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Microplegia in cardiac surgery: Systematic review and meta-analysis

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Abstract

Background: Consensus on the optimum choice of cardioplegia remains elusive. One possibility that has been suggested to have beneficial properties is microplegia, a cardioplegia of reduced crystalloid volume. The aim of this meta-analysis is to comprehensively investigate microplegia against a range of clinical outcomes.

Methods: To identify potential studies, systematic searches were carried out in four databases (eg, Pubmed, EMBASE). The search strategy included the key concepts of "microplegia" OR "mini-cardioplegia" OR "miniplegia" AND "cardiac surgery." This was followed by a meta-analysis investigating: mortality, crystalloid volume; cardiopulmonary bypass time; cross-clamp time; intra-aortic balloon pump use; spontaneous heartbeat recovery; inotropic support; low cardiac output syndrome; myocardial infarction; acute renal failure; atrial fibrillation, reoperation for bleeding; creatine kinase myocardial band (CK-MB); intensive care unit (ICU) time and hospital stay.

Results: Eleven studies comprising 5798 participants were analyzed. Microplegia used a lower volume of crystalloids and led to a higher spontaneous return of heartbeat, odds ratio (OR) 4.271 (95% confidence intervals [CIs]: 1.935, 9.423; $I^2 = 76.57\%$; $P < .001$) and a lower requirement for inotropic support, OR: 0.665 (95% CI: 0.47, 0.941; $I^2 = 3.53\%$; $P = .021$). Microplegia was also associated with a lower CK-MB release, mean difference (MD) −6.448 ng/mL (95% CI: −9.386, −3.511; $I^2 = 0\%$; $P < .001$) and a shorter ICU stay, MD: −0.411 days (95% CI: −0.812, −0.009; $I^2 = 17.65\%$; $P = .045$). All other comparisons were nonsignificant.

Conclusions: Microplegia has similar effects to other types of cardioplegia and is beneficial with regard to spontaneous return of heartbeat, inotropic support, ICU stay, and CK-MB release.

KEYWORDS

coronary artery disease, valve repair/replacement

1 | INTRODUCTION

Cardiopulmonary bypass (CPB) provides physiological support through an extracorporeal circuit, circumventing the heart, which is afforded a bloodless field by aortic cross-clamp. Uncontrolled myocardial oxygen consumption in these conditions and at the time of unclamping could predispose the myocardium to injury. By perfusing the heart with a cardioplegic solution to induce and maintain electromechanical arrest, Sarkar et al[1] acknowledge that cardioprotective strategies arise from managed myocardial oxygen consumption.

Cardioplegia modalities were based on three main principles: chemical arrest, hypothermia, and the addition of extra antiischaemic chemicals.[2] Over the years, there have been many variations of cardioplegia in terms of the ingredients of crystalloid cardioplegia, the temperature and the direction of delivery.[3] One of the most enduring debates is whether to use blood or crystalloid cardioplegia. The argument for blood cardioplegia centres around its buffering ability, normal oncotic pressure, free radical scavenging potential, and improved oxygen delivery.[3,4] The two meta-analyses that have been carried out, suggest a lower risk of perioperative myocardial infarction (MI),[4] a lower incidence of low cardiac output syndrome (LCOS), and lower creatine kinase myocardial band (CK-MB) release with blood cardioplegia.[5]

Standard formulation of blood cardioplegia tends to be either four or eight parts blood to one part crystalloid.[6] Pure blood cardioplegia of reduced volume and delivered intermittently,[7] otherwise known as microplegia is an alternative to this. The main advantages reported here include less haemodilution, reduced myocardial oedema, and rapid recovery of ventricular function.[6-8] In addition, the intermittent dosing in microplegia could play a vital role in managing harmful inflammatory responses to global ischemia and regional reperfusion, whereas diluted cardioplegia could have less control in its single-dose modality.[1]

Early clinical trials reported the use of less vasopressors[8] and better postoperative left ventricular function[9] with microplegia. More recent trials have consistently shown a higher establishment of spontaneous heartbeat return using microplegia when compared to standard diluted blood cardioplegia.[10,11] One drawback to these studies was low statistical power suggesting the need for a larger analysis/meta-analysis to investigate for true differences. There has been one meta-analysis conducted, which investigated studies up to May 2013. This old meta-analysis contained a limited number of studies and outcomes.[12] The aim of the current comprehensive meta-analysis (CMA) was to investigate the effect of microplegia in a range of clinical and biochemical outcomes to other types of cardioplegia for myocardial protection for patients undergoing cardiac surgery.

