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REVIEW

Unilateral Versus Bilateral Antegrade Cerebral Perfusion: A Meta-Analysis of Comparative Studies

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Background Antegrade cerebral perfusion (ACP) is an essential adjunct for prolonged hypothermic circulatory arrest (HCA) during aortic arch surgery. However, it has yet to be established whether ACP should be delivered unilaterally or bilaterally. The aim of the present meta-analysis is to investigate outcomes of unilateral ACP (uACP) compared to bilateral ACP (bACP) in comparative studies.

Methods Electronic searches were performed using four databases from their inception to February 2017. Relevant comparative studies with adult patients who underwent aortic arch surgery using unilateral or bilateral ACP were included. Data was extracted by two independent researchers and analysed according to pre-defined endpoints using a random-effects model. Meta-regression was used to identify predictors of primary outcomes.

Results Nine comparative studies were identified, comprising 967 uACP patients and 879 bACP patients. No significant differences in age, sex, or proportion of total arch replacements were identified. The uACP cohort had a greater proportion of acute dissections (86% vs 75%, $p = 0.04$). Hypothermic circulatory arrest and cerebral perfusion times were similar between both groups. No significant differences were seen between unilateral and bilateral groups in terms of mortality (odds ratio [OR] 0.97; 95% confidence interval [CI] 0.64–1.48; $p = 0.90$; $I^2 = 0\%$), permanent neurological deficit (PND) (OR 1.04; 95% CI 0.74–1.45; $p = 0.85$; $I^2 = 0\%$), temporary neurological deficit ($p = 0.74$), acute kidney injury ($p = 0.36$) or reoperation for bleeding ($p = 0.65$). No factors affecting mortality or PND were identified on meta-regression.

Conclusion For patients undergoing aortic arch surgery, the available evidence supports either uACP or bACP as an adjunct to HCA. However, there is insufficient comparative evidence available to determine the benefit of either modalities in patients with longer durations of circulatory arrest.

Keywords Aortic arch surgery • Unilateral antegrade cerebral perfusion • Bilateral antegrade cerebral perfusion • Meta-analysis

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Introduction

In patients undergoing aortic arch surgery, antegrade cerebral perfusion (ACP) is commonly used to provide neuroprotection during prolonged hypothermic circulatory arrest (HCA). However, ACP can cause neurological injuries due to inadequate or excessive cerebral blood flow and embolisation of air or atheroma [1].

Techniques for ACP often differ between institutions, including perfusion rate, perfusion pressure, cannulation site, cannulation technique, or which vessels to cannulate. The last factor is highly contentious, with split opinions amongst experts [2]. While some advocate unilateral cerebral hemisphere perfusion via the axillary or innominate axillary, others prefer to perfuse both hemispheres by also cannulating the left common carotid or left subclavian arteries [3]. It is argued that, although bilateral ACP (bACP) may potentially increase the risk of atheroembolisation compared with unilateral ACP (uACP), it may also decrease the risk of cerebral hypoperfusion.

Recent meta-analyses of uACP and bACP have demonstrated comparable mortality, permanent neurological deficit (PND) and temporary neurological deficits (TND) [4,5]. However, these reviews included single-arm studies, which may have introduced bias due to factors such as institutional variations in surgical practice and perioperative management. This current review was therefore undertaken to evaluate all studies that directly compared unilateral ACP with bilateral ACP in aortic arch surgery.

Method

Literature Search

Electronic searches were performed on four databases (Medline, EMBASE, PubMed, Scopus) between date of inception to February 2017 to compare outcomes of patients who underwent aortic arch surgery with unilateral ACP with patients who had bilateral ACP. The search terms (''antegrade cerebral perfusion'' OR ''selective cerebral perfusion'' OR ''selective brain perfusion'' OR ''antegrade brain perfusion'' OR ''ACP'') AND ''aortic arch surgery'' were used either as key terms or MeSH headings. All identified articles were systematically evaluated by three independent researchers (DHT, AW-S, SKK) according to the inclusion/exclusion criteria.

