Intraoperative Cell Salvage in Surgery for Ovarian Cancer: Time for Action

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Abstract

Background: Cytoreductive surgery for ovarian cancer is often an extensive procedure, associated with substantial intraoperative blood loss. Blood lost during surgery is conventionally replaced using donor (allogeneic) blood. Intra-operative cell salvage may be an alternative, suggested to improve outcomes in terms of morbidity and survival.

Objectives: To compare the safety of intraoperative cell salvage (IOCS) vs. allogeneic blood transfusion in women undergoing surgery for ovarian cancer in terms of overall and disease free survival.

Methods: We performed a systematic search of Medline, the four full text collections (Science Direct, Ingenta Select, Ovid full text and Wiley Interscience) from 1966 until Jan 2014. The Cochrane Gynaecological Cancer Collaborative Review Group’s Trial Register was also searched. For databases other than Medline, the search strategy had been adapted accordingly. In addition we searched abstracts of scientific meetings and reference lists of review articles. Two review authors independently assessed whether potentially relevant studies met the inclusion criteria.

Results: The search strategy identified 18 unique references of which 15 were excluded on the basis of title and abstract. The remaining 3 articles were retrieved in full, but none satisfied the inclusion criteria. No studies comparing intraoperative cell salvage vs. blood transfusion were identified.

Authors’ conclusions: We found no comparative studies assessing the overall and disease free survival for intraoperative cell salvage versus allogeneic blood transfusion in women undergoing surgery for ovarian cancer. Based on the findings in other tumour sites, a randomised controlled trial is needed to compare intraoperative cell salvage and allogeneic transfusion with women with ovarian cancer.

BACKGROUND

Description of the condition

Ovarian cancer is the leading cause of death from gynaecological cancer in the United Kingdom with a lifetime risk of developing epithelial ovarian cancer of around 2% (approximately 1 in 54) [1]. Surgery is important both in the initial diagnosis and staging, and in the standard management of primary ovarian cancer. Because residual disease after surgery is the main prognostic factor in ovarian cancer [2], optimal cytoreductive surgery (defined as residual nodules less than 1cm) [3] and platinum-based chemotherapy are the mainstays of treatment. Cytoreductive surgery for ovarian cancer is often an extensive procedure, associated with substantial intraoperative blood loss. The quantity of blood lost during surgery is affected by the surgeon’s experience, the patients’ age and pelvic anatomy [4]. Blood lost during surgery is conventionally replaced using donor (allogeneic) blood transfusion. The use of allogeneic blood transfusion is associated with a range of hazards including mortality, wound, pulmonary and renal complications, as well as systemic sepsis and prolonged hospital stay [5].

Description of the intervention

Intraoperative cell salvage (IOCS) refers to the practice of recovering red cells from blood lost in operative field and returning them to the patient [6]. This process involves the
separation, centrifugation, washing and filtration of heparinised red cells, before re-suspension in a saline vehicle to a final haematocrit of 0.5-0.7 and reinfusion into the patient’s blood.

How the intervention might work

The use of IOCS reduces dependence on the limited pool of banked blood, is immediately available in theatre at modest expense, and avoids the biological issues that occur with deterioration of stored blood products, such as oxidative damage [7], accumulation of free cell haemoglobin and sequestration of vasodilator nitric oxide [8]. Furthermore, the problem of transfusion associated reactions and transmitted infectious agents is minimised. Several studies in oncology surgery have determined that the use of conventional blood transfusion is associated with higher rates of cancer recurrence [9], increased postoperative infection and alloimmunisation compared to IOCS [10].

Why it is important to do this review

Intraoperative cell salvage remains controversial in gynaecological surgery, in part because of the theoretical risk of disseminating malignant tumour cells into a patient’s bloodstream. However, so far there are no studies substantiating poorer survival outcomes in ovarian cancer with IOCS.

A systematic review and meta-analysis are important to identify any relevant publications to make a reliable evaluation of the potential benefits and risks of IOCS use in women undergoing surgery for ovarian cancer.

OBJECTIVES

- To compare the overall survival and disease free survival for intraoperative cell salvage (IOCS) vs. allogeneic blood transfusion in women undergoing surgery for ovarian cancer
- To evaluate the rate of post-operative complications and length of hospital stay for intraoperative cell salvage vs. allogeneic blood transfusion in women undergoing surgery for ovarian cancer

METHODS

Criteria for considering studies for this review

Types of studies: Studies comparing autologous versus allogeneic blood transfusion in surgery for ovarian cancer

Types of participants: Adult women undergoing surgery (laparotomy) for ovarian cancer

Exclusion criteria

- Women undergoing surgery for recurrent ovarian cancer
- Women with concurrent malignancies

Types of interventions:

- Autologous blood from cell salvage
- Allogeneic (donor) blood transfusion

Excluded were pre-operative blood donation or autologous blood donation, which is a coordinated donation process planned prior to a scheduled surgical procedure, but it is not considered blood salvage