2 | METHODS

This systematic review and meta-analysis were performed in accordance with the PRISMA guidelines (see Supporting Information Files).

2.1 | Search strategy

To identify potential studies systematic searches were carried out using: EMBASE, PubMed, Web of Science, and the Cochrane Central Registry of Controlled Trials. The search was supplemented by scanning the reference lists of eligible studies. The search strategy included the key concepts of "microplegia" OR "mini-cardioplegia" OR "miniplegia" AND "cardiac surgery" (see Supporting Information Files). 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 1st February 2020. Data were extracted using predesigned extraction tables.

2.2 | Types of trials to be included and excluded

Included trials were those that directly compared the use of microplegia versus any other type of cardioplegia in open-heart surgery. There were no language restrictions. Animal studies and review papers were excluded. Studies that did not have any of the desired outcome measures were excluded. Incomplete data, or data from an already included study, were excluded. Other treatment modalities and interventions for coronary artery disease such as percutaneous coronary intervention and valvular disease such as transcatheter aortic valve intervention were excluded.

2.3 | Participants/population

This meta-analysis analysed randomized controlled trials (RCTs) and case-control trials of both male and female adult (≥18 years) patients with coronary artery disease or valvular disease who were undergoing cardiac surgery using either microplegia or other types of cardioplegia.

2.4 | Intervention(s), exposure(s)

This meta-analysis considered all RCTs and case-control trials where microplegia or another type of cardioplegia were used in either coronary artery bypass graft (CABG) or in patients treated for valvular disease. More specifically, all RCTs and retrospective trials where the intervention of carrying out cardiac surgery using microplegia was performed.

2.5 | Search results

Our initial search found 46 articles of which 25 duplicate studies were excluded. A further four studies were excluded as they were investigating paediatric cases; one study was excluded as it had no reported outcomes; one paper was excluded because it was a review; one paper was excluded because it contained duplicate data; and, three studies were excluded because they had no

comparator group (Figure 1). Eleven studies were included in our analysis.[6,8-11,13-18]

2.6 | Outcomes

The primary outcomes analysed were: mortality, volume of crystalloids used, CPB time, aortic cross-clamp time, intra-aortic balloon pump (IABP) use, spontaneous heartbeat recovery, inotropic support, LCOS, MI, acute renal failure, atrial fibrillation (AF), reoperation for bleeding, CK-MB, intensive care unit (ICU) time and hospital stay.

2.7 | Risk of bias (quality) assessment

Risk of bias was assessed using a modified Jadad scale for randomized controlled trials[19] and the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) for case-control studies. Publication bias was investigated using funnel plots.[20]

2.8 | Data synthesis

In the following analyses, the non-microplegia group is referred to as diluted cardioplegia. Odds ratios (OR) were calculated for dichotomous data. Continuous data were compared using mean differences (MDs). Where necessary medians and interquartile ranges were converted into means and standard deviations using the method of Hozo et al.[21] Subgroup analyses were carried out to investigate differences in the diluted cardioplegia arm. All analyses were conducted using CMA version 3. Heterogeneity was quantified using the Cochrane Q test[22] and all comparisons were made using random effects. We used a 5% level of significance and 95% confidence intervals (CIs); figures were produced using CMA. Funnel plots were used to analyse publication bias. Ideally, the results of all trials carried out to investigate the effects of microplegia in comparison to other types of cardioplegia would be published. Unfortunately, in reality, not all trials are published, potentialy leading to selective reporting or publication bias. This can be detected in a funnel plot that is asymmetrical.

