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Neuroprotective strategies with circulatory arrest in open aortic surgery – A meta-analysis

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Abstract

Objective: Deep hypothermic circulatory arrest (DHCA) in aortic surgery is associated with morbidity and mortality despite evolving strategies. With the advent of antegrade cerebral perfusion (ACP), moderate hypothermic circulatory arrest (MHCA) was reported to have better outcomes than DHCA. There is no standardised guideline or consensus regarding the hypothermic strategies to be employed in open aortic surgery. Meta-analysis was performed comparing DHCA with MHCA + ACP in patients having aortic surgery.

Methods: A systematic review of the literature was undertaken. Any studies with DHCA versus MHCA + ACP in aortic surgeries were selected according to specific inclusion criteria and analysed to generate summative data. Statistical analysis was performed using STATS Direct. The primary outcomes were hospital mortality and post-operative stroke. Secondary outcomes were cardiopulmonary bypass time (CPB), post-operative blood transfusion, length of ICU stay, respiratory complications, renal failure and length of hospital stay. Subgroup analysis of primary outcomes for Arch surgery alone was also performed.

Results: Fifteen studies were included with a total of 5869 patients. There was significantly reduced mortality (Pooled OR = +0.64, 95% CI = +0.49 to +0.83; $p = 0.0006$) and stroke rate (Pooled OR = +0.62, 95% CI = +0.49 to +0.79; $p < 0.001$) in the MHCA group. MHCA was associated significantly with shorter CPB times, shorter duration in ICU, less pulmonary complications, and reduced rates of sepsis. There was no statistical difference between the two groups in terms of circulatory arrest times, X-Clamp times, total operation duration, transfusion requirements, renal failure and post-op hospital stay.

Conclusion: MHCA + ACP are associated with significantly better post-operative outcomes compared with DHCA for both mortality and stroke and majority of the secondary outcomes.

Keywords

Cerebral protection, aortic surgery, aortic disease, hypothermic circulatory arrest, selective antegrade cerebral protection

Introduction

Aortic arch surgery has undergone significant evolution, owing to the devotion of substantial efforts by the clinicians and laboratory researchers over the years.[1] The long-term outcomes of open aortic surgery have been impacted by the implementation of different neuroprotective strategies. Deep hypothermic circulatory arrest (DHCA) has been the cornerstone in minimising end organ injuries especially cerebral injury by decreasing cerebral metabolic activities. The duration and the degree of temperature to conduct safe hypothermic circulatory arrest in aortic operations were reported in observational studies.[2]

Though supplemented with selective antegrade cerebral perfusion (SACP)[3] and /or retrograde cerebral perfusion

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(RCP),[4] to mitigate prolonged circulatory arrest time and the resulting neurological outcomes,[5] DHCA still had its own limitations. The implementation of SACP also reported technical glitches of axillary cannulation,[6] dissection of epiaortic vessels[7] and dislodgement of atheromatous plaques.[8] There are reports on successful conduction of moderate hypothermic circulatory arrest (MHCA) to mitigate the adverse events due to DHCA.[9] This meta-analysis aims to compare the outcome of patients who had aortic surgeries implementing either MHCA + ACP or DHCA.

Material and methods

Literature search strategy

A systematic review was conducted by applying the following two search strategies in the US National Library of Medicine – National Institutes of Health PubMed search engine:

1. (Deep(Title)) OR Moderate(Title)) OR Hypothermia(Title) OR Hypothermic(title) OR Circulatory Arrest(Title))
2. (Aortic(title) OR Arch(title) OR Ascending(title) OR Hemiarch(title))

The resulting titles and abstracts were screened for relevance, followed by evaluation of the remaining publications in their entirety.

Selection criteria

The meta-analysis included comparative studies in which patient cohorts underwent either DHCA or MHCA + SACP for aortic surgeries. As per the Expert Consensus published in 2013, deep hypothermia is defined as the nasopharyngeal temperature range of 14.1°C–20°C, while moderate hypothermia ranges from 20.1°C–28°C.[2] This criterion was applied to include the study for meta-analysis, to standardise the results (Supplemental Table 1). In our selected studies, two (Misfeld and Halkos) measured bladder temperature while one study (Wiedemann) measured oesophageal temperature for core temperature.

