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Impact of transfusion on stroke after cardiovascular interventions: Meta-analysis of comparative studies☆

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ABSTRACT

Purpose: To evaluate the impact of transfusion on the development of stroke after cardiovascular interventions.
Methods: A literature search was performed to identify comparative studies on the impact of blood transfusion on the occurrence of stroke after adult cardiac surgery and interventional cardiology procedures.
Results: Twenty-four studies compared the outcome of 80 283 patients who received and 2 260 709 patients who did not receive blood transfusion after cardiovascular interventions. Pooled analysis showed that transfused patients had a higher risk of postoperative stroke (2.1% vs 0.9%; $P < .001$; risk ratio [RR], 2.563; 95% confidence interval [CI], 1.615-4.069; $I^2 = 94\%$) compared with patient who did not receive blood transfusion. The leave-one-out analysis confirmed the consistency of the overall series (RR ranged from 2.367 [95% CI, 1.978-2.834] to 2.676 [95% CI, 1.679-4.265]). Transfusion was associated with increased risk of stroke after either interventional cardiology interventions (3.2% vs 1.1%; RR, 3.325; 95% CI, 1.579-7.004) or cardiac surgery (1.9% vs 0.8%; RR, 2.260; 95% CI, 1.845-2.769). Generic inverse variance analysis of 11 studies reporting adjusted odds ratios for baseline characteristics showed that transfusion after cardiovascular interventions was an independent predictor of stroke (RR, 1.53; 95% CI, 1.10-2.14; $I^2 = 0\%$).
Conclusion: Blood transfusion is associated with a significantly increased risk of postoperative stroke in patients undergoing cardiovascular interventions.
Registration: The present meta-analysis is registered in PROSPERO, code CRD42016046426.

1. Introduction

Postoperative stroke is not an uncommon complication of cardiovascular interventions and has a major impact on the immediate and late outcome of these patients [1-4]. Thromboembolisms from the left heart cavities and aorta are well-established mechanisms underlying embolic stroke after cardiac surgery and interventional cardiology procedures [2,5]. Recent studies [6-11] suggested that blood transfusion during the perioperative period may be associated with an increased risk of postoperative stroke. The pathogenesis of transfusion-related stroke may be related to the enhanced systemic inflammatory reaction and prothrombotic effect of transfusion of allogeneic red blood cells (RBCs) [9-12]. Furthermore, reduced oxygen delivery secondary to perioperative anemia as well as hypotension secondary to significant surgical bleeding may result in cerebral ischemia [8]. However, definitive evidence of a causative effect of blood transfusion on the development of postoperative stroke is still lacking [13]. The aim of the present meta-analysis was to investigate the possible impact of transfusion on the development of postoperative stroke in adult patients undergoing cardiac surgery and interventional cardiology procedures.

2. Methods

The present systematic review and meta-analysis is registered in PROSPERO, an International prospective register of systematic reviews, with the reference code CRD42016046426.

2.1. Search strategy

A literature review was performed through PubMed, Scopus, and Google Scholar on August 2016, and further refined through Cochrane and CINAHL on October 2016, to identify any study published from 1990 to 2016 evaluating the occurrence of postoperative stroke after cardiovascular interventions in patients receiving or not blood

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transfusion. The retrieval terms were "transfusion" combined with "coronary" OR "cardiac surgery" OR "TAVI" OR "TAVR." Hand searching from reference lists of the obtained articles was performed. The guidelines for Preferred Reporting Items for Systematic reviews and Meta-Analyses (Supplementary Table 1) [14] and the Meta-analysis Of Observational Studies in Epidemiology (Supplementary Table 2) [15] were applied. Literature search was performed by an experienced medical doctor with large experience in systematic reviews (FB). Two authors (NGM and DB) independently reviewed the retrieve abstracts and articles. Reference lists of retrieved articles were searched as well.

2.2. Treatment definition and inclusion/exclusion criteria

Eligible studies were those reporting on the incidence of postoperative stroke in patients receiving blood transfusion compared with those not receiving any blood transfusions after adult cardiac surgery and interventional cardiology interventions. Cardiac surgery procedures eligible for the present analysis were any adult cardiac surgery operation such as coronary surgery, surgery on heart valves, and surgery on the ascending aorta and aortic arch. Interventional cardiology interventions eligible for this analysis were percutaneous coronary interventions and transcatheter procedures on the heart valves.

Once the abstracts of potentially relevant studies were scrutinized, each study was independently evaluated by 3 coauthors (NGM, DB, FB) for inclusion or exclusion from this analysis. Studies that met the Population, Interventions, Comparisons, and Outcomes criteria (Table 1) have been included in the present meta-analysis.