FIGURE 1 Consort figure

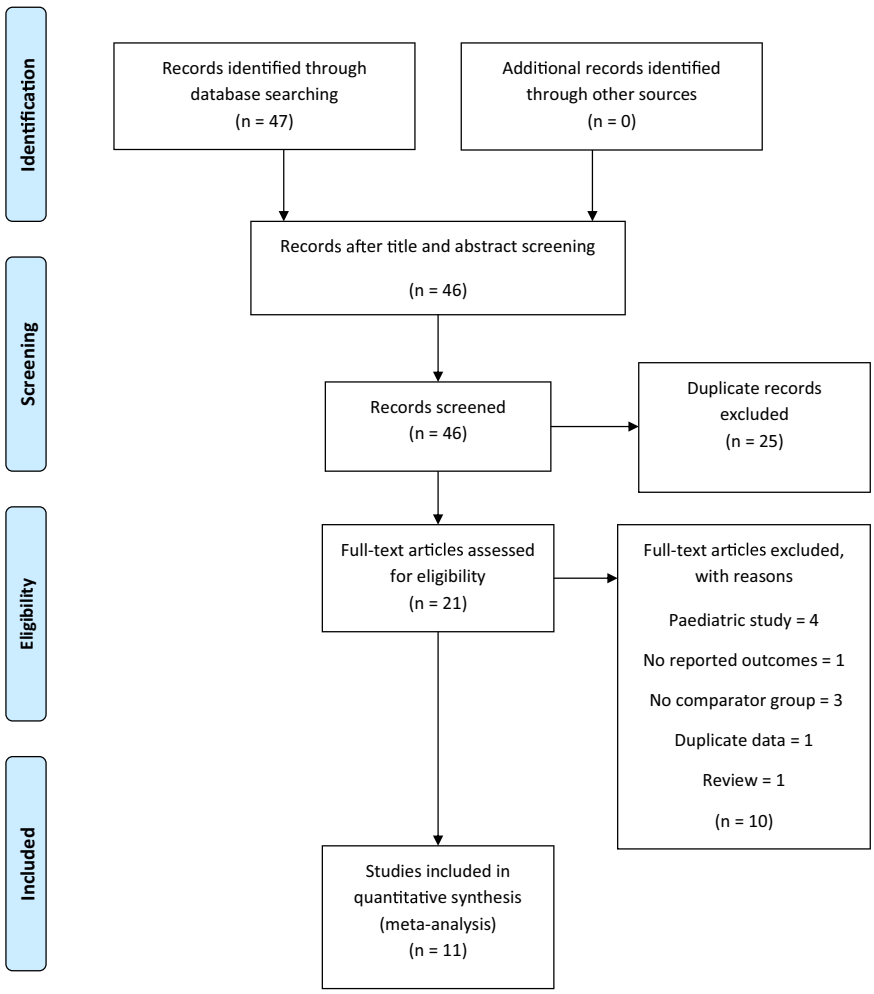

TABLE 1 Characteristics of included trials

Study	Retros/ RCT	Surgery	Type of diluted CP	Delivery direction	Tem-perature	N CP (MP)	Age CP (MP) mean ± SD	% Male CP (MP)	Outcomes
Albacker et al[17]	Retros	Any	Blood	Ante	Cold	151 (144)	79 ± 49.2 (79 ± 48)	63 (51)	Acute renal failure Arrhythmia CPB time Cross-clamp time Hospital stay Inotropic support IABP Mortality Reoperation for bleeding
Algarni et al[6]	Retros	CABG	Blood	Ante	Cold	1980(1980)	64.4 ± 9.5 (64.3 ± 10.2)	77 (78)	Acute renal failure CPB time Cross-clamp time Hospital stay IABP ICU stay LCOS MI Mortality
El Hamamsy[15]	RCT	CABG	Blood	Ante	Warm	25 (34)	>70	88 (79)	Arrhythmia CK-MB CPB time Cross-clamp time Hospital stay LCOS MI
Hayashi et al[10]	RCT	CABG	Blood	Ante then retro	Warm	35 (35)	69.1 ± 6.9 (66.2 ± 7.9)	66 (74)	Arrhythmia CK-MB Inotropic support Spontaneous heartbeat recovery
Hayashi et al[11]	RCT	AVR	Blood	Ante	Warm	15 (15)	71.5 ± 6.3 (66.9 ± 8.6)	53 (60)	Arrhythmia CK-MB CPB time Cross-clamp time Inotropic support Spontaneous heartbeat recovery
Hayashida et al[9]	RCT	CABG	Blood	Ante	Warm	18 (19)	63.7 ± 9.3 (63.1 ± 10)	72 (84)	CK-MB CPB time Cross-clamp time
Koechlin et al[18]	Retros	CABG	Crystalloid	Ante	NR	155 (56)	68.7 ± 8.2 (69.3 ± 8.4)	80 (80)	Aortic cross-clamp time Arrhythmia CKMB CPB time Hospital stay

