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Review

The prognostic role of perioperative allogeneic blood transfusions in gastric cancer patients undergoing curative resection: A systematic review and meta-analysis of non-randomized, adjusted studies

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ABSTRACT

The impact of allogeneic perioperative blood transfusions (APTs) on the prognosis of gastric cancer patients undergoing curative-intent gastrectomy is still a highly debated topic. Two meta-analyses were published in 2015, and new studies report conflicting results.

A literature review was conducted using PubMed, Scopus, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, updated to March 1, 2016. Thirty-eight non-randomized studies reporting data on overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS) and postoperative complications (PCs) were included. An inverse variance random-effects meta-analysis was conducted.

APTs showed an association with worse OS, DFS, DSS and an increased number of PCs. The hazard ratio (HR) for OS was 1.49, with a 95% confidence interval (95% CI) of 1.32–1.69 ($p < .00001$; Q-test $p = .001$, I-squared = 56%). After outlier exclusion, the HR for OS was 1.34 (95% CI = 1.23–1.45, $p < .00001$; Q-test $p = .64$, I-squared = 0%). The HR for DFS was 1.48 (95% CI = 1.18–1.86, $p = .0007$; Q-test $p = .31$, I-squared = 16%), and the HR for DSS was 1.66 (95% CI = 1.5–2.19, $p = .0004$; Q-test $p = .96$, I-squared = 0%). The odds ratio for PCs was 3.33 (95% CI = 2.10–5.29, $p < .00001$; Q-test $p = .14$, I-squared = 42%).

This meta-analysis showed a significant association between transfusions and OS, DFS, DSS and PCs. The quality of the evidence was low. Aggregation, selection and selective reporting bias were detected. The biases shifted the results towards significance. Further studies using accurate adjustment methods are needed. Until such additional studies are performed, caution in administering transfusions and optimization of cancer patient blood management are warranted.

Introduction

During the last 30 years, multiple investigations have been conducted to assess a possible detrimental prognostic role of allogeneic perioperative transfusions (APTs) in gastric cancer (GC) patients undergoing curative-aim gastrectomy. These investigations aimed to determine the possible role of blood components as immunosuppressors. In fact, in experimental settings, APTs have been shown to impair both innate and acquired immunity. This effect could be synergistic with other immunosuppressive perioperative factors that are surgery- and anaesthesia-related [1–4]. The detrimental consequences could be an increase in postoperative complications and a negative impact on long-term prognosis due to impaired control of the minimal disease remaining after radical surgery by the immune system. This would result in an increased risk of cancer recurrence and death [2,3,5,6]. The immunosuppressive role of APTs in GC patients undergoing surgery has been confirmed in many settings [7–9], but its actual clinical implications are still a matter of debate. The main limitation of the clinical studies on this topic resides in the fact that the effects of APTs must

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necessarily be evaluated primarily through non-randomized controlled trials (NRCTs), as the nature of and rationale for transfusions do not allow randomized clinical trials (RCTs) to be conducted for ethical reasons [8]. However, the results of NRCTs have a high risk of being influenced by selection bias and confounding variables [10]. Indeed, transfused patients are often those affected by worse preoperative conditions (anaemia, comorbidities) or those with a more advanced stage of the disease (with larger or more extended tumours that increase the technical difficulties of surgery and increase the risk of intraoperative blood loss); thus, these characteristics could be the factors most associated with detrimental outcomes [11–13].

Two systematic reviews and meta-analyses of NRCTs addressing the prognostic role of APTs in GC patients undergoing curative-aim gastrectomy have already been published. Their evidence is based on literature published through October 2014 [14,15]. Both demonstrated decreased overall survival in patients undergoing APTs, and one demonstrated a further negative effect of transfusions on disease-free survival and on the incidence of postoperative complications. However, in these systematic reviews, only a partial review of the literature was conducted [16]. Furthermore, these studies measured survival outcomes using a collection of dichotomous data, which are considered less appropriate than time-to-event data for documenting survival outcomes [17,18], and meta-analyses were conducted only on non-adjusted data. Given the inherent risks of selection bias and confounding variables in NRCTs, the analytical strategy of the meta-analyses described in these studies produced results at high risk of bias and with a predictable bias direction towards the significance of APTs as risk factors for worse prognosis. Finally, since the publication of these systematic reviews, additional studies reporting conflicting results have been published [19–24].