Inclusion/Exclusion Criteria

Eligible studies for the present meta-analysis included those in which adult patients undergoing surgery on the thoracic aortic arch with either uACP or bACP as the primary neuroprotection strategy. No limitation was placed on the temperature of circulatory arrest, extent of surgery, or indication for surgery. Studies which did not provide specific primary outcomes or with less than 10 patients for either cohorts were also excluded, as were those examining pediatric populations or animal studies. All publications were limited to English. Letters, editorials, case reports, conference abstracts and review articles were excluded. Where hospitals have published duplicating trials, only the most up to date or comprehensive study was included. It is acknowledged that patient selection varied amongst institutions and between time periods.

Quality Assessment and Outcome Measures

Quality assessment was performed using a modified schema based on a quality appraisal tool for case series developed by the Institute of Health Economics in Canada [6]. In short, studies were scored based on six main domains: clarity of objective, characteristics of the study population, description of the intervention, adequate outcome measures, suitable statistical analysis, and appropriate results/conclusions (Supplementary Table 1). Each manuscript was scored out of 13, with 12–13 deemed as high-quality, 9–11 as medium-quality, and 8 or less as low-quality.

Primary outcomes of interest were 30-day/in-hospital mortality and permanent neurological deficit (PND). Temporary neurological deficit (TND) was considered as a secondary outcome of interest due to institutional variabilities in definitions. Other secondary outcomes included incidence of acute kidney injury, spinal cord injury, reoperation for bleeding, and intensive care unit stay and in-hospital stay. Outcome measures were only analysed if at least 50% of studies reported such results.

All data were extracted independently from abstracts, texts, figures, and tables, by two independent researchers (AW-S, SKK) into Microsoft Excel. Discrepancies between the two researchers were resolved by the senior researcher (DHT).

Statistical Method

Meta-analysis was performed by combining the reported incidence of the primary outcomes. To account for variations in surgical practice and patient selection, a random-effects model was used. Odds ratio (OR) and mean difference (MD) were used as summary statistics for binary and continuous outcomes, respectively. Meta-analysis of means or proportions was used to aggregate individual variables. I^2 statistic was used to estimate the percentage of total variation across studies due to heterogeneity rather than chance. An I^2 value of greater than 50% was considered substantial heterogeneity. If substantial heterogeneity was identified, the possible clinical and methodological reasons for this were explored qualitatively. For primary outcomes, secondary analyses were conducted including leave-one-out sensitivity analysis and radial plot analysis to evaluate the influence of outliers and visually assess for heterogeneity within the data (as reflected by the extent of vertical scatter) [7]. Meta-regression was undertaken to determine factors that influenced primary outcomes. Variables with a p-value less than 0.20 on univariable regression were entered into a multivariable stepwise-backwards regression model. Evidence of publication bias was sought using the methods of Egger et al. [8] and

Begg et al. [9]. A contour-enhancing funnel plot was generated to aid in interpretation of potential publication bias. If studies appear to be missing in areas of low statistical significance, then it is possible that the asymmetry is due publication bias. P-values less than 0.05 were considered significant.

All statistical analyses were performed in Review Manager (version 5.3, Cochrane Collaboration, Oxford, UK), Comprehensive Meta-Analysis (version 3.3, Biostat Inc., Englewood, NJ, USA), or R (version 3.2.5, R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall 1,350 records were identified through the literature search (the PRISMA diagram is shown in Supplementary Figure 1). Following review of records and full articles, 10 studies were deemed suitable for quantitative analysis as per the inclusion/exclusion criteria [10–18]. One study was a propensity-matched retrospective analysis [10], and the remaining nine were unmatched retrospective cohort studies (Table 1). An international surgical dissection registry was excluded due to variations in operative approaches amongst included centres [19]. Of the included studies, more than half had at least 150 patients in their analysis (interquartile range: 37–397 patients). Three studies only included acute dissection cases, and six remaining studies recruited a mixture of elective and emergent cases. Only one study was deemed as high quality [13]; all remaining studies were medium quality.

