. Even so, the thought of the potential risk of tumor cells being collected intraoperatively along with blood and then reinfused into patients who may result in tumor metastasis, most surgeons do not take IBS into account. However, there are no large-sample multicenter random control trials to support this thesis and is based on a case report in 1975 that reported that tumor cells were found in the cell saver.[5] This finding directly resulted in the American Medical Association Council on Scientific Affairs stopping intraoperative autologous transfusion used for cancer surgery.[6]

Nowadays, IBS has been proven that it could reduce postoperative complications and has shown to be cost-effective.[2] However, whether intraoperative autologous transfusion truly increases the risk of tumor metastasis remains controversial. Great efforts have been made to prove this technique to be efficient and safe. In the present study, we found no significant differences between the IBS and ABT groups in overall survival outcomes, disease-free outcomes, or recurrence rates. These results are consistent in the 1-year, 3-year, and 5-year subgroup analyses. However, we must emphasize that this result is based on different kind of tumor studies. Additionally, this meta-analysis included only a few kinds of malignant diseases, such as hepatocellular carcinoma and urogenital tumors. On the one hand, considering the tumor heterogeneity, the metastasis risk is completely different in different kinds and stages of tumors.[38–40] Considering the variety of malignant diseases, the results of these analyses may have selection bias. On the other hand, there was only one prospective study, and other included studies were retrospective studies. The natural limitation of retrospective studies cannot be neglected.
**Figure 3.** Meta-analysis forest plot of the recurrence rate. (A. 1-year recurrence rate, B. 3-year recurrence rate, C. 5-year recurrence rate).

| Study or Subgroup | IBS Group | ABT Group | ODDS RATIO (M-H, Fixed, 95% CI) |
|-------------------|-----------|-----------|---------------------------------|
| **A 1-year Overall Survival Outcomes** | | | |
| Jong Man et al. 2013 | 11/121 | 17/109 | 4.1% | 0.54 [0.24, 1.21] |
| Michael A et al. 2012 | 19/395 | 62/1467 | 6.2% | 1.15 [0.68, 1.94] |
| Rafael LC Araujo et al. 2016 | 7/112 | 1/36 | 0.4% | 2.33 [0.26, 19.63] |
| Sangbin et al. 2016 | 26/283 | 14/114 | 4.5% | 0.72 [0.36, 1.44] |
| **Subtotal (95% CI)** | 91/1176 | 152/1726 | 15.2% | 0.89 [0.61, 1.28] |
| **Total events** | 63 | 94 | | |
| Heterogeneity: Ch² = 3.47, df = 3 (P = 0.32); I² = 14% |
| Test for overall effect: Z = 0.65 (P = 0.52) |

| **B 3-year Overall Survival Outcomes** | | | |
| Jong Man et al. 2013 | 20/121 | 23/109 | 5.0% | 0.74 [0.38, 1.44] |
| Michael A et al. 2012 | 50/395 | 175/1467 | 16.2% | 1.07 [0.76, 1.50] |
| Rafael LC Araujo et al. 2016 | 15/112 | 6/36 | 2.0% | 0.77 [0.28, 2.17] |
| Sangbin et al. 2016 | 47/283 | 23/114 | 6.6% | 0.79 [0.45, 1.37] |
| **Subtotal (95% CI)** | 91/1176 | 152/1726 | 30.0% | 0.93 [0.72, 1.21] |
| **Total events** | 132 | 227 | | |
| Heterogeneity: Ch² = 1.59, df = 3 (P = 0.66); I² = 0% |
| Test for overall effect: Z = 0.54 (P = 0.59) |

| **C 5-year Overall Survival Outcomes** | | | |
| Alan M. Nieder et al. 2005 | 40/265 | 139/773 | 15.0% | 0.81 [0.55, 1.19] |
| D. Foyt et al. 2011 | 5/40 | 18/90 | 2.3% | 0.62 [0.21, 1.80] |
| Jong Man et al. 2013 | 20/121 | 25/109 | 5.5% | 0.67 [0.35, 1.28] |
| Michael A et al. 2012 | 69/395 | 236/1467 | 20.6% | 1.10 [0.62, 1.94] |
| Rafael LC Araujo et al. 2016 | 19/112 | 8/36 | 2.5% | 0.72 [0.28, 1.81] |
| Sangbin et al. 2016 | 54/283 | 31/114 | 9.0% | 0.63 [0.38, 1.05] |
| **Subtotal (95% CI)** | 1216/5495 | 2595 | 54.8% | 0.86 [0.71, 1.05] |
| **Total events** | 207 | 457 | | |
| Heterogeneity: Ch² = 5.37, df = 5 (P = 0.37); I² = 7% |
| Test for overall effect: Z = 1.46 (P = 0.15) |

