On- vs. off-pump coronary artery bypass grafting: a systematic review and meta-analysis

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Funding source: none

Conflicts of interest: none declared

Key words: coronary artery bypass graft; stroke; off-pump; on-pump; hospital costs

Running head: On- vs. Off-pump during CABG

Word Count – Full text: 5,080 words

ABSTRACT

Background: To reduce complications during coronary artery bypass grafting (CABG) off-pump CABG was introduced; however, results have been mixed. The aim of this work was to conduct a systematic review and meta-analysis of off-pump vs. on-pump CABG.

Methods: To identify potential studies systematic searches were carried out using various databases. The search strategy included the key concepts of "cardiopulmonary bypass" AND "coronary artery bypass grafting" AND "off pump". This was followed by a meta-analysis investigating post-operative atrial fibrillation, myocardial infarction, ≤30 day mortality, stroke, ventilation time, intensive care unit (ICU) stay and hospital stay.

Results: Fifty four studies (59 intervention groups), totalling 16,261 participants were analysed. Off pump CABG led to a significantly lower incidence of post-operative atrial fibrillation Odds ratio (OR) 0.87 (95% confidence interval [CI] 0.78 to 0.97, p=0.01), but no differences in either myocardial infarction OR 0.98 (95% CI 0.82 to 1.15, p=0.77) or ≤30 day mortality OR 0.85 (95% CI 0.68 to 1.06, p=0.16). There was a strong trend toward a reduced incidence of stroke OR 0.77 (95% CI 0.59 to 1.00, p=0.05); however this did not quite reach significance. Ventilation time mean difference (MD) -3.78 hours (95% CI -4.75 to -2.82, p<0.00001); ICU stay MD -0.34 days (95% CI -0.50 to -0.17, p<0.0001); and hospital stay MD -0.9 days (95% CI -1.25 to -0.56, p<0.00001) were all significantly shorter in the off-pump group.

Conclusions: Off-pump CABG has some benefits over on-pump CABG, particularly in relation to post-operative atrial fibrillation.

Word Count: 248

KEYWORDS: coronary artery bypass graft; hospital costs; off-pump; on-pump

INTRODUCTION

The usual approach to surgical revascularisation is coronary artery bypass grafting (CABG) involving cardiopulmonary bypass (CPB). This procedure is not without risk as aortic manipulation and CPB increase the possibility of aortic damage, adverse neurologic events such as stroke, and renal damage [1]. At the micro level CPB is associated with pro-inflammatory responses such as the release of cytokines, increased production of reactive oxygen species and stimulation of the release of stress hormones [2]. Bleeding problems can lead to anaemia which is associated with acute myocardial infarction (MI) and higher 30-day mortality [2].

To reduce these complications off-pump CABG was introduced [1]. Originally developed in the 1960s, off-pump CABG became increasingly popular as tools were developed for immobilising the myocardium (for examples see Figure 1 in [1]). However, enthusiasm over this approach has been tempered by difficulties in accessing lateral or posterior wall vessels [1] and the surgeon's expertise and experience. In a large multi-centre study (CORONARY) off-pump CABG was associated with lower rates of postoperative blood transfusion and reoperation for bleeding but no differences in MI, stroke and new-onset renal failure at either 30 days or 1-year [3-4]. This pattern of reduced bleeding complications and new onset atrial fibrillation but no effect on MI and stroke has been repeated in other trials [5]. Because of its failure to reduce the incidence of stroke and the possible need for repeat revascularisation, off-pump CABG is not without its detractors (for example [6]).

There has been a number of meta-analyses comparing on-pump vs. off-pump, such as those by Afilalo et al [5] and Kuss et al [7] and the 2012 Cochrane review [8]. New studies are emerging all the time and these meta-analyses have been superseded by more recent studies [9, 10]. The current meta-analysis includes more studies (and intervention groups) than that by Deppe et al [9] and also considers resource allocation (ventilation time, ICU stay, hospital stay) which was not analysed by Kowalewski et al [10]. In total our analyses included incidence of post-operative atrial fibrillation, incidence of myocardial infarction, mortality, incidence of stroke, ventilation time, ICU stay and hospital stay.

METHODS

Search strategy

To identify potential studies systematic searches were carried out using the following databases: EMBASE, PubMed, Web of Science and the Cochrane Central Registry of Controlled Trials (CENTRAL). The search was supplemented by scanning the reference lists of eligible studies. The search strategy included the key concepts of “cardiopulmonary bypass” AND “coronary artery bypass grafting” AND “off pump”. All identified papers were assessed independently by two reviewers. A third reviewer was consulted to resolve disputes. Searches of published papers were conducted up until January 1st, 2016.

Types of studies to be included

Only randomized controlled trials (RCTs) and their substudies where this did not involve duplication of data of off-pump vs. on-pump in patients undergoing CABG were included. There were no language restrictions. Animal studies, review papers and non-randomized controlled trials were excluded. Studies that did not have any of the desired outcome measures or participants who were treated by other modalities such as percutaneous coronary intervention were excluded. Incomplete data, or data from an already included study, were excluded. Studies that included interventions other than off-pump vs. on-pump CABG were excluded.