There were 967 patients who received unilateral ACP compared to 879 patients who received bilateral ACP. The average age was 59 years old overall, with 68.0% male patients (Table 2, Supplementary Table 2). Acute dissection was more frequent in uACP than bACP patients (86% vs 75%, $p = 0.04$). The proportion of hemiarch repairs and total arch replacements were similar in both groups.

For three studies, temporal changes in hospital protocols determined the use of uACP or bACP [11,15,16], while in two studies the perfusion strategy was dependent on the surgeon's preference [13,17]. In one study uACP was switched to bACP if near infrared spectroscopy (NIRS) monitoring reduced to below 75% of baseline [12], while in another study bACP was described as used for complex surgeries [18]. Three studies did not provide a rationale for selection of perfusion strategy.

The right axillary artery was the preferred ACP inflow site for the unilateral cohort, while axillary with left common carotid artery cannulation was the preferred approach for the bilateral cohort (Supplementary Table 3). Antegrade cerebral perfusion flow rate varied 8–15 mL/kg/min or 650–1200 mL/min overall, depending on the reported unit of measure. ACP pressures varied between 40–75 mmHg. Near infrared spectroscopy was used in all but one study which did not mention monitoring modalities [13]. Circulatory arrest temperature ranged between 18–28 °C. Circulatory arrest time was similar between uACP and bACP (44 vs 48 minutes, $p = 0.67$) (Supplementary Table 4). No difference in cerebral perfusion time was seen (50 vs 59 minutes, $p = 0.10$).

Mortality amongst all patients was 10.6%. No significant differences were seen between uACP and bACP in terms of mortality (OR 0.97; 95% CI 0.64–1.48; $p = 0.90$; $I^2 = 0\%$, Figure 1), PND (OR 1.04; 95% CI 0.74–1.45; $p = 0.85$; $I^2 = 0\%$, Figure 2), TND (OR 1.06; 95% CI 0.75–1.51; $p = 0.74$; $I^2 = 0\%$), acute kidney injury (OR 0.78; 95% CI 0.46–1.32; $p = 0.36$; $I^2 = 39\%$), or reoperation for bleeding (OR 0.91; 95% CI 0.59–1.39; $p = 0.65$; $I^2 = 0\%$) (Table 3, Supplementary Table 5).

Subgroup analysis of the three acute dissection studies found an overall mortality of 14.2% and PND rate of 12.3%, with no significant differences between both cohorts for either outcome. No significant predictors of mortality and PND were identified on meta-regression, including median year of study, average age, proportion of men, proportion of acute dissections, proportion of total arch, ACP pressure, circulatory arrest temperature, cardiopulmonary bypass time, circulatory arrest time, and cerebral perfusion time.

Table 1 Summary of studies comparing unilateral antegrade cerebral perfusion (uACP) with bilateral antegrade cerebral perfusion (bACP).

Author	Year	Hospital	Study period	Study type	Patients (uACP)	Patients (bACP)
Olsson	2006	Uppsala University Hospital, Sweden	2001-2004	Propensity matched	17	17
Krahenbuhl	2010	Bern University Hospital, Switzerland	2004-2007	Retrospective	118	162
El-Sayed Ahmad	2016	Johann-Wolfgang-Goethe University Frankfurt am Main, Germany	2000-2015	Retrospective	393	194
Misfeld	2012	Leipzig Heart Center, Germany	2003-2009	Retrospective	123	242
Aoyagi	1994	Kurume University School of Medicine, Japan	1989-1993	Retrospective	19	16
Lu	2012	Zhongshan Hospital, China	2005-2011	Retrospective	135	128
Inamura	2006	Tokai University School of Medicine, Japan	2003-2006	Retrospective	19	19
Wiedemann	2013	Vienna Medical University, Austria	1987-2011	Retrospective	53	38
Preventza	2015	Texas Heart Institute, USA	2005-2013	Retrospective	90	63