Publications were excluded if they were:

- Not available in English.
- Involved animal studies.
- Pertained to literature reviews or single case reports.

The criteria were widened further by using the 'related article' function during the search. Additionally, a manual search was performed for publications in keeping with the above criteria. CINAHL, DARE, ACP, LILACS, SCOPUS, Google Scholar and EMBASE databases were also used to conduct the search from 1966 to 2020. This search was supplemented by a hand search of published abstracts from 1980 to 2020 in meetings of the Society of Academic and Research Surgery, Surgical Research Society, Society of Cardiothoracic Surgeons, World Congress of Cardiothoracic Surgery, the European Society of Cardiothoracic Surgeons, Society of Thoracic Surgeons (STS) and The American Association of Thoracic Surgery. Finally, the Current Controlled Trials Register, The Cochrane Database of Controlled Trials and Science Citation Index Expanded were searched. The reference lists of all articles obtained were also examined to identify additional relevant studies. Review articles were also obtained to determine other possible studies. We applied the PRISMA guidelines for meta-analysis inculcating also the principles of MOOSE guidelines.[10–12]

Eligibility for study inclusion into the meta-analysis and study quality assessment was performed independently by two of the authors (IM and MU). Study data was extracted onto standard forms. Any disagreements were resolved by the senior authors. Studies were only included if they were trials in which direct comparisons were made between patients who had Moderate Hypothermic Circulatory Arrest (MHCA) versus Deep Hypothermic Circulatory Arrest (DHCA) during aortic surgery. Any unclear or missing information was obtained by contacting the authors of the individual trials. For duplicate publications, the smaller dataset was excluded.

The quality of each study was assessed by use of Newcastle-Ottawa scale, which is a nine-point scale that assigns points on the basis of the process of selection (0–4 points), comparability (0–2 points), and identification of the outcomes of study participants (0–3 points).[13]

The primary outcome measures were peri-operative death and stroke or permanent neurological deficit (PND). Peri-operative deaths was defined as deaths occurring within the same hospital stay or within 30 days. PND was defined as stroke with/without coma as reported in the earlier reviews[14]

Secondary outcomes were categorised into intra-operative and post-operative measures. The former included duration of surgery, cardiopulmonary bypass time, cross clamp time, and hypothermic circulatory arrest times. The latter included total intubation time, blood transfusion requirements, length of ICU stay, length of hospital stay and post-operative complications (pulmonary, renal and sepsis).

Only trials that reported at least one of the primary or secondary outcome measures were included in the meta-analysis. Subgroup analysis was also performed looking at primary outcomes of mortality and stroke after isolated aortic arch surgery which by definition, was any aortic surgery involving total arch replacement with reimplantation of branch vessels.

Statistical analysis

Data from the individual eligible studies were entered into a spreadsheet for further analysis. StatsDirect 2.5.7(StatsDirect, UK) was used to perform the statistical analysis. Weighted mean differences (WMD) were calculated for the effect size of continuous variables such as Hospital/ITU stay and CPB/X-Clamp times. Pooled odds-ratios (OR) were calculated for discrete variables such as stroke and in-hospital mortality rates.

The random-effects models (DerSimion Laird) were used to calculate the outcomes of both binary and continuous data to control any heterogeneity between the studies. Heterogeneity amongst the trials was determined by means of the Cochran Q value and quantified using the I^2 inconsistency test In this study, we did not perform meta-regression or sensitivity analysis because of the small number of studies included. All p-values were 2-sided and a five percent (0.05) level was considered significant.

Results

The search criteria as stated in the methods section were performed. The publication selection process is illustrated in Figure 1.