TABLE 1 (Continued)

Study	Retros/ RCT	Surgery	Type of diluted CP	Delivery direction	Tem-perature	N CP (MP)	Age CP (MP) mean ± SD	% Male CP (MP)	Outcomes
									ICU stay MI Mortality Reoperation for bleeding Renal failure
Lopez Menendez et al[13]	Retros	AVR	Crystalloid	Surgeon's choice	Cold	412 (219)	74 ± 3.4 (73 ± 3)	NR	Acute Renal failure CPB time Cross clamp time Inotropic support IABP Mortality Reoperation for bleeding Spontaneous heartbeat recovery
Lopez Menendez et al[14]	Retros	CABG	Crystalloid	Retro	Cold	261 (114)	66.6 ± 9.3 (65.3 ± 10.1)	83 (83.3)	Acute Renal failure CPB time Cross-clamp time ICU length of stay Inotropic support IABP Mortality Reoperation for bleeding Spontaneous heartbeat recovery
Menasche et al[8]	RCT	CABG	Blood	Retro	Warm	25 (25)	63.3 ± 9 (62.5 ± 11)	84 (80)	CPB time Cross clamp time Inotropic support LCOS Spontaneous heartbeat recovery
Onorati et al[16]	RCT	CABG	Blood	Ante	Cold	40 (40)	66.1 ± 2.2 (65.1 ± 1.4)	55 (65)	CPB time Cross-clamp time Hospital stay ICU length of stay Inotropic support IABP LCOS Spontaneous heartbeat recovery

Abbreviatons: Ante, antegrade; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CK-MB, creatine kinase myocardial band; CP, cardioplegia; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; ICU, intensive care unit; LCOS, low cardiac output syndrome; MI, myocardial infarction; MP, microplegia; NR, not reported; RCT, randomized controlled trial; Retro, retrograde; Retros, retrospective.

3 | RESULTS

The eleven studies[6,8-11,13-18] included in the analysis had an aggregate of 5684 participants, 2681 of whom were microplegia patients versus 3003 who received other types of cardioplegia. The characteristics of the included studies are summarized in Table 1. The excluded RCT's and reasons for exclusion are listed in Table S1. The results are summarized with mortality leading, followed by intra-operative and then post-operative variables. A summary of the results is presented in Table 2.

3.1 | Mortality

Five studies involving 5358 patients reported the incidence of mortality. The OR for the comparison was 1.36 (95% CI: 0.95-1.93; $I^2 = 0\%$; $P = .090$) (Figure 2). There was no significant difference in the odds of mortality between the two groups. The funnel plot was symmetrical.

3.2 | Volume of crystalloids

The majority of trials reported a difference in the volume of crystalloids in the microplegia compared to the diluted cardioplegia. The exceptions were Koechlin et al[18] and Onorati[16] where volumes were not reported. In the two trials by Lopez Menendez et al,[13,14] the volume of crystalloids in the microplegia was not given but reported to be "minimal." In Menasche et al[8] the volume of diluted cardioplegia was 1000 mL compared to 58 ± 14 mL ($P = .0001$), whilst in Albacker et al[17] the volume of crystalloids in the diluted cardioplegia was 740 CC (95% CI: 690-794) compared to 65 CC (95% CI: 62-67) ($P < .01$). Four trials involving 196 patients reported the volume of crystalloids in mL used in the cardioplegia. The MD between the groups was −396.77 mL (95% CI: −422.93, −370.62; $I^2 = 94.07\%$; $P < .001$) (Figure S1). The volume of crystalloids used in the microplegia group was significantly lower than the diluted cardioplegia group. The funnel plot was symmetrical.