In the present study, a new systematic review and meta-analysis of the prognostic role of APTs in GC patients undergoing curative gastrectomy that follows the most recent guidelines for reporting systematic reviews and meta-analyses of NRCTs [18,25] was conducted to comprehensively assess and update the evidence regarding the influence of APTs on the postoperative outcomes of GC patients and to assess the quality of published studies in terms of bias adjustment. The primary audience for this review consists of clinicians managing GC patients in the perioperative period and researchers investigating the topic of perioperative transfusions. The scope of disseminating results is to aid decision-making regarding transfusions when managing GC patients in the perioperative period and to comprehensively assess the body of literature on this topic, identifying gaps that need to be filled and defining potential areas for improvement in the research setting.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews [25] and the checklist reported by the NRSMG of the Cochrane Collaboration for meta-analyses of NRCTs [26].

Eligibility criteria

a) Patients (P): adult patients with GC undergoing surgery with a curative intent. We excluded studies conducted on patients with remnant GC, patients undergoing both curative and non-curative treatments and combined populations consisting of both gastric and oesophageal cancer patients if these characteristics had not been separately reported or adjusted by univariate and/or multivariate analysis within the studies;
b) Intervention (I): the use of APTs;
c) Comparison (C): patients who did not receive APTs;
d) Outcomes (O): overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS) and postoperative complications (PCs). All of the included studies reported at least one of the primary outcomes;
e) Study design (S): peer-reviewed prospective and retrospective studies with a minimum sample size of 100 patients;
f) Timing: all studies published through March 1, 2016;
g) Setting: no restriction according to type of setting;
h) Language: English.

Search strategy

The International Prospective Register of Systematic Reviews was searched for ongoing or recently completed similar reviews, without results. PubMed, Scopus, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews were searched for potentially eligible studies up to March 1, 2016.

The detailed search strategies are reported in Appendix 2.

A list of titles and abstracts of potentially relevant studies was generated and imported using reference management software (RefWorks™, ProQuest, Ann Harbor, Michigan, US).

Study selection

Two authors independently screened titles and abstracts to identify articles for full-text examination. The full text of all articles was obtained. The reference lists of the articles were screened for additional eligible studies. If multiple investigations conducted in the same period and in the same department were reported, only data from the latest study or from the study with the largest dataset were selected for inclusion. We did not exclude articles reporting different outcomes.

Data collection and quality assessment

Data were independently extracted by two authors. When time-to-event outcome data were not explicitly provided, we used the Excel spreadsheet provided by Tierney et al. [17] for extraction and the software Engauge Digitizer, version 4.1, to reproduce data from the survival curves.

Information on the following was extracted from each study:

- P: age, gender, comorbidity rate, stage, T and N status, tumour size, tumour location, type of gastrectomy (total vs. subtotal), lymph node dissection (D1 vs. D2 and >D2), splenectomy rate, laparoscopy rate, preoperative haemoglobin, estimated blood loss (EBL), and chemotherapy (neoadjuvant and/or adjuvant);
- I: number of transfused and non-transfused patients, transfusion criteria, number and volume of units transfused, blood products administered, timing of transfusions, and definition of “perioperative”;
- O: non-adjusted data, stage-adjusted data, data adjusted by multivariate Cox regression and data adjusted by propensity score for OS, non-adjusted data, stage-adjusted data, data adjusted by multivariate Cox regression for DFS and DSS, non-adjusted data and data adjusted by multivariate logistic regression for PCs, and covariates used in the multivariate analysis;
- S: first author, publication year, primary aim, group selection, data collection (prospective/retrospective), country, geographic location, recruitment period, sample size, and median follow-up.

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