Search strategies #1 and #2 described above yielded 173 and 241 results, respectively. Of the 173 results from search strategy #1, 163 were excluded on screening, two were excluded due to lack of parameters of interest and one was excluded due to overlapping cohort, leaving 7 publications for analysis. Of the 241 results from search strategy #2, 225 were excluded on screening. On further evaluation, 8 publications were excluded due to lack of parameters of interest and three were excluded due to overlapping cohort leaving 5 publications for analysis.

A further manual search was conducted which yielded 11 studies. Eight of these were duplicate studies as they were common to the search strategies #1 and #2 so were excluded. The remaining 3 studies were added to the above 12 studies yielding a total of 15 studies for our final analysis.[15–29] Publication dates ranged from 2004 to 2018 (Table 1).

From these 15 studies,[15–29] there were a total of 5869 patients. Of these 4051 had MHCA compared 1818 patients who had DHCA during aortic surgery. Table 2 shows the characteristics of the included trials. The aetiology of these patients were predominantly aortic dissections (acute and chronic) and a third of the patients had degenerative aneurysm.

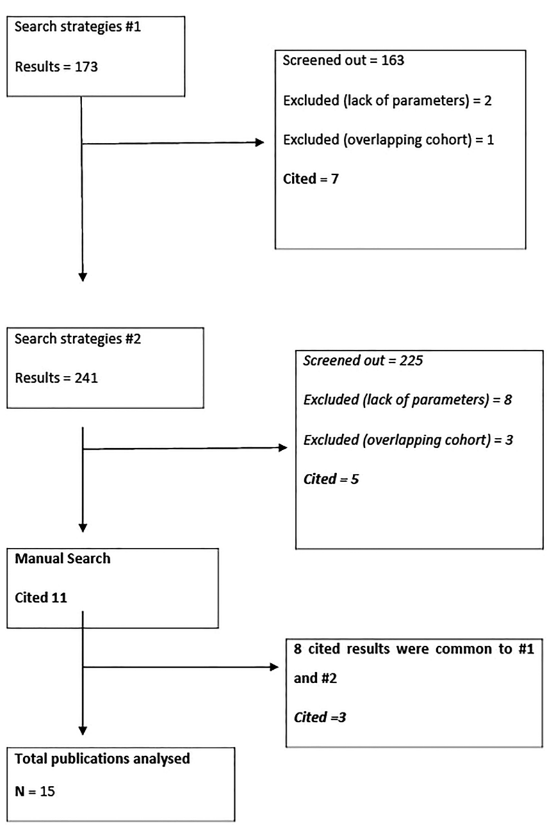

Figure 1. Quorum chart showing study selection for meta-analysis.

Primary outcomes

Mortality. All fifteen studies reported on the mortality rate after aortic surgery between MHCA ($n = 4051$) and DHCA ($n = 1818$) groups. There was no statistical heterogeneity between the studies (Cochran $Q = 18.7$, $p = 0.33$; $I^2 = 25.2\%$, 95%CI = 0%to59.1%). In the random-effects model, there was a significantly reduced mortality in the MHCA group compared to the DHCA group (Pooled OR = +0.64, 95%CI = +0.49 to +0.83; $p = 0.0006$) (Figure 2A).

Subgroup analysis was performed on seven studies which reported mortality rate after aortic arch surgery between MHCA ($n = 3008$) and DHCA ($n = 992$). There was no statistical heterogeneity between the studies (CochranQ = 6.87, $p = 0.13$; $I^2 = 12.6\%$, 95%CI = 0% to63.5%). In the random-effects model, there was a reduced mortality in the MHCA group compared to the DHCA group after arch surgery but this not significant (Pooled OR = +0.68, 95%CI = +0.45 to +1.03; $p = 0.07$) (Supplemental Figure 2A).

Stroke. All fifteen studies reported on the stroke rate after aortic surgery between MHCA ($n = 4051$) and DHCA ($n = 1818$) groups. There was no statistical heterogeneity between the studies (CochranQ = 15.2, $p = 0.36$; $I^2 = 8.1\%$, 95%CI = 0% to50.6%). In the random-effects model, there was a significantly reduced stroke rate or PND in the MHCA group compared to the DHCA group (Pooled OR = +0.62, 95%CI = +0.49 to +0.79; $p < 0.001$) (Figure 2B).