Primary outcomes

Overall survival: survival until death from all causes, survival was assessed from the time when women were diagnosed with ovarian cancer

Secondary outcomes

Disease free survival (DFS)

Postoperative complications: type of complication and timing

- Return to theatre
- Postoperative infection
- Need for re-transfusion on ward
- Mortality (death within 30 day)

Mortality (death within 30 day)

Hospital length of stay

Search methods for identification of studies

Electronic searches: The protocol for the systematic review was based on the PRISMA statement [11]. We performed a systematic search of Medline, The Cochrane Gynaecological Cancer Collaborative Review Group’s Trial Register. We also searched the four full text collections (Science Direct, Ingenta Select, Ovid full text and Wiley Interscience). For databases other than Medline, the search strategy had been adapted accordingly. Databases had been searched from 1966 until Jan 2014. In addition we searched abstracts of scientific meetings and reference lists of review articles.

Data collection and analysis

Selection of studies: All titles and abstracts retrieved by electronic searching were downloaded to the reference management database Endnote X5.0.1. The duplicates were removed and the remaining references were examined by two authors (KG,AL) independently. Those studies that clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers was assessed independently by the two review authors. Reasons for exclusion were documented.

RESULTS

Results of the search

The search strategy identified 20 references in Medline, 34 in Embase, and none in the central and the specialised register (Figure 1). When the search results were merged into Endnote and duplicates were removed, there were 18 unique studies. Two reviewers read the abstracts independently, and articles that clearly did not meet the inclusion criteria were excluded at this stage. A total of three articles were retrieved in full. The full text screening of these references excluded all of the studies for the reasons described in the (Table 1); Characteristics of excluded studies. Two reviewers independently searched the grey literature; these searches did not identify any relevant studies.

Included studies

No studies met our inclusion criteria.
Excluded studies

The full text was obtained for three references (Nagarsheth 2009 [12], Catling 2008 [13], Nagarsheth [1] 2009 [14]), all were excluded from the review for the reasons given in (Table 1); characteristics of excluded studies. The three articles that were retrieved for full text screening did not evaluate allogeneic transfusion versus autologous transfusion.

The article by Nagarseth et al.[1] reported on three cases in which autologous blood from cell salvage was used. Only one case was diagnosed with stage IV ovarian cancer and received cell salvage during debulking surgery, while the other two women were diagnosed with respectively a uterine leiomyosarcoma and a gastro-intestinal stromal tumour [14].

Catling et al assessed the use of a leucocyte filter to remove tumour cells from intra-operative cell salvage blood. Although the filter was proven successful, no cell salvaged blood was returned to the patients, as this was not the focus of the study [13]. Finally, Nagarseth et al outlined bloodless surgery (the avoidance of allogeneic transfusion) as it applies to the gynaecologic oncology population in a review article [12].

DISCUSSION

Allogeneic blood transfusion have reportedly been associated with poor outcomes including increased mortality, wound, pulmonary and renal complications, this has been attributed to transfusion-induced immune modulation (TRIM) [15], a transient depression of the immune system following transfusion with blood products. TRIM has also been implicated in the higher rates of cancer recurrence and shorter times to recurrence associated with the transfusion of allogeneic blood, which have been widely reported over the last 25 years [16]. The observed association has been the subject of particular attention in colorectal surgery [17,18] and urological surgery [19,20]. In colorectal surgery the Cochrane meta-analysis of randomised trials estimated the effect of perioperative allogeneic blood transfusion on recurrence with an odds ratio of 1.42 (95% CI, 1.20 to 1.67) against transfused patients [17]. Long-term results from an earlier trial suggest that this effect of allogeneic blood transfusion is persistent [18]. This led to the suggestion of introducing measures that would help limit the use of allogeneic blood transfusion [21].

Intraoperative cell salvage is such a measure that would potentially reduce the dependence on allogeneic transfusion. It was initially contraindicated in cancer, in part because of the theoretical risk of disseminating malignant tumour cells into patients’ bloodstream [22,23]. However, in patients undergoing surgery for a gynaecological malignancy, leucocyte depletion filter was shown to effective in eliminating viable nucleated malignant cells from the returned blood [13]. Similarly, in vitro work shows that depletion filters are highly efficient at removing malignant cells, leading to removal rates of between 80 and 100% [24,25]. In addition, there is evidence from a range of different cancer surgeries that operative manipulation of tumour during surgery leads to peripheral blood concentrations of malignant cells many times higher than could be attained with cell salvage alone [26,28]. The presence of circulating tumour cells is prevalent in cancer surgery but is not associated with survival, and it has been suggested that circulating tumour cells with the potential to form metastatic lesions are rare [29,30].