Table 2 Summary of patient and operative characteristics.

	uACP	bACP	MD/OR (95% CI)	I^2	P-value	Patients (studies)
Age (years)	59.2	59.1	0.55 (-0.90 – 2.01)[a]	0%	0.46	521 vs 647 (7 studies)
Males	69.1%	66.4%	1.21 (0.89 - 1.65)[b]	21%	0.22	967 vs 879 (9 studies)
Acute dissection	85.9%	74.6%	2.27 (1.04-4.99)[b]	81%	0.04	967 vs 879 (9 studies)
Total arch replacement	26.2%	29.2%	0.77 (0.37-1.62)[b]	71%	0.50	439 vs 506 (6 studies)
ACP flow rate (range)	8-15 mL/kg/min or 800-1200 mL/min	8-15 mL/kg/min or 250-1200 mL/min	NA	NA	NA	967 vs 879 (9 studies)
ACP pressure (range)	40-75 mmHg	40-75 mmHg	NA	NA	NA	753 vs 564(5 studies)
Arrest temperature (range)	18-28 °C	18-28 °C	NA	NA	NA	948 vs 860 (8 studies)
Cardiopulmonary bypass time (mins)	193 (156-232)	204 (158-250)	−8.9 (-24.9 - 7.1)[a]	83%	0.28	456 vs 523 (7 studies)
Circulatory arrest time (mins)	44 (36-51)	48 (36-60)	−1.6 (-9.2 – 5.9)[a]	89%	0.67	439 vs 557 (7 studies)
Antegrade cerebral perfusion time (mins)	50 (40-60)	59 (48-71)	−8.4 (-18.3 - 1.6)[a]	93%	0.10	280 vs 243 (5 studies)

Abbreviations: ACP, antegrade cerebral perfusion; bACP, bilateral antegrade cerebral perfusion; CI, confidence interval; uACP, unilateral antegrade cerebral perfusion

[a]Values represent mean difference (MD).

[b]Values represent odds ratio (OR). NA, not applicable.

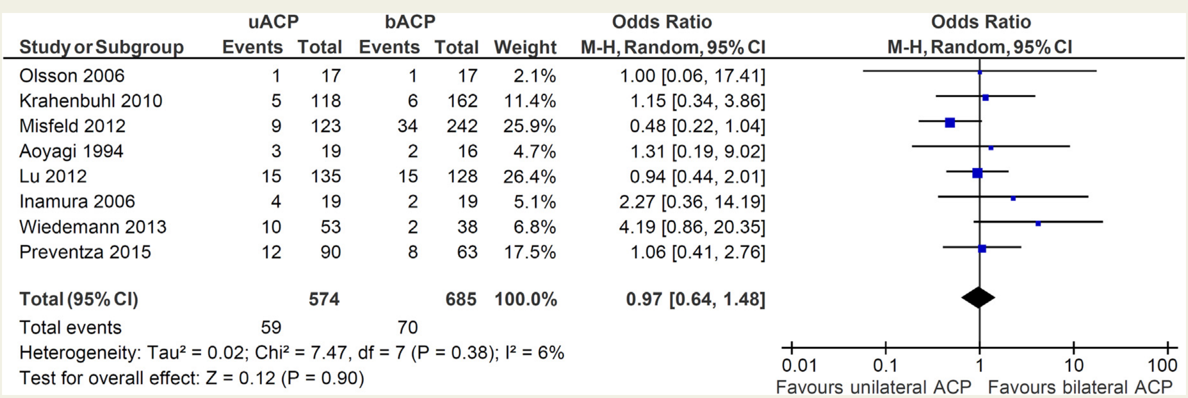

Figure 1 Forest plot of the odds ratio (OR) of mortality for comparative studies using unilateral antegrade cerebral perfusion (uACP) or bilateral antegrade cerebral perfusion (bACP). The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number randomised is shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics.