Subgroup analysis was performed on seven studies which reported stroke rate after aortic arch surgery between MHCA ($n = 3008$) and DHCA ($n = 992$). There

Table 1. Summary of characteristics of selected studies on aortic surgeries comparing deep hypothermic circulatory arrest (DHCA) and moderate hypothermic circulatory arrest + selective antegrade cerebral perfusion (MHCA + SACP).

Study	Reference	Year of publication	Study period	Journal	Study type	Number of patients			Newcastle – Ottawa Score
						MHCA + SCP	DHCA	Total	
Kaneda et al.	16	2005	Sept 1995–Sept 2003	Scan J Surg	Retrospective cohort study	51	17	68	7
Halkos et al.	17	2009	Jan 2004–May 2007	J Thorac Cardiovasc Surg	Retrospective cohort study	196	66	262	8
Harrington et al.	18	2004	June 2001 January 2003	Circulation	Randomized Control trial	25	15	40	8
Gong et al.	19	2016	August 2014–July 2015	Journal of Thoracic Disease	Retrospective cohort study	39	35	74	7
Ming Ma et al.	20	2015	2010–2013	Thoracic and Cardiovascular Surgeon	Retrospective cohort study	47	52	99	7
Vallabhajosula et al.	21	2015	2008–2012	Ann Thorac Surgery	Retrospective cohort study	75	75	150	8
Cook et al.	22	2006	Dec 1995–Dec 2002	J Card Surg	Retrospective cohort study	20	52	72	7
Tsai et al.	23	2013	Dec 2006–May 2009	J Thorac Cardiovasc Surg	Retrospective cohort study	143	78	221	8
Algarni et al.	24	2014	1990–2010	J Thorac Cardiovasc Surg	Retrospective cohort study	75	53	128	8
Wiedemann et al.	25	2013	Apr 1987–Jan 2011	J Thorac Cardiovasc Surg	Retrospective cohort study	91	238	329	8
Misfield et al.	26	2012	Jan 2003–Nov 2009	Ann Thorac Surgery	Retrospective cohort study	365	220	585	8
Minatoya et al.	27	2008	Jan 2002–2007	Ann Thorac Surgery	Retrospective cohort study	148	81	229	7
Di Eusanio et al.	28	2003	Jan 1995–Sep 2001	J Thorac Cardiovasc Surg	Retrospective cohort study	161	128	289	8
Kamenskaya et al.	29	2017	Jan 2011–Dec 2012	J Extra Corpor Technol	Randomized Control trial	29	29	58	8
Keeling et al.	30	2018	2000–2015	Ann Thorac Surgery	Retrospective cohort study	2586	679	3265	8

was no statistical heterogeneity between the studies (Cochran $Q = 6.62$, $p = 0.36$; $I^2 = 9.3\%$, 95%CI = 0% to 62.2%). In the random-effects model, there was a significantly reduced stroke rate in the MHCA group compared to the DHCA group after arch surgery (Pooled OR = +0.64, 95% CI = +0.41 to +0.98; $p = 0.04$) (Supplemental Figure 2B).

Secondary outcomes

The secondary outcomes measured were both peri-operative and post-operative variables, which are tabulated above (Supplemental Table 2). In general, not all the secondary outcomes were measured in all the studies mentioned and hence the difference in the total number of patients for different variables. Sepsis was analysed in only two studies and three studies mentioned about total ventilation period, total operation time and total length of hospital stay.