To enter this analysis, studies had to (1) provide details on the type of procedure and the occurrence of postoperative stroke in patients who received or not blood transfusion; (2) be a prospective or retrospective observational investigation; (3) be published in English, Spanish, or Italian language as a full article; and (4) be published after 1990. Data reported only in abstracts or unpublished material were not included in this analysis.

Articles were ineligible for study inclusion if they (1) reported ambiguous or inaccurate data (discrepancies between data reported in the text and tables), (2) did not provide any information on treatment modality and the study end point, (3) did not provide specific information on patients receiving or not blood transfusion, (4) reported data on other than cardiac surgery or interventional cardiology interventions, and (5) included pediatric patients.

2.3. Data extraction

Data were independently collected from the retrieved articles by 2 investigators (NGM and DB) and checked by a third investigator (FB). Disagreement on collected data was settled by consensus between these investigators. No attempt was made to obtain specific or missing data from the authors. The following data were extracted: first author, year of publication, study period, type of intervention, number of patients, gender, major comorbidities, and primary outcome measures.

The quality of the included studies was independently assessed by 3 investigators (FB, NGM, and DB) using the National Heart, Blood, and Lung Institute criteria for study quality assessment of case-control series (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case-control; accessed on August 7th, 2016; Supplementary Table 3) and the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp; accessed on October 26th, 2016; Supplementary Table 4).

Table 1
Participants, Interventions, Comparisons and Outcomes (PICO) of the present meta-analysis

Population	All patients with any cardiac disease treated invasively from 1990 to 2016
Intervention	Any cardiac surgery and interventional cardiology procedures
Comparison	Patients who received blood transfusions in the perioperative period compared with those who did not receive any blood transfusion
Outcomes	Postoperative stroke

2.4. Outcome measures

The main end point of this analysis was postoperative stroke. The definition of stroke was the one adopted by the investigators of the included studies. Transient ischemic attack was not considered an end point of this study.

2.5. Statistical analysis

Statistical analysis was performed using the Open Meta-Analyst software (Brown University, Providence, RI; http://www.cebm.brown.edu/openmeta/) and the Review Manager (RevMan) software, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). To control for the anticipated heterogeneity among observational studies, absolute values and means were pooled using random-effects models. The results are expressed as pooled proportions, means, and risk ratios (RRs) with 95% confidence intervals (CIs). Baseline characteristics were pooled and their differences assessed using random-effect tests. Leave-one-out sensitivity analysis was performed to confirm consistency of the overall analysis. Further sensitivity analyses were performed according to each type of cardiovascular intervention, that is, cardiac surgery and interventional cardiology procedures as well as isolated coronary surgery, any adult cardiac surgery, percutaneous coronary intervention, and transcatheter aortic valve implantation. The impact of differences in preoperative risk factors and type of procedure on postoperative stroke was evaluated by meta-regression. Furthermore, generic inverse variance analysis was used to pool-adjusted effect estimates as reported in the available studies. In 2 cases [9,13], logistic regression including RBC transfusion as a binary covariate was performed to adjust the risk of stroke. Heterogeneity across studies was evaluated using the I^2 test and was considered not significant when $I^2 < 40\%$. Funnel plots were assessed to evaluate publication bias. A $P < .05$ was considered statistically significant.

3. Results

Twenty-four articles fulfilled the prespecified selection criteria and were included in this analysis [7,9,13,16-36] (Supplementary Fig. 1),

Twenty-four studies compared the outcome of 80 283 patients who received and of 2 260 709 patients who did not receive blood transfusion after cardiovascular interventions. Sixteen studies included patients who underwent cardiac surgery procedures and 8 studies included patients who underwent interventional cardiology procedures. The characteristics of the included studies are summarized in Table 2.

Four studies were considered of good quality, 12 studies of fair quality, and 8 studies of poor quality according to the National Heart, Blood, and Lung Institute criteria (Supplementary Table 3). Eleven studies had a Newcastle-Ottawa Scale score higher than 4 (Table 1, Supplementary Table 4). Eleven studies provided adjusted risk estimates of postprocedural stroke.

Two studies included as transfused population only patients receiving less than 2 units of blood [28-30], 1 study included only patients who received a single unit of blood transfusion [21], and 1 study included only patients who received less than 8 units of blood [18].

Transfused patients were older (mean age, 70.2 vs 66.2 years; $P < .001$) and had a higher prevalence of women (41.9% vs 29.9%; $P < .001$), diabetes (27.8% vs 25.8%; $P < .001$), atrial fibrillation (14.0% vs 11.7%; $P = .001$), and emergency procedures (10.6% vs 6.5%; $P < .001$) compared with patients who were not transfused (Table 3).