3.3 | CPB time

Nine studies involving 5403 patients reported the length of time on CPB. The MD between the two groups was −0.87 minutes (95% CI: −4.51 to 2.78; $I^2 = 92\%$; $P = .640$) (Figure S2). There was no significant difference in CPB time between patients receiving microplegia and patients receiving diluted cardioplegia. The funnel plot was asymmetrical.

3.4 | Aortic cross-clamp time

Nine studies involving 4983 patients reported the time of aortic cross-clamping. The MD between the groups was −1.07 minutes (95% CI: −4.54 to 2.39; $I^2 = 90\%$; $P = .544$) (Figure S3). There was no significant difference in aortic cross-clamp time between the two groups. The funnel plot was asymmetrical.

3.5 | Intra-aortic balloon pump

Four studies involving 4939 patients reported the requirement for IABP. The OR for the comparison was 0.81 (95% CI: 0.50-1.31; $I^2 = 0\%$; $P = .386$) (Figure S4). The two groups showed no significant difference in their requirement for IABP. The funnel plot was symmetrical.

3.6 | Spontaneous heartbeat recovery

Six studies involving 1122 patients reported the incidence of spontaneous heartbeat recovery after aortic unclamping. The OR was 4.27 (95% CI: 1.94-9.42; $I^2 = 77\%$; $P < .001$) (Figure 3). There was a significantly higher incidence of spontaneous heartbeat recovery in the microplegia group than in the diluted cardioplegia group. The funnel plot was asymmetrical.

3.7 | Inotropic support

Five studies involving 1233 patients reported the need for post-operative inotropic support. The OR was 0.67 (95% CI: 0.47-0.94; $I^2 = 4\%$; $P = .021$) (Figure S5). There was a significantly lower requirement for inotropic support in the microplegia group compared to the diluted cardioplegia group. The funnel plot was symmetrical.

3.8 | Low cardiac output syndrome

Four studies involving 4149 patients reported the incidence of LCOS. The OR for the comparison was 0.67 (95% CI: 0.37-1.20; $I^2 = 27\%$; $P = .175$) (Figure S6). The incidence of LCOS was not statistically significant between the two groups. The funnel plot was symmetrical.

3.9 | Myocardial infarction

Three studies involving 4230 patients reported the incidence of MI as a postoperative complication. The OR for the comparison was 0.86 (95% CI: 0.26-2.92; $I^2 = 0\%$; $P = .811$) (Figure S7). There was no significant difference in MI incidence between the two groups. The funnel plot was symmetrical.

3.10 | Acute renal failure

Five studies involving 5358 patients reported the incidence of acute renal failure. The OR for the comparison was 0.96 (95% CI: 0.56-1.65; $I^2 = 43\%$; $P = .876$) (Figure S8). There was no significant difference in the odds of postoperative acute renal failure between the two groups. The funnel plot was symmetrical.

TABLE 2 Summary of results

Parameter	Effect measure	LL	UL	P	I^2 (%)
Mortality	1.36 OR	0.95	1.93	.090	0
Volume of crystalloids	−396.77 mL MD	−422.93	−370.62	<.001	94.07
CPB time	−0.87 min MD	−4.51	2.78	.640	92
Aortic cross-clamp time	−1.07 min MD	−4.54	2.39	.544	90
Intra-aortic balloon pump use	0.81	0.5	1.31	.386	0
Spontaneous heartbeat recovery	4.27 OR	1.94	9.42	<.001	77
Inotropic support	0.67 OR	0.47	0.94	.021	4
Low cardiac output syndrome	0.67 OR	0.37	1.2	.175	27
Myocardial infarction	0.86 OR	0.26	2.92	.811	0
Acute renal failure	0.96 OR	0.56	1.65	.8766	43
Atrial fibrillation	0.88 OR	0.34	2.26	.784	43
Reoperation for bleeding	1.15 OR	0.51	2.58	.741	21
CK-MB release	−6.45 ng/mL MD	−9.39	−3.51	<.001	0
ICU time	−0.41 d MD	−0.81	−0.01	.045	18
Hospital stay	−1.73 d MD	−1.73	0.17	.109	57

Abbreviations: CK-MB, creatine kinase myocardial band; CPB, cardiopulmonary bypass; ICU, intensive care unit; LL, lower 95% confidence interval; MD, mean difference; OR, odds ratio; UL, upper 95% confidence interval.

