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Is Autologous Salvaged Blood a Viable Option for Patient Blood Management in Oncologic Surgery?☆,☆☆

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ABSTRACT

Oncologic surgery is sometimes associated with substantial blood loss, and principles of patient blood management can be applied in the perioperative care of these patients. Although autologous salvaged blood is an option for perioperative blood conservation, it is often not used in oncologic surgery over concern of reinfusing tumor cells and thereby causing tumor dissemination. We reviewed the literature regarding safety and effectiveness of salvaged blood in oncologic surgery. Salvaged blood seems to be comparable to allogeneic blood in terms of safety. Because patients with primary or metastatic cancer are known to have circulating tumor cells in the absence of surgery, the concern of reinfusing malignant cells from the salvaged blood may be overstated. Reinfusion of salvaged blood has not been found to promote tumor dissemination or distant metastases. When used in patients with substantial blood loss, salvaged blood can be cost-effective. Intraoperative salvaged blood may be a useful adjunct to allogeneic blood resources.

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Cancer is a major problem afflicting the aging all over the world. The prevalence of metastatic cancer is on the rise owing to improved survival resulting from newer basic and adjuvant treatment in cancer patients. The most common organs in the body to which metastasis takes place are the lung and liver followed by the skeleton [1]. Surgery has established its place as either curative or palliative treatment modality in cancer patients. Surgery in oncologic conditions can be associated with significant blood loss. Surgery of the spine, which is the most common site for skeletal metastasis, can result in significant blood loss [2,3].

Recently, there has been a significant focus on optimizing the perioperative blood management in patients undergoing major surgical procedures, which can be extrapolated to oncologic surgical procedures. To establish this, the World Health Assembly adopted the patient blood management (PBM) concept by resolution WHA63.12, urging all 193 member states of the World Health Organization to promote the availability of PBM and related modalities as a new standard of care [4,5]. Patient blood management is an evidence-based patient-tailored approach aimed at reducing the need for allogeneic transfusion by managing anemia, perioperative blood conservation, surgical hemostatic, and drug use [5]. Perioperative blood conservation includes interventions such as the administration of agents to diminish blood loss (eg, aprotinin, tranexamic acid, epsilon aminocaproic acid, fibrin sealant), agents that promote red

Abbreviations: ABT, allogeneic blood transfusion; PBM, patient blood management; 95% CI, 95% confidence interval.

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blood cell production (eg, erythropoietin), and techniques for reinfusing a patient's own blood (eg, preoperative autologous donation, acute normovolemic hemodilution, cell salvage). Among these, cell salvage has been used and studied extensively in the surgical setting. Cell salvage, alternatively known as "auto-transfusion," includes techniques that salvage blood from operative fields or wound sites, and reinfuse the blood back into the patient.

The surgical blood loss in cancer patients is currently replenished with allogeneic blood at most centers all over the world [6]. Using salvaged blood ensures replenishment of lost blood instead of being discarded. Previous randomized and nonrandomized studies have provided evidence that the use of intraoperative cell salvage can reduce the need for allogeneic blood transfusion (ABT) [7]. A systematic review [8] of 75 randomized trials highlighted that salvaged blood transfusion reduced the rate of exposure to ABT by 38% (relative risk, 0.62; 95% confidence interval [95% CI], 0.55-0.70). The absolute reduction in risk of receiving ABT was 21% (95% CI, 15%-26%). The use of cell salvage resulted in an average saving of 0.68 units of allogeneic RBC per patient (weighted mean difference, −0.68 units; 95% CI, −0.88 to −0.49). Despite the routine use of salvaged blood in various types of major surgery such as open heart surgery, abdominal aortic aneurysm repair, and trauma and major orthopedic surgery, it has not found wide application in oncologic surgery. Concern exists that blood collected by intraoperative cell salvage might result in reinfusion of tumor cells and subsequent distant metastases. We reviewed the literature to investigate the current status of autologous salvaged blood transfusion in oncologic surgery with respect to its safety and efficacy, contraindications, and adverse effects.

Methods

We searched Medline and Scopus for relevant publications from the past 20 years (January 1, 1986–March 31, 2016). We decided to have a starting date of the search strategy to be 1986 because it was when the use of salvaged blood in cancer surgery was strongly contraindicated in a statement by American Medical Council [9]. We also supplemented the results by searching related key articles from before this period. Relevant articles were selected using combinations of the following search terms: "cancer surgery," "metastatic cancer surgery," "intraoperative cell salvage," "autologous salvaged blood," and "circulating tumor cells." Additional literature was identified through manual searches of reference lists of identified studies. Only articles published in the English language were included in the review.