Participants/population

This meta-analysis analysed RCTs and their substudies where this did not involve duplication of data of both male and female adult (≥18 years) patients with coronary artery disease who were undergoing CABG using either off- or on-pump. Other treatment modalities and interventions for coronary artery disease such percutaneous coronary intervention were excluded.

Intervention(s), exposure(s)

This meta-analysis considered all RCTs and their substudies where this did not involve duplication of data where patients with stable angina or acute coronary syndrome being treated with CABG were exposed to either on-pump or off-pump. More specifically, all RCTs and their substudies where this did not involve duplication of data where the intervention of carrying out CABG without the use of cardiopulmonary bypass were performed.

Comparator(s)/control

The studies in this analysis compared off-pump CABG with a usual care control group receiving on-pump CABG.

Search Results

Our initial search found 2,161 articles. Of these 2,055 studies were excluded on the basis of title and abstract. 36 studies were excluded as they were not RCTs. Of the RCTs we excluded 16 studies, because they had none of the reported measures (see supplementary Figure S1). Fifty five studies were included in our analysis [3, 11-63].

Outcome(s)

The primary outcomes analysed were: incidence of post-operative atrial fibrillation, incidence of myocardial infarction, ≤30 day mortality, incidence of stroke, ventilation time, ICU stay and length of hospital stay.

Risk of bias (quality) assessment

Risk of bias was assessed using a modification of the JADAD scale [64].

Strategy for data synthesis

Odds ratios were calculated for dichotomous data. An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an

outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Mean differences were calculated for continuous data. Meta-analyses were completed for continuous data by calculating the mean difference between intervention and control groups from post-intervention data only. It is an accepted practice to only use post-intervention data for meta-analysis, but this method assumes that random allocation of participants always creates intervention groups matched at baseline for age, disease severity. All analyses were conducted using Revman 5.0 (Nordic Cochrane Centre, Denmark). A fixed effects inverse variance model was used unless heterogeneity was >75%, then a random effects model was used. Heterogeneity was quantified using the Cochrane Q test [65]. We used a 5% level of significance and 95% confidence intervals; figures were produced using Revman 5.3.

RESULTS

The 54 studies (59 intervention groups) included in the analyses had an aggregate of 16,255 participants, 8,156 of which had on-pump CABG and 8,099 had off-pump CABG. Table 1 summarizes the characteristics of the included studies. Supplementary Table S1 lists the excluded RCTs and reasons for exclusion.

Post-operative Atrial Fibrillation

Nineteen studies (22 intervention groups) reported post-operative atrial fibrillation. The odds ratio (OR) for the pooled analysis was 0.87 (95% Confidence Interval (CI) 0.78 to 0.97, p=0.01), see Figure 1. Post-operative atrial fibrillation occurred significantly more often in the on-pump group than in the off-pump group. Overall, the incidence of post-operative atrial fibrillation was 19.4% in the off-pump group, which was less than the 21.8% in the on-pump group.

Incidence of myocardial infarction

Thirty three studies (34 intervention groups) reported the incidence of myocardial infarction. The OR for the pooled analysis was 0.98 (95% CI 0.82 to 1.15, p=0.77) see Figure 2. Myocardial infarction was as likely to occur in the off-pump group as in the on-pump group. Overall, the incidence of myocardial infarction was 4.8% in the off-pump group, which was not significantly different to the 4.7% in the on-pump group.

≤30-day mortality

Forty one studies (43 intervention groups) reported ≤30-day mortality. The OR for the pooled analysis was 0.85 (95% CI 0.68 to 1.06, p=0.16), see Figure 3. Patients were as likely to die in the off-pump group as they were in the on-pump group. Overall, the incidence of ≤30-day mortality in the off-pump group was 1.9% which was slightly less than the 2.2% incidence in the on-pump group.

Incidence of stroke

Thirty four studies (36 intervention groups) reported the incidence of stroke. The odds ratio (OR) for the pooled analysis was 0.77 (95% CI 0.59 to 1.00, p=0.05), see Figure 4. This means that there was a strong trend towards a lower incidence of stroke in the off-pump group; however, this did not quite reach significance. Overall, the incidence of stroke in the off-pump group was 1.3% compared to 1.7% in the on-pump group.

Ventilation time

Twenty six studies (28 intervention groups) reported the ventilation time in hours. The mean difference for the pooled analysis was -3.78 hours (95% CI -4.75 to -2.82, P<0.00001), see Figure 5. Off-pump patients had significantly shorter ventilation times. The effect size was 0.77 (95% CI 0.49 to 1.06).

Intensive Care Unit (ICU) stay

23 studies (25 intervention groups) reported the duration of stay in the ICU in days. The mean difference for the pooled analysis was -0.34 days (95% CI -0.50 to -0.17, p<0.0001), see Figure 6. Off-pump patients had significantly shorter stays in the ICU. The effect size was 0.68 (95% CI 0.38 to 0.99).