Of the secondary outcomes reported, MHCA + ACP was significantly better than DHCA in terms of CPB times (Pooled wmd = −23.3, 95% CI = −43.23 to −3.46; $p = 0.02$) (Figure 3A), ventilation period (Pooled wmd = −37.19, 95% CI = −58.71 to −15.67; $p = 0.0007$) (Figure 4B), total length of ICU stay (Pooled wmd = −37.64, 95% CI = −69.00 to −6.28; $p = 0.02$) (Figure 4C), sepsis (Pooled OR = 0.53, 95% CI = 0.28 to 0.99; $p < 0.046$) (Supplemental Figure 1C) and reduction in pulmonary complications including respiratory distress syndrome and lower respiratory tract infection (Pooled OR = 0.48, 95%CI = 0.35 to 0.66; $p < 0.0001$) (Supplemental Figure 1B). There was no significant difference between the two groups for peri-operative variables including total operation time (Figure 3D), cross clamp time (Figure 3C) and circulatory arrest time) (Figure 3B). Post-operative variables like renal failure (Supplemental Figure 1A), blood transfusion requirement (Figure 4A) and total length of hospital stay (Figure 4D) were comparable between the two groups.

Discussion

There is no consensus regarding the optimal cerebral protection strategy in aortic surgery.[30] Most high-volume aortic centres still implement DHCA alone without any CP due to its simplicity. The STS database in 2017 reported DHCA to be the most used method without any additional cerebral protection strategies.[31]

DHCA has been associated with complications including neuronal damage and increased organ dysfunction.[32] Moderate HCA induces less inflammatory responses and hence leads to improved survival outcomes.[33,34] There are

Table 2. Summary of operative characteristics of selected studies on aortic surgeries comparing deep hypothermic circulatory arrest (DHCA) and moderate hypothermic circulatory arrest + selective antegrade cerebral perfusion (MHCA + SACP).

Study	Total number (n)	Moderate hypothermia (n)	Deep hypothermia (n)	Aorta	Temperature	ACP performed	RCP used
Kaneda et al.	68	51	17	Ascending aorta/arch	28–30C	Yes	No
Halkos et al.	262	196	66	Proximal aortic surgery	23.2 ± 4.2C	Yes	No
Harrington et al.	40	25	15	Aortic arch surgery	NS	Yes	No
Gong et al.	74	39	35	Aortic arch surgery	20–28C	Yes	No
Ming Ma et al.	99	47	52	Aortic arch surgery	21–26.5C	Yes	No
Vallabhajosula et al.	150	75	75	Transverse hemiarch	>25C	Yes	No
Cook et al.	72	20	52	Aortic arch	>22C	Yes	No
Tsai et al.	221	143	78	Aortic arch surgery	22.9 ± 1.4C	Yes	No
Algarni et al.	128	75	53	Aortic root, ascending and arch surgery	24.1 ± 1.8C	Mostly	No
Wiedemann et al.	329	91	238	Ascending aorta and Arch surgery	25C	Yes	yes
Misfield et al.	585	365	220	Aortic root, ascending and arch surgery	NS	Yes	yes
Minatoya et al.	229	148	81	Aortic arch surgery	>25C	Yes	No
Di Eusanio et al.	289	161	128	Ascending aorta and hemiarch	22–26C	Yes	No
Kamenskaya et al.	58	29	29	Ascending aorta and arch surgery	23–24C	Yes	No
Keeling et al.	3265	2586	679	Total aortic arch replacement	20–28C	Yes	No