We focused on studies evaluating the use of intraoperative salvaged blood in cancer surgery. We excluded publications where salvaged blood was used in benign cancer surgery and also excluded case reports. Our initial search revealed 154 articles; 104 articles were excluded based on their titles and abstracts. From the potentially 50 relevant articles, 18 were omitted based on factors such as very small case series with less than 5 patients and use of other blood conservation techniques in combination with cell salvage. Five additional articles were identified through contacts and reference list searches. Finally, 37 articles were included for review.

Autologous Salvaged Blood in Oncologic Surgical Procedures: Background

Transfusion of autologous salvaged blood in oncological surgery has been controversial. This stems from a 1986 statement by the American Medical Council, which stated that autologous salvaged blood transfusion is contraindicated in oncologic surgery [9]. This concern arose after a single case report in 1975 where a 52-year-old patient undergoing pneumonectomy was found to have malignant cells in salvaged blood investigated using the cell block technique [10]. During oncologic surgery, when the tumor is manipulated and resected, quantities of malignant cells are assumed to be spilled in the operative field [11]. This led to concern regarding reinfusion of malignant cells to the patient when intraoperative blood is salvaged and transfused.

Detection of Tumor Cells in Blood Collected by Intraoperative Cell Salvage

Early in vitro studies reported that malignant cells remained in the blood processed by a cell salvage device [12,13]. However, this finding was not confirmed in other reports which "spiked" blood with tumor cells before processing with the cell saver device and then passing the processed blood through a leukoreduction filter [14-18]. Spiking studies, however, used tumor cell lines which may not precisely mimic the in vivo situation.

Subsequently, several clinical reinfusion studies (wherein salvaged blood is reinfused to the patients) and nonreinfusion studies (wherein salvaged blood is not reinfused to the patients) were reported suggesting that salvaged blood may have an acceptable safety profile [19,20]. Nonreinfusion studies demonstrated that blood salvaged during oncologic surgical procedures and then filtered using a leukoreduction filter did not have detectable tumor cells [21-23]. Catling and colleagues [21] studied patients undergoing major surgery for endometrial, cervical, and ovarian cancer, thereby demonstrating that after passing salvaged blood through a leukoreduction filter, only tumor fragments that were conjectured to be incapable of causing metastasis, that is, nonnucleated cellular fragments, could be found in the salvaged blood. Researchers in uro-oncology studied gene amplification of prostate tumor–specific genes using blood salvaged during radical prostatectomy and pelvic lymphadenectomy. They observed that the combination of leukofiltration and gamma irradiation resulted in negative gene amplification results [23]. In thoracic-oncology, Perseghin and colleagues [22] also observed that passage of shed blood processed by an intraoperative cell salvage device during lung cancer surgery and passed through a leukoreduction filter resulted in samples without detectable tumor cells. In hepatobiliary oncology, Martin et al [24] showed undetectable levels of tumor cells when salvage blood was leukofiltered. However, it should be noted that in vitro studies share a problem of sampling error and an uncertain lower limit of detection of tumor cells. Thus, the absence of tumor cells in a sample of salvaged blood cannot be used to conclude that no cancer cells are present in the entire collected product. The issue of limit of detection may have been relevant in the report by Liang et al [25], who showed positive tumor cells in salvaged blood in 2 participants where there was major tumor rupture during surgery.

Our own experimental studies involved metastatic spine tumor surgery [26,27]. Blood samples from salvaged blood were analyzed for the presence of tumor cells before and after leukofiltration using cell block immunohistochemistry. Samples were obtained from patients operated on by 4 different spine surgeons who used different surgical techniques when removing the tumor mass. Although tumor cells were observed in certain cases, none of the samples showed the presence of tumor cells after leukofiltration, despite different concentrations of tumor cells in the original collections.

More recently, flow cytometry has been applied to the detection of tumor cells in blood. Cytometry offers a lower limit of detection than can be achieved by cell block studies. Martin and colleagues [24] first reported the number of tumor cells in salvaged blood using flow cytometry. Subsequently, we reported that the number of tumor cells in leukofiltered salvaged blood was significantly less than that in patient's circulation. These patients had metastases to the spinal column from various primaries, namely, lung, breast, prostate, kidney, and nasopharynx.

Circulating Tumor Cells in Primary and Metastatic Cancer Patients

Patients with primary or metastatic cancer are known to have circulating tumor cells (CTCs) in the blood. The concentration of CTCs varies widely depending on tumor type and stage of disease [28]. Allard and colleagues [28] estimated that the number of CTCs in patients with metastatic cancer diseases can be as high as 23 618 per 7.5 mL of blood.