There is emerging evidence suggesting that, far from compromising outcomes, intraoperative autologous transfusion is associated with improved outcomes in surgery for other gynaecological cancers such as cervical cancer. Several studies in early stage (I-IIA) cervical cancer patients report that intraoperative autologous transfusion significantly reduces the need for allogeneic blood transfusion, without compromising survival or post-operative complication rates [31-33]. In addition, no distant recurrences have been reported [31,32]. However, these studies are limited by their non-randomised nature, retrospective design, and use of historic controls.

The use of intraoperative cell salvage in oncological surgery has recently been reviewed by Kumar et al, supporting its use in malignancy in general. The review showed that ICS resulted in equivalent or even better results across all clinical outcome parameters including survival, metastasis and recurrence rates, post-operative complications and allogeneic blood transfusion requirements, compared with patients who did not receive

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Table 1: Characteristics of excluded studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason(s) for exclusion</th>
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<tr>
<td>Catling et al. [14]</td>
<td>This study investigated the ability of leucocyte depletion filtration and cell salvage to remove malignant cells during gynaecological cancer surgery. Patients did not receive cell-salvaged blood.</td>
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<tr>
<td>Nagarsheth et al. [15]</td>
<td>Case series of three patients with cancer who had reinfusion of cell salvage blood, of which only one patient was diagnosed with ovarian cancer (all reinfusions were performed after filtration with a LRF). There was no comparative group having allogeneic transfusion.</td>
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Results of the search; Medline: 20 references Embase: 34 references

Removal of duplicate studies

18 studies

Abstract screening: 15 studies did not meet the inclusion criteria

3 studies

Full text screening: None of the studies met the inclusion criteria

No relevant studies

Figure 1 Search strategy and selection of studies.
IOCS [34]. These improved outcomes may be explained by the lack of immune modulatory effects of salvaged blood, and possible immune stimulatory effects of cell salvage, reducing postoperative infection risk [6]. In addition, the National Institute for Health and Clinical Excellence (NICE) has endorsed the use of IOCS in urological oncology surgery, by recommending it use during radical prostatectomy and cystectomy [35].

We performed a comprehensive search, including a thorough search of the grey literature. We were not able to identify any studies that evaluated the effectiveness and safety of intraoperative cell salvage in ovarian cancer surgery. The three articles that were retrieved for full text screening did not evaluate allogeneic transfusion versus autologous transfusion. The article by Nagarseth et al. [1] reported on three cases in which autologous blood from cell salvage was used. Only one case was diagnosed with stage IV ovarian cancer and received cell salvage during debulking surgery. After one year, the ovarian cancer patient developed recurrent disease, which was attributed to dissemination due to the extensive stage IV disease at diagnosis rather than dissemination through autologous cell salvage [14]. Catling et al assessed the use of a leucocyte filter to remove tumour cells from intra-operative cell salvage blood. Although the filter was proven successful, no cell salvaged blood was returned to the patients, as this was not the focus of the study [13]. Finally, Nagarseth et al outlined bloodless surgery (the avoidance of allogeneic transfusions) as it applies to the gynaecologic oncology population in a review article [12].

Consequently, there is no data available to answer the key question posed by our review; whether intraoperative cell salvage provides a useful alternative to allogeneic transfusion when comparing overall survival, disease free survival, post-operative complications and hospital stay of both transfusion modalities in women undergoing surgery for ovarian cancer.

Potential biases in the review process

We restricted our inclusion criteria to studies comparing different transfusion modalities (autologous, allogeneic transfusion) in surgery for ovarian cancer. The greatest threat to the validity of the review is likely to be publication bias i.e. studies that did not find the treatment to be effective might not have been published. We were unable to assess this possibility, as we did not find any studies that met the inclusion criteria.

CONCLUSIONS

Implications for practice

We are unable to make any evidence-based recommendations, as we found no comparative studies assessing the use of intraoperative cell salvage versus allogeneic blood transfusion in terms of survival, post-operative complications and hospital stay in women undergoing surgery for ovarian cancer.

Implications for research

Based on the findings in other tumour sites, ideally, a large randomised controlled trial is needed to compare intraoperative cell salvage and allogeneic blood transfusion for women with ovarian cancer. However, if such a trial is not possible then it is important to conduct well-designed non-randomised studies that use multivariate analysis to adjust for baseline imbalances.

CONTRIBUTIONS OF AUTHORS

All authors made substantial contribution to conception and design, and/or acquisition of data and/or analysis and interpretation of data; participated in drafting the article or revising it critically for important intellectual content; and gave final approval of the version to be submitted and any revised version to be published.

The protocol for this systematic review was published in PROSPERO. Khadra Galaal, Alberto Lopes, Nagindra Das, Adam Brook. Intraoperative cell salvage vs. conventional blood transfusion in surgery for ovarian cancer; PROSPERO 2013:CRD42013004532

DECLARATIONS OF INTEREST

K Galaal is the primary investigator (PI) of a randomised controlled trial ‘Trial of Intraoperative Cell Salvage vs. Transfusion in Ovarian Cancer (TIC TOC). None of the other authors report any conflict of interest.

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