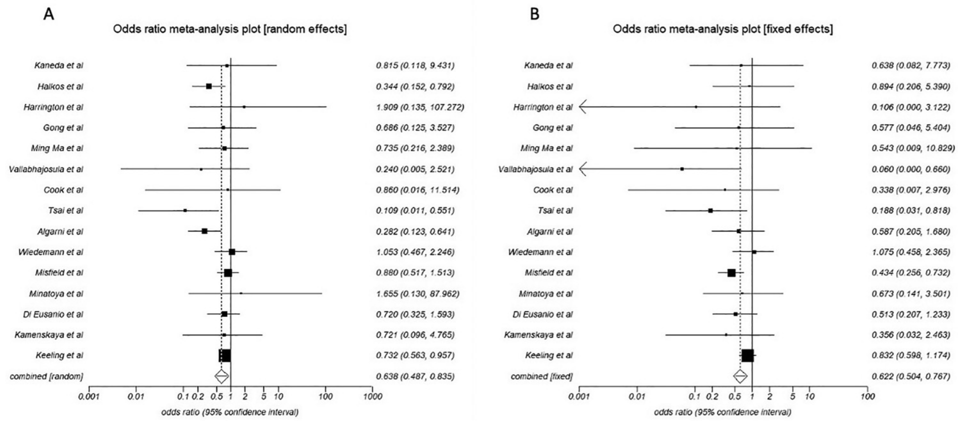

Figure 2. (A) Forest plot of the odds ratio (OR) of post-operative mortality comparing aortic arch surgeries using deep hypothermic circulatory arrest (DHCA) or using moderate hypothermic circulatory arrest with selective antegrade cerebral protection (MHCA + SACP) as cerebral protection strategies. (B) Forest plot of the odds ratio (OR) of post-operative stroke comparing aortic arch surgeries using deep hypothermic circulatory arrest (DHCA) or using moderate hypothermic circulatory arrest with selective antegrade cerebral protection (MHCA + SACP) as cerebral protection strategies.

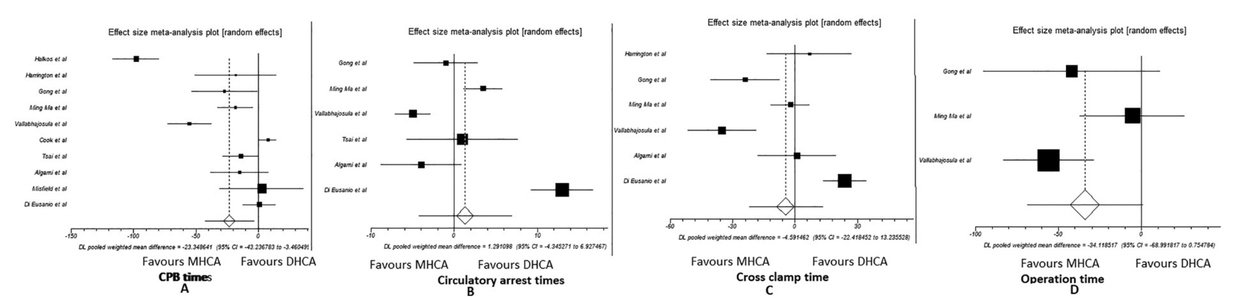

Figure 3. Forest plot of the weighted mean differences (wmd) of peri-operative operative continuous variables including (A) CPB (B) circulatory arrest time (C) cross clamp time and (4) operation time during aortic arch surgeries using DHCA or using moderate MHCA + SACP as cerebral protection strategies.

variable reports of successful outcomes of aortic surgeries performed at different hypothermic temperatures.[9] With the advent of SACP and RCP, finding the optimal temperature for circulatory arrest was the challenge for many aortic surgeons. There are reports of aortic surgeons implementing a warmer HCA with CP strategies and achieving better survival and neurological outcomes than without CP.[35]

Different methods of cerebral perfusion strategies have been reported in aortic surgeries, though the most implemented ones are the SACP through axillary artery or direct arch vessel cannulation followed by RCP through SVC cannulation. Though the HCA time for aortic surgery limits the safe period to less than 60 min with deep hypothermia, the cerebral perfusion strategies with hypothermia have given the flexibility of increased safe circulatory arrest period.[36] The SACP and RCP have got the shortcomings of being non-pulsatile and cold blood flow, though it partially maintains the cerebral circulation.[37] Despite this, complex aortic surgeries have been performed with better results after the implementation of cerebral perfusion strategies.

The present meta-analysis demonstrated that MHCA + ACP was associated with better survival and reduced stroke rate when compared with DHCA. This is in consistence with the recent network meta-analysis done by Hameed et al. who reported lower operative mortality and post-operative stroke due to implementation of additional CP strategies compared to DHCA alone.[38] We cannot hence attribute the better outcomes due to MHCA alone but could be due to the inclusion of cerebral perfusion as well.