| **Total (95% CI)** | 4027 | 778 | | |
| Heterogeneity: Ch² = 10.63, df = 13 (P = 0.64); I² = 0% |
| Test for overall effect: Z = 1.63 (P = 0.10) |
| Test for subgroup differences: Ch² = 0.20, df = 2 (P = 0.90); I² = 0% |

**Figure 4.** Meta-analysis forest plot of survival outcomes of hepatocellular carcinoma patients (A. 5-year overall survival outcomes, B. 5-year recurrence rate).
We noticed that 5 studies focused on hepatocellular carcinoma. Therefore, we performed a subgroup analysis comparing the 5-year overall survival outcomes between the IBS and ABT groups. Compared with ABT, IBS did not improve the mortality risk with long-term follow-up for patients with hepatocellular carcinoma who underwent liver transplantation surgery. Interestingly, we found that the 5-year recurrence rate in the IBS group was significantly lower than that in the ABT group. This result may be because transfusion-related immune modulation would accelerate cancer progression. Two meta-analyses have shown that ABT is associated with postoperative survival in colorectal cancer and carcinoma of the duodenal ampulla.[41–43] Even though we need more evidence in the other types of cancer surgery; however, more studies may imply that we should strive to reduce the intraoperative ABT. However, limited numbers of studies were included in these analyses. This phenomenon illustrates that IBS is not inferior to allogeneic blood transfusion and may even be better than ABT.

Circulating tumor cells may be the key factor that results in distal metastasis of the tumor. The leukocyte filter was proven to filter the hemangiosarcoma and hepatocellular carcinoma cells completely in experiments.[44,45] Meanwhile, Kumar et al.[46] found that intraoperative cell salvage with a leucocyte filter can effectively eliminate tumor cells from salvaged blood in spinal tumor surgery. However, whether tumor cells are completely filtered in clinical settings and whether the filter eliminates the risk of tumor cell metastasis are still pending. However, with the development of technology, the combined use of the new generation leukocyte filter may be the hope for the widespread promotion of IBS.

In addition, several studies have successfully confirmed that the autologous transfusion strategy can reduce the need for allogeneic blood during an operation.[1,2] However, these conclusions were made by comparing all 3 subtype methods of autologous transfusion and allogeneic blood transfusion.[19,20] Current evidence supports the idea that IBS could reduce the need for a blood transfusion. Only 4 included studies compared the allogeneic blood transfusion volume between 2 groups, but the heterogeneity was high ($I^2=85\%$). Therefore, it is difficult to conclude that the IBS can save the amount of allogeneic blood. To evaluate the safety and efficiency of IBS, this meta-analysis included 9 studies and showed that IBS was comparable with ABT. However, several limitations are also included in the present study, as follows: we only included studies that compared IBS with ABT, and most of the included studies were retrospective research; the selection bias cannot be neglected. The study included several malignant diseases, and the natural difference between these tumors may affect the prognosis of patients; the hybrid effect brought by the retrospective study and different kinds of tumors may lead to a bias of the final results. Therefore, a further large-sample size randomized control study with each kind of tumor surgery is expected to solve these limitations.

5. Conclusions

During surgery for malignant tumors, intraoperative blood salvage did not increase the tumor recurrence rate and had comparable survival outcomes with allogeneic blood transfusion. However, due to the limitation of evidence, the wide application of intraoperative blood salvage requires further multicenter randomized control trials to verify these results.

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Author contributions

Wei-Wei Wu and Wei-Yi Zhang conceived the project with input from Tao Zhu. Wei-Wei Wu and Wei-Yi Zhang designed the study and wrote the protocol with the input from all authors. Wei-Wei Wu and Wei-Yi Zhang did the literature searches and processed the trial data.

Wei-Wei Wu, Wei-Yi Zhang, Wei-Han Zhang designed the statistical analyses, and Wei-Wei Wu, Lei Yang, and Xiao-Qian Deng performed the statistical analyses. Wei-Wei Wu and Wei-Yi Zhang drafted the manuscript. All authors have seen and commented on the drafts and approved the final version.

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