3.11 | Atrial fibrillation

Three studies involving 300 patients reported the incidence of postoperative AF. The OR for the comparison was 0.88 (95% CI: 0.34-2.26; $I^2 = 43\%$; $P = .784$) (Figure S9). There was no significant difference in the odds of triggering AF between the two groups. The funnel plot was symmetrical.

3.12 | Reoperation for bleeding

Three studies involving 1103 patients reported the incidence of reoperation for bleeding. The OR for the comparison was 1.15 (95% CI: 0.51-2.58; $I^2 = 21\%$; $P = .741$) (Figure S10). The two groups showed no significant difference in the need to reoperate for bleeding. The funnel plot was symmetrical.

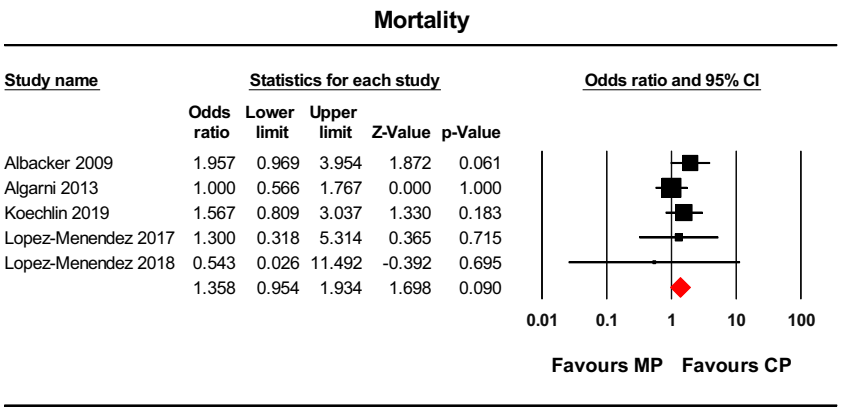

FIGURE 2 Mortality. On the left is a table displaying the odds ratio, lower limit, upper limit, *Z* value, and *P* value for each of the pooled studies with the final line presenting the overall statistics. On the right is a forest plot, which displays the odds ratio (squares) and 95% confidence intervals (whiskers) for each of the individual studies. Also shown is the overall odds ratio (diamond) where the width of the diamond represents the 95% confidence intervals. CP, diluted cardioplegia; MP, microplegia

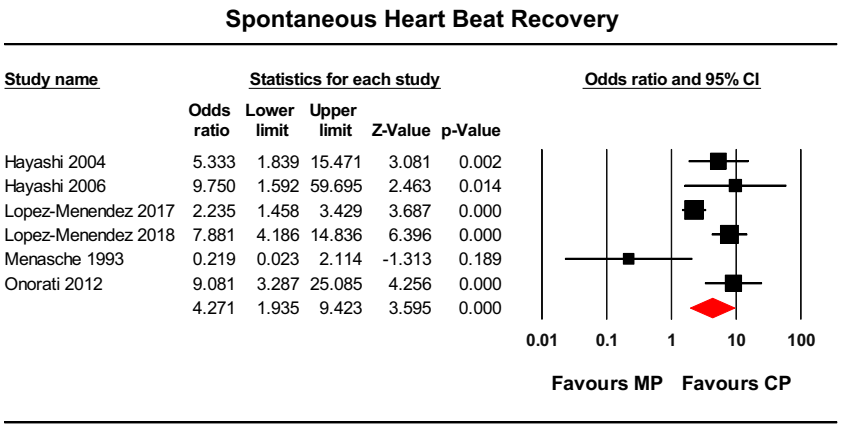

FIGURE 3 Spontaneous return of heartbeat. All details as Figure 1

3.13 | Release of CK-MB

Five studies involving 504 patients reported the postoperative CK-MB plasma levels. The MD between the groups was −6.45 ng/mL (95% CI: −9.39 to −3.51; $I^2 = 0\%$; $P < .001$) (Figure 4). The postoperative concentration of CK-MB in the microplegia patients was significantly lower than in the diluted cardioplegia patients. The funnel plot was symmetrical.