On subgroup analysis on patients who had total arch replacement, we found a continued reduced mortality and stroke rate after surgery in the MHCA group compared to DHCA. However, it was only significant for stroke rates and not for mortality. Only three studies mentioned

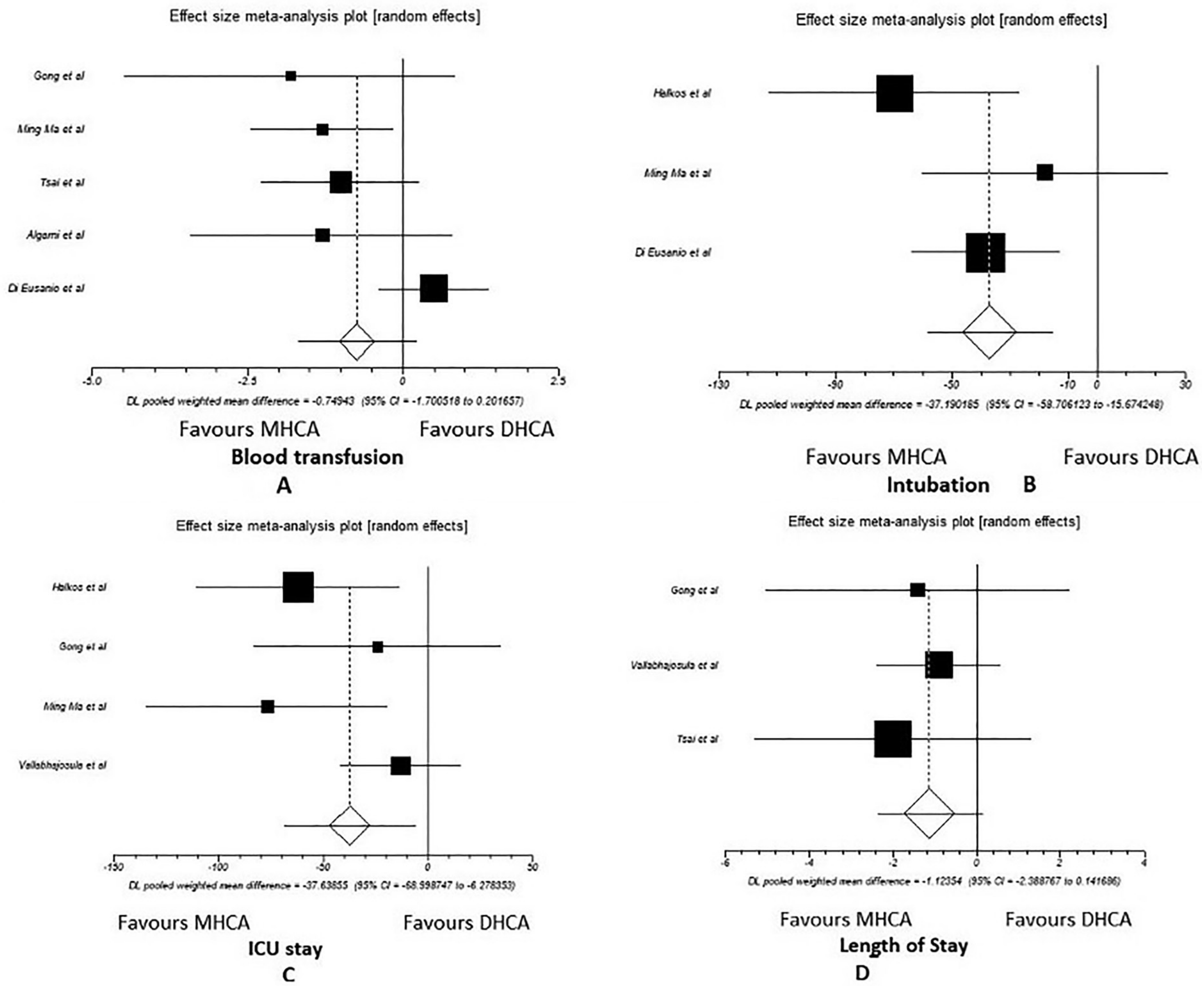

Figure 4. Forest plot of the weighted mean differences (wmd) of post-operative operative continuous variables including (A) blood transfusion (B) intubation (C) ICU stay and (4) LOS, during aortic arch surgeries using DHCA or using moderate MHCA + SACP as cerebral protection strategies.

