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Review

Use of minimal extracorporeal circulation improves outcome after heart surgery; a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: The question whether use of minimal extracorporeal circulation (MECC) influences patients' outcome remains unanswered. We performed a systemic review of the literature and a meta-analysis of randomized controlled trials to evaluate the impact of MECC compared to conventional extracorporeal circulation (CECC) on mortality and major adverse cardiovascular events in patients undergoing heart surgery.
Methods: We independently conducted a systemic review of English and non-English articles using Medline, Embase and Cochrane database. Random allocation to treatment with a minimum of 40 patients in both groups was considered mandatory for inclusion in the meta-analysis. Primary outcomes were operative mortality and major adverse cardiac and cerebrovascular events comprising death before discharge, myocardial infarction and neurologic damage.
Results: We included 24 studies comparing MECC vs. CECC with a total of 2770 patients. Use of MECC was associated with a significant decrease in mortality (0.5% vs. 1.7%, $P=0.02$), in the risk of postoperative myocardial infarction (1.0% vs. 3.8%, $P=0.03$) and reduced rate of neurologic events (2.3% vs. 4.0%, $P=0.08$). Additionally, MECC was associated with reduced systemic inflammatory response as measured by polymorphonuclear elastase, hemodilution as calculated by hematocrit drop after procedure, need for red blood cell transfusion, reduced levels of peak troponin release, incidence of low cardiac output syndrome, need for inotropic support, peak creatinine level, occurrence of postoperative atrial fibrillation, duration of mechanical ventilation and intensive care unit stay.
Conclusions: Use of MECC in heart surgery resulted in improved short-term outcome as reflected by reduced mortality and morbidity compared with conventional extracorporeal circulation.

1. Introduction

The number of cardiac surgical procedures increases worldwide. Coronary artery bypass grafting (CABG) is associated with improved long-term results in severe coronary artery disease compared to percutaneous techniques [1]. Refinements in surgical technique regarding valve procedures reduced morbidity and mortality even in high risk patients [2]. Use of cardiopulmonary bypass (CPB) remains the gold standard perfusion strategy to perform cardiac surgery. Induction of systemic inflammatory response (SIRS) and the coagulation cascade during CPB, triggered mainly by the contact of blood with foreign surfaces and complement activation, is related to end-organ injury postoperatively [3].

Avoidance of extracorporeal circulation (ECC) emerged as a valuable alternative to conventional coronary surgery aiming to eliminate its deleterious effects on remote organs; however, this was not confirmed in large multicenter randomized studies [4]. A major limitation is that off-pump techniques apply only in coronary surgery (OPCAB) and preclude all other cardiac surgical pathology. Concerns regarding incomplete revascularization and lack of proven clinical benefits have limited OPCAB from being performed routinely [5]. Moreover, ROOBY Study recently showed a worse one-year clinical outcome and poor graft patency in patients operated on beating heart [6].

Minimal ECC (MECC system) has been introduced in clinical practice more recently than OPCAB in 1999. It is designed in order to dramatically reduce the side effects caused by CPB, thus resulting in a low inflammation response as for OPCAB and at the same time allowing for a complete myocardial revascularization as for standard CPB [7]. Moreover, MECC can be effectively applied in aortic valve surgery as well as in other cardiac surgical procedures [8,9]. This system acts as a closed, self-regulated circuit, which resembles a mechanical circulatory assist device rather than an ECC. The rationale is to increase biocompatibility by using a heparin-coated short circuit, reduce foreign surfaces

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requiring low priming volume and avoid air–blood interaction. Venous blood returns through active drainage with a centrifugal instead of roller pump to a membrane diffusion oxygenator. No venous reservoir and cardiotomy suction of shed blood is used. Oxygenated blood enters the circulation with minimized hemodilution and mechanical trauma reducing SIRS and preserving coagulation.

The question whether use of MECC influences patients' outcome remains unanswered. Numerous studies have evaluated the effect of MECC on various clinical and laboratory parameters. This heterogeneity of data dispersed in the literature as well as the fact that the net clinical outcome of this technology is still unclear impedes its penetration to routine practice. In light of more recent studies an updated systematic review and meta-analysis of randomized controlled trials (RCTs) are required to clarify most of these unresolved issues. Therefore we aimed to systematically review existing evidence regarding use of MECC and compare the findings with conventional ECC (CECC) in a meta-analysis. We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline for randomized trials to evaluate the impact of MECC compared to CECC on mortality and major adverse cardiac and cerebrovascular events (MACCE) in patients undergoing heart surgery [10].

2. Patients and methods

2.1. Search strategy and selection criteria

Relevant studies were searched by four trained investigators. The most recent update (December 11th, 2010) was searched in Medline (1975–present), Embase (January 1980–present) and Cochrane review of aggregate data for reports written in any language. The full PubMed search strategy is available in Appendix A. Additionally, backward snowballing (i.e. scanning of retrieved articles references and pertinent reviews) for further suitable studies was employed. Moreover, hand or computerized search involving the recent (1999–2010) conference proceedings from the *Society of Thoracic Surgeons*, *European Association for Cardiothoracic Surgery* and *European Society for Cardiovascular Surgery* congresses was performed. ClinicalTrials.gov was explored in order to identify any ongoing or unpublished trials. Data were extracted from the reports independently by two reviewers (KA, PA). Disagreements were resolved by discussion between the two authors.

Minimal extracorporeal circulation (MECC) was defined as a closed heparin-coated low-prime volume circuit, baring a centrifugal pump, with absence of venous or cardiotomy reservoir precluding blood-air contact. Shed-mediastinal blood was retrieved exclusively by a cell-saving device. Venting lines, when incorporated, were driven into the cell-saver or into a vacuum bag reservoir. As conventional extracorporeal circulation (CECC) was considered any system comprising an open venous reservoir with cardiotomy suction that collects shed blood and returns it into the circuit.