3.14 | Intensive care unit time

Four studies involving 411 patients reported the length of stay in the ICU. The MD between the groups was −0.41 days (95% CI: −0.81 to −0.01; $I^2 = 18\%$; $P = .045$) (Figure S11). Patients receiving microplegia spent significantly less time in ICU than their diluted cardioplegia counterparts. The funnel plot was asymmetrical.

3.15 | Hospital stay

Four studies involving 4310 patients reported the postoperative length of stay in hospital. The MD between the groups was −0.78 days (95% CI: −1.73 to 0.17; $I^2 = 57\%$; $P = .109$) (Figure S12). There was a trend toward the microplegia patients having less hospital stay time, however, this did not reach statistical significance. The funnel plot was asymmetrical.

3.16 | Subgroup analyses

A subset analysis was carried out examining all parameters in studies under 10 years old. These results are presented in Table S2. It was found that spontaneous return of heartbeat and LCOS were significantly in favour of the microplegia group with all other comparisons nonsignificant.

Subgroup analyses were also performed for RCTs. These results are shown in Table S3. The results for CK-MB, CPB time, aortic cross-clamp time, ICU time, inotropic support, and spontaneous return of heartbeat were all significantly in favour of the microplegia group.

Further subgroup analyses were carried out with the results presented in Table S4. These results largely followed the main data.

3.17 | Study quality

Two study quality tests were utilized: The Jadad Scale for RCTs and the Newcastle-Ottawa Scale for case-controlled trials. The former revealed a median score of 4 (Table S5). The Newcastle-Ottawa Scale

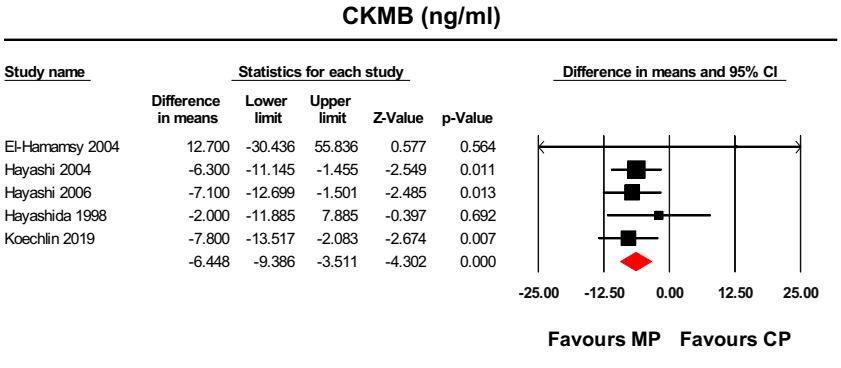

FIGURE 4 Creatine kinase myocardial band release. Details similar to Figure 1 except the statistics presented are mean differences

reported largely good results with a median score of 8 out of 9 (Table S6).

4 | CONCLUSIONS

This CMA included 11 studies and compared the potential cardioprotective capabilities of microplegia and diluted cardioplegia. We found that microplegia used a lower crystalloid volume and was beneficial with respect to spontaneous heartbeat recovery, inotropic support, CK-MB release, and ICU stay time. All of the other comparisons including mortality were not statistically significant. This suggests that microplegia has similar effects compared to diluted cardioplegia and may have some benefits.

The observation of spontaneous heartbeat recovery at aortic unclamping was statistically different between all of the microplegia and diluted cardioplegic groups, excepting in one individual study.[8] This was also true in most of the subgroup analyses, with the notable exceptions of aortic valve surgery, retrograde delivery, and warm delivery. Spontaneous return of heartbeat is proposed as an indicator of good myocardial protection.[13] Furthermore, it has been suggested by Onorati et al[16] that better myocardial protection using microplegia could be responsible for their improved postoperative measurements in diastolic function.