specifically about paraplegia which were not statistically significant between the two groups.[22,25,27]

There are many factors which could attribute to better neurological outcomes in addition to cerebral perfusion. One of the major concerns during the cardiopulmonary bypass or cross clamping of the aorta is dislodging of atheromatous thrombi during cannulation or clamping of aorta. This can be alleviated with a meticulous approach of cannulation, thorough deairing and retrograde cerebral perfusion. Majority of the aortic centres monitor cerebral oxygen saturation during surgery which could indirectly measure cerebral perfusion.

Among the antegrade cerebral perfusion methods, it is still debateable whether bilateral ACP has superiority over unilateral SCP.[39,40] It is reported that complete circle of Willis occurs in less than fifty percent of the observed patients.[41] Our institution routinely performs bilateral ACP after opening the aortic arch and directly cannulating left common carotid artery, in addition to the right axillary artery cannulation if no contraindication. Of the studies mentioned above, implementation of bilateral or unilateral ACP in the MHCA + SACP group was according to the surgeons' or centres' preference.

Of the secondary outcomes analysed, MHCA group had significantly shorter CPB, total intubation time, total ICU stay and reduced pulmonary complications. There was however no significant difference between the two groups with regards to cross clamp time, HCA time, total operating time, transfusion requirements,[42] total length of hospital stay and renal impairment.

One would expect increased utilisation of blood products in the DHCA group due to deep hypothermia and resultant coagulopathy. A recent study on hypothermia induced coagulopathy at different temperatures including 18°C and 24°C reported prolonged clotting time and clot formation at or below 18°C.[43] Our meta-analysis however did not demonstrate this significant difference. Similarly, the total operating times between the two groups were comparable despite longer cooling and rewarming time for the DHCA group. Renal failure was again, comparable between the two groups though the DHCA had significantly longer CPB time than the MHCA + SACP group. So though some of the secondary outcomes were significantly different between the two groups favouring the MHCA + SACP group, the complications associated with it were comparable. We could argue that most of the secondary outcomes were not consistently analysed and hence could not be validated clinically. A definite conclusion hence could not be drawn for the secondary outcomes between the two groups. One of the suggestions to overcome this incomplete analysis would be to have a multicentre, large RCT looking at specific aortic pathologies and a standard operating technique with uniform reporting of the variables. One could also look into a standard reporting registry like International Registry of Acute Aortic Dissection where most of the required variables could be analysed.

This meta-analysis has a few limitations. Except for two RCTs, majority of the studies in our meta-analysis were retrospective, observational studies, as was the norm in earlier aortic surgeries. There were also variations in arch pathologies, operating techniques across different aortic centres, differing timing of surgeries and the mode of presentation. Emergency surgeries, including aortic dissection, are essentially an independent risk factors which contributes to poorer outcomes.[44,45] Thus, a true comparison could not be made in our study due to difference in aortic pathologies.

Keeling et al. compared the two HCA strategies undergoing only total arch replacement and were able to demonstrate comparable survival outcomes with MHCA.[21] The ongoing COMMENCE trial is designed as a multicentre single-blind trial comparing mild versus moderate HCA in hemiarch surgery.[46] We need similar studies comparing specific aortic pathology with higher level of evidence and consistent reporting to reiterate our analysis.

In conclusion, the present meta-analysis demonstrated a significant difference in the primary outcomes favouring MHCA + SACP but failed to show the mortality benefit when investigated for a specific aortic pathology. The secondary outcomes are inconsistent and infrequently reported and hence need a standard platform to measure and validate.

Declaration of conflicting interests

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Ethical approval

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Informed consent

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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