All studies that were eligible for inclusion in the systematic review compared MECC with either CECC or OPCAB in adult patients. Random allocation to treatment was considered mandatory for inclusion in the meta-analysis. In order to exclude bias from small underpowered studies, only RCTs with a minimum of 40 patients in both groups were selected. Exclusion criteria were: experimental studies, lack of outcome data and duplicate publication (in which case the most recent article or the one with the largest cohort of patients was selected).

2.2. Data collection

For each study included in the meta-analysis we extracted information about study design, type of MECC circuit, sample size, surgical procedure and CPB characteristics. The prespecified primary outcomes were operative mortality and major adverse cardiac and cerebrovascular events (MACCE) comprising death before discharge, myocardial infarction (as defined in individual study) and neurologic damage (any neurologic event lasting more than 24 hours). The prespecified secondary outcomes were: SIRS (as measured by biochemical markers polymorphonuclear elastase, interleukin-6 [IL-6] or C-reactive protein [CRP]); hemodilution (defined as hematocrit drop after CPB); rate of red blood cell (RBC) or fresh frozen plasma (FFP) transfusion; preservation of platelet count; postoperative blood loss and rate of re-exploration for bleeding; myocardial protection (defined as peak troponin release, need for inotropic support, incidence of low cardiac output syndrome and intra-aortic balloon pump use postoperatively); postoperative renal function (assessed by peak creatinine and rate of acute renal failure defined as elevation of creatinine >2 mg/dl); new onset of atrial fibrillation; time on mechanical ventilation, Intensive Care Unit (ICU) stay and time to hospital discharge.

2.3. Internal validity and risk of bias assessment

To ascertain the validity of eligible RCTs an experienced investigator (ABH) determined the adequacy of randomization and concealment of allocation, blinding of patients, health care providers, data collectors and outcome assessors. Risk of bias was appraised according to the Cochrane risk of bias tool [11].

2.4. Statistical analysis

Meta-analyses were conducted using random-effects models in Review Manager (RevMan) 5.0 (Cochrane Collaboration, 2008). Random-effects models incorporate variation both within and between studies and typically provide wider confidence intervals when heterogeneity is present [12]. The random-effects method is a more conservative approach, while it will give identical results with the fixed-effects method when there is no heterogeneity among studies. Binary outcomes were reported as odds ratios and continuous outcomes were reported with mean difference or with weighted mean difference (WMD) whenever the outcome was not measured in the same scale. The Mantel–Haenszel method was used to synthesize dichotomous data. We considered $P<0.05$ (two sided) as significant and reported individual trial and summary results with 95% confidence intervals. Since contemporary use of MECC applies mainly to CABG and AVR surgery, we explored effects by trial characteristics; prespecified subgroup analyses were planned by surgical procedure. Additionally, MECC vs. OPCAB analysis was performed.

Statistical heterogeneity was tested using the Q statistic generated from the χ^2 test and was considered statistically significant for $P<0.010$. The extent of heterogeneity was estimated using the I^2 measure and published guidelines were used for low ($I^2=25$–49%), moderate ($I^2=50$–74%), and high ($I^2\geq75$%) heterogeneity [13]. Finally, the possibility that larger studies showed systematically different effects to those of smaller studies was examined by visually inspecting the inverted funnel plots for asymmetry [14]. The publication bias in dichotomous outcomes was assessed with the Arcsine Thompson test, for outcomes with data from more than 10 studies, which showed to have greater power than other tests, as proposed by Rücker et al. [15]. These tests were implemented in the R-package meta [16].

3. Results

3.1. Study selection

Database searching (Medline, Embase, Cochrane) yielded a total of 1497 citations and 16 abstracts were retrieved from Congresses records; four ongoing trials without published results were identified in ClinicalTrials.gov database. One-hundred and four manuscripts (88 full-text articles, 16 abstracts) were included in the systematic review. From the screening process 71 studies (58 full-text articles, 13 abstracts) were assessed for eligibility according to the prespecified inclusion criteria [17-87]; 37 studies (27 full-text articles and 10 abstracts) were discarded because they were not randomized [17-53], one study was found to have different control group [54] and seven RCTs were excluded due to restricted number of patients (<40) [55-61]. A total of 26 citations (23 full-text articles and 3 abstracts) were included in the meta-analysis; see flow diagram (Fig. 1) [62-87]. Twenty-four RCTs comparing MECC vs. CECC consisted the main group of this meta-analysis, while two RCTs comparing MECC vs. OPCAB were included in a separate meta-analysis (Table 1) [70,74].

3.2. Study characteristics

The 24 RCTs comparing minimal versus conventional CPB included a total of 2770 patients (1387 allocated to MECC vs. 1383 allocated to CECC); CABG was the procedure for 2049 patients (1026 operated on MECC vs. 1023 operated on CECC), while 721 patients underwent aortic valve replacement (AVR) or aortic root surgery (361 operated on MECC vs. 360 operated on CECC). Additionally, 360 patients having coronary surgery were randomized to MECC vs. OPCAB in two RCTs (180 included in each group). Only one study was multicentric [64]. No patients having cardiac re-intervention were included. Most studies used the Jostra MECC system. Warm-blood cardioplegia was administered in the vast majority of cases. Priming volume was statistically significantly lower in MECC compared to CECC group (614 ± 174 vs. 1640 ± 158 ml, $P<0.001$). Details of CPB characteristics and heparin management are reported in Table 2.

Study quality appraisal showed that most studies appeared of suboptimal quality, as testified by the common lack of details on the method used for randomized sequence generation and allocation (Table 3).