CK-MB is a highly specific and sensitive marker of myocardial cell wall injury. Concentrations of this biomarker were significantly increased in the diluted cardioplegia patients in all included individual studies[9-11,15,18]; in every subgroup analysis and in the meta-analysis overall. This could point to more optimal perioperative protection in the microplegia patients but whether this translates to more positive clinical outcome needs to be cross-examined with other results. For example, CK-MB's diagnostic accuracy of over 90% sensitivity in MI[23] did not appear to correlate to MI incidence as there was no difference between microplegia and diluted cardioplegia in the three studies which were included in this meta-analysis.[6,15,18] It should be noted, however, that the incidence of MI can be based on other parameters such as ECG changes. Two papers did not state the method used to identify MI,[6,18] and the other used a variety of diagnostic measures.

Systemic inflammation causing generalized vasodilation is a common response in CPB. Furthermore, vasopressor agents used to combat this may have a negative impact on native and graft coronary flow[24] so a demonstrable benefit of using microplegia in improving graft patency and postoperative myocardial perfusion could be evident in the significantly decreased incidence of inotropic support in this meta-analysis. However, as shown by the subgroup analysis this may be limited to CABG surgery and more applicable to the blood cardioplegia group.

No differences were found in mortality incidence, No significant differences were found in mortality incidence, although the odds leant toward the diluted cardioplegia group. The main contributing trial of mortality as a key outcome was Albacker et al.[17] In this trial, a significant crude mortality figure became insignificant when preoperative and operative differences were accounted for. The consensus that mortality incidence is not dissimilar in whole blood cardioplegia and diluted cardioplegia is concluded in a meta-analysis by Zeng et al[4] stating a clearer clinical correlation to reduced myocardial injury by decreased release of enzymatic markers than to mortality incidence.

ICU time was significantly reduced in microplegia patients. Independent predictors of the length of time in ICU are multifactorial but if we focus on the role of cardioplegia in protecting the myocardium from inflammatory response during ischemia and reperfusion, any reduction in myocardial oedema could, according to Onorati et al[16] improve LV functioning. This would in turn shorten the time taken for the patient to reach haemodynamic stability suitable for discharge from the ICU. A study on factors influencing prolonged ICU stay in heart surgery found a significant association between length of ICU stay and low LVEF less than 40%.[25] A shortened stay in ICU is also beneficial with respect to the mobilization of the patient reducing the risk of development of ICU-acquired weaknesses reported in 50% of patients discharged from the ICU and associated with increased 90-day mortality incidence.[26] In addition to the significantly shorter ICU stay, the hospital stay time was approximately three-quarters of a day shorter. These shortened stays could indicate a significant financial saving.

4.1 | Limitations

Unfortunately, there is no consensus surrounding the choice of cardioplegia. This, therefore, created difficulty in finding a consistent control arm for this study. To overcome this subgroup, analyses were carried out for the significant results. This showed that some of microplegia's benefits were constrained under certain conditions. It was noticeable though that no matter how the data were segregated, there was always a lower CK-MB release in the microplegia group.

In the majority of the significant analyses, the funnel plot was symmetrical. The exception was spontaneous heartbeat recovery suggesting the possible existence of some publication bias in this finding.

Prospectively randomizing patients to either treatment technique was performed in six of the studies.[8-11,15,16] As the sample sizes in these studies were generally smaller, this meant that only 4.7% of the 5798 participants were randomized.

4.2 | Conclusions

A clear consensus on the optimal cardioplegic solution has been challenged by extensive variation in the composition, volume, temperature, and delivery technique of cardioplegia across surgical practices. Microplegia is one of several different alternatives mooted. This meta-analysis shows that microplegia is similar to other cardioplegia choices and may offer some advantages in terms of early return to spontaneous heartbeat, less requirement for inotropic support, shorter ICU stay, and lower CK-MB release.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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