Hospital stay

Twenty four studies (26 intervention groups) reported hospital stay in days. The mean difference for the pooled analysis was -0.90 days (95% CI -1.25 to -0.56, p<0.00001), see Figure 7. Off-pump CABG patients had significantly shorter hospital stays. The effect size was 0.37 (95% CI 0.22 to 0.51).

Risk of bias

Only 13 of the 54 studies had carried out allocation concealment, only 24 studies had carried out blinding and only 21 studies had performed an intention to treat analysis.

DISCUSSION

Stroke is a major cause of morbidity and mortality following cardiac surgery, especially in high risk patients. In an attempt to reduce the incidence of stroke and other post-operative complications off-pump CABG was introduced in the 1960s. However, results remain equivocal with a Cochrane review finding no differences in the incidence of mortality, stroke and myocardial infarction [8] compared with more recent meta-analyses that showed an increased incidence of stroke in the on-pump group [9, 10]. In our meta-analysis, on-pump CABG was associated with a higher incidence of post-operative atrial fibrillation, no difference in either myocardial infarction or mortality, a strong trend towards a reduced incidence of stroke in the off-pump group, and significantly shorter duration of ventilation, ICU stay and hospital stay in the off-pump group.

The incidence of post-operative atrial fibrillation was significantly lower in the off-pump group (Figure 1). Although this was the result of the pooled data analysis, it should be noted that some studies showed no difference in the incidence of post-operative atrial fibrillation [66]. Atrial fibrillation is not a life-threatening occurrence, though its presence could predispose to haemodynamic compromise, thromboembolic events, anxiety and increased costs [15]. One of the primary reasons why off-pump CABG may elicit less atrial fibrillation is that it avoids atrial cannulation.

There was no difference in the incidence of myocardial infarction (Figure 2) or ≤30 day mortality (Figure 3) between the two groups. This result is consistent with the four largest studies to date [3, 21, 28, 54] and also with recent meta-analyses [9, 10].

It is estimated that the incidence of stroke after CABG ranges from 1.1-5.7% [67]. In their systematic review on this topic Mao et al [67] identified the following as risk factors: advanced age, prior (before CABG) cerebrovascular disease/stroke, prior carotid artery stenosis, prior peripheral vascular disease, prior unstable angina, and prolonged cardiopulmonary bypass time. Post-operative atrial fibrillation was identified as an independent predictor [67]. Five of the trials involved in our meta-analysis involved patients with a mean age ≥ 70 years [see Table 1]. Off-pump CABG provided no greater protection against stroke in any of these studies (results not shown). This was also the case in the whole cohort of patients (Figure 4), although there was a strong trend towards a beneficial effect with off-pump CABG. The incidence of stroke was also not significantly different in any of the four largest trials to date [3, 21, 28, 54] and neurocognitive function was not affected in the ROOBY trial [68-69]. Our results contrast those of Deppe et al [9] possibly due to the inclusion of more studies. These conflicting findings suggest that the question as to whether off-pump CABG serves as a protector against stroke is too close to call.

In the current economic climate the cost of hospital stays is of considerable interest. In 2014-15 it was estimated that excess hospital stays cost the UK National Health Service

an estimated £303 per day [70]. The cost per day for an ICU stay rises to approximately £1500 (http://www.bbc.co.uk/news/health-11503873). This might suggest that the significantly shorter ventilation time (Figure 5), ICU stay (Figure 6) and hospital stay (Figure 7) experienced by off-pump patients could reduce healthcare costs. This is supported by the results of one study [71]; however, two other reports in the literature refute this [72-73].

Study limitations: One of the limitations of the current study is the relatively small size of many of the included trials. Only three trials included >1000 patients in both the on- and off-pump groups [3, 21, 54] with many of the trials including <100 patients in both groups [e.g. 13, 17-18] and some as little as <20 per experimental group [e.g. 19, 25-26]. There were also differences in the procedure used for cardiopulmonary bypass (CPB), with some groups using normothermic CPB [e.g. 16, 19-20], whilst others used hypothermic CPB [e.g. 11, 18, 23-25] and a number of studies did not mention the type of CPB used [e.g. 26, 28-29]. In addition there were some differences in the type of cardioplegic arrest used in the on-pump groups wherein: some groups used cold blood cardioplegia [e.g. 11, 17, 19-20]; others used warm blood cardioplegia [e.g. 13-15]; some used cold crystalloid cardioplegia [e.g. 16] and others did not mention the type of cardioplegia used [e.g. 26, 29] or left this to the surgeon's discretion [e.g. 21]. The experience of the surgeons in performing off-pump procedures was rarely mentioned. Future studies on this topic should pay further attention to allocation concealment, blinding and intention to treat analysis.

Acknowledgements

We would like to thank the cardiac surgeon, Adrian Marchbank for critical reading of the manuscript.

CONFLICTS OF INTEREST

None declared

FUNDING SOURCE

None

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List of Figures and Tables

Supplementary file