The forest plots of leave-one-out sensitivity analysis and radial plots for the primary outcomes did not find any significant outliers (Supplementary Figures 2, 3). Inclusion of the German Registry for Acute Aortic Dissection Type A database slightly altered the treatment effects, but did not change the significance of clinical outcomes (mortality OR 0.89; 95% CI 0.69–1.16; p = 0.39; PND OR 0.96; 95% CI 0.75–1.22; p = 0.71) [19]. No significant publication bias was found for mortality using Begg's test and Egger's test (p = 0.275 and p = 0.09), although examination of the funnel plot for mortality identified mild asymmetry favouring bACP (Supplementary Figure 4). Trim and fill adjusted odds ratio for mortality was subsequently calculated to be 0.82 (95% CI 0.51–1.31, p = 0.41). No significant publication bias was found PND (Begg's p = 0.12; Egger's p = 0.88). Adjusted odds ratio for PND was 0.98 (95% CI 0.68–1.40, p = 0.91).

Discussion

Recent surveys have highlighted significant variability amongst aortic surgeons in the provision of ACP during HCA [2,20]. In light of this, the optimal method of brain perfusion during aortic arch surgery remains highly relevant,

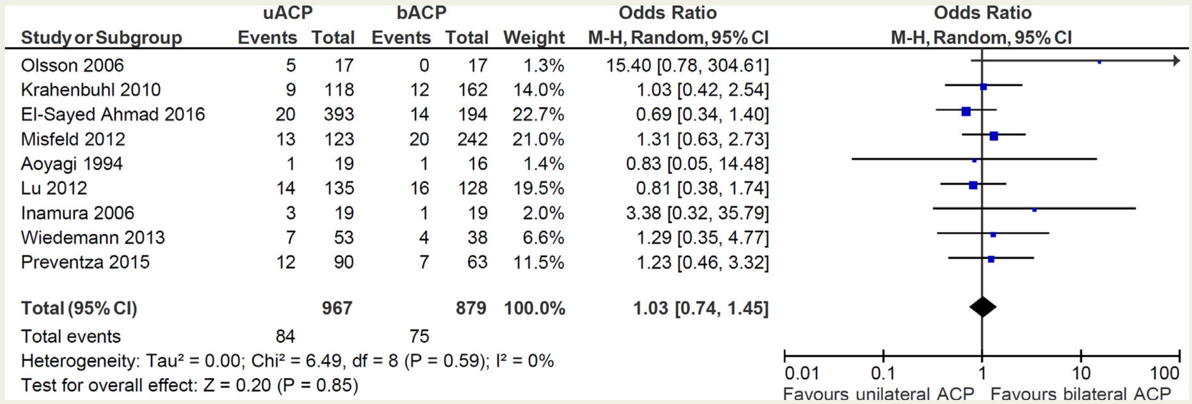

Figure 2 Forest plot of the odds ratio (OR) of permanent neurological deficit for comparative studies using unilateral antegrade cerebral perfusion (uACP) or bilateral antegrade cerebral perfusion (bACP). The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number randomised is shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics.
Abbreviation: M-H, Mantel-Haenszel

Table 3 Summary of clinical outcomes for studies comparing unilateral antegrade cerebral perfusion (uACP) and bilateral antegrade cerebral perfusion (bACP).

	uACP	bACP	OR (95% CI)	I^2	P-value	Patients (studies)
Mortality	11.3%	9.9%	0.97 (0.64 - 1.48)	0%	0.90	574 vs 685 (8 studies)
Permanent neurological deficit	10.6%	8.8%	1.04 (0.74 - 1.45)	0%	0.85	967 vs 879 (9 studies)
Temporary neurological deficit	9.8%	9.4%	1.06 (0.75-1.51)	0%	0.74	878 vs 808 (6 studies)
Acute kidney injury	14.8%	17.7%	0.78 (0.46-1.32)	41%	0.36	420 vs 487 (5 studies)
Reoperation for bleeding	10.0%	14.0	0.91 (0.59-1.39)	0%	0.65	456 vs 523 (7 studies)

Abbreviations: CI, confidence interval; OR, odds ratio.

especially given the trend over recent years shifting to favour warmer HCA targets. Proponents of uACP argue that manipulations of the supra-aortic vessels in acute aortic dissections may be hazardous, especially when the arterial tissues are fragile or atheromatous [21]. Separate cannulation of the left carotid artery also increases clutter of the surgical field. As such, some surgeons advocate commencing with uACP and only cannulating the left carotid if there is evidence of hypoperfusion [18]. In contrast to an earlier meta-analysis [5], our study only included comparative studies of uACP and bACP. This reduces the risk of introducing confounding variables from single-arm studies (such as variations in hospital practice). Despite this, we also did not find a significant difference in mortality or PND between uACP and bACP.

The efficacy of uACP has been thought to be dependent on a patent Circle of Willis to ensure perfusion of the contralateral cerebral hemisphere. Because anatomic and angiographic studies have found that the Circle may not be patent in up to 60% of patients, some authors have suggested that routine preoperative computed tomography angiography or magnetic resonance imaging be performed to identify patients in whom bACP should be used [22]. However, this approach was used in only one of the studies included in our review, which utilised Doppler ultrasound of extracranial vessels, digital subtraction angiography of extracranial and intracranial vessels, and carotid compression testing with electroencephalogram monitoring in all elective patients [21]. Nevertheless, an increased incidence of neurological deficits has not been demonstrated in patients with non-patent Circles of Willis receiving uACP [23]. There are several possible reasons for this. Firstly, a watershed infarct in the contralateral cerebral hemisphere may have a variable clinical presentation, and may not be routinely diagnosed. Secondly, there may be collateral cerebral vessels, such extracranial arteries, that provide some contralateral perfusion in these patients. Thirdly, it is possible that bACP may be superior to uACP for prolonged HCA [5]. However, in the present review, only two studies had mean circulatory arrest durations of greater than 35 minutes [14,16]. While these two studies had small numbers (78 patients, 4.2% of total included in the present study), both demonstrated a trend for reduced mortality for bilateral ACP. In contrast to prior reviews which performed meta-regression separately on uACP and bACP cohorts, our meta-regression of comparative studies did not identify significant impact of circulatory arrest duration on outcomes, although this may have been limited by our stricter inclusion criteria.

There are several techniques that may be used to assess the adequacy of ACP. These include assessment of backbleeding from the left common carotid or subclavian artery, transcranial Doppler sonography of the left middle cerebral artery blood flow and NIRS. However, these techniques are not without their limitations: preoperative testing is not available to all patients, particularly those presenting with aortic dissections, and intraoperative Doppler studies are unable to detect insufficiencies in the vertebrobasilar system. Although NIRS is widely used to monitor regional cerebral saturation and to guide ACP management, with significant deviations from baseline addressed by alterations in cerebral perfusion approach, it is unable to monitor brainstem perfusion or identify potential infarct events at non-monitored sites [12,24].

The results of this review are subject to several limitations. First, there was insufficient data to evaluate additional baseline characteristics and risk factors, such as history of cerebrovascular disease. Second, over 75% of patients included in the present review were acute dissections, and the incidence of preoperative cerebral malperfusion was inconsistently reported. Third, in all but two studies the average circulatory arrest time was less than 35 minutes. It may well be that the true difference between uACP and bACP is apparent with more complex aortic arch operations, as seen in other reviews of non-comparative studies [5], which may explain why no significant difference was identified in this review.

Taken together, the present meta-analysis of comparative studies demonstrates similar mortality and PND outcomes between unilateral ACP and bilateral ACP. Further studies, particularly focussing on operations requiring prolonged circulatory arrest time, will be useful in determining the true effect of uACP and bACP.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.hlc.2019.01.010.

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