Similar cerebral protective effectiveness of antegrade and retrograde cerebral perfusion combined with deep hypothermia circulatory arrest in aortic arch surgery: A meta-analysis and systematic review of 5060 patients

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ACD

Objective: Our objective was to determine if antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP) combined with deep hypothermia circulatory arrest in aortic arch surgery results in different mortality and neurologic outcomes.

Methods: The Cochrane Library, Medline, EMBASE, CINAHL, Web of Science, and the Chinese Biomedical Database were searched for studies reporting on postoperative strokes, permanent neurologic dysfunction, temporary neurologic dysfunction, and all causes mortality within 30 days postoperation in aortic arch surgery. Meta-analysis for effect size, *t* test, and I^2 for detecting heterogeneity and sensitivity analysis for assessing the relative influence of each study was performed.

Results: Fifteen included studies encompassed a total of 5060 patients of whom 2855 were treated with deep hypothermic circulatory arrest plus ACP and 1897 were treated with deep hypothermic circulatory arrest plus RCP. Pooled analysis showed no significant statistical difference ($P > .01$) of 30-day mortality, permanent neurologic dysfunction, and transient neurologic dysfunction in the 2 groups. Before sensitivity analysis, postoperative stroke incidence in the ACP group was higher than in the RCP group (7.2% vs 4.7%; $P < .01$). After a study that included a different percentage of patients with a history of central neurologic events in the 2 groups was ruled out, postoperative stroke incidence in the 2 groups also showed no significant statistical difference ($P > .01$).

Conclusions: ACP and RCP provide similar cerebral protective effectiveness combined with deep hypothermia circulatory arrest and could be selected according to the actual condition in aortic arch surgery. A high-quality randomized controlled trial is urgently needed to confirm this conclusion, especially for stroke morbidity following ACP or RCP. (J Thorac Cardiovasc Surg 2014;148:544-60)

Despite the progress made in the past decades in aortic arch surgery, this kind of procedure is associated with a high rate of mortality and morbidity.[1] This is not due to the technical difficulties of the procedure, but mainly to the necessity of protecting the integrity of the central nervous system during the period of arch exclusion.[2]

Deep hypothermic circulatory arrest (DHCA) has been used in aortic arch surgery as an effective cerebral protective technique for more than 3 decades and has been refined by Griepp and colleagues.[3,4] Although hypothermia has proven to be a feasible means of protection of any organ, a time-dependent cascade of events resulting in brain cell injury is initiated. Concerns about the increased mortality and risk of neurologic deficit led to implementation of adjuncts, such as antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP), which might enhance the safety of the DHCA technique.[5]

Both ACP and RCP have their own advantages and disadvantages. ACP can provide independent control of temperature and/or flow to the cerebral and systemic circulation, but has the potential for embolization. RCP can flush potential embolus from the cerebral circulation and it avoids manipulation of the arch vessel, but the cerebral perfusion capability of RCP is unclear.[6,7] Furthermore, venous valves may compromise blood flow and RCP may result in cerebral edema.[8]

Unfortunately, a high-quality, multicentric, randomized controlled trial comparing the effectiveness of ACP and

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Abbreviations and Acronyms

ACP	= antegrade cerebral perfusion
DHCA	= deep hypothermic circulatory arrest
PND	= permanent neurologic dysfunction
RCP	= retrograde cerebral perfusion
TND	= transient neurologic dysfunction

RCP combined with DHCA in preventing neurologic deficit is absent, making it difficult to draw any meaningful conclusions as to which treatment option is better. The aim of our study was to assess the risk of neurologic complications by meta-analysis of published trials comparing ACP and RCP combined with DHCA.

METHODS

We searched the Cochrane Central Register of Controlled Trials in the Cochrane Library, Medline, EMBASE, CINAHL, Web of Science, and the Chinese Biomedicine Database for studies until April 26, 2013. The following free text search string was used: "human and antegrade cerebral perfusion or retrograde cerebral perfusion or selective cerebral perfusion or antegrade brain perfusion or ACP or ASCP or RCP or cerebral protection or hypothermia circulatory arrest or HCA or DHCA and comparative study or randomized controlled trial."

Studies that evaluated the cerebral protective effectiveness of ACP and RCP combined with DHCA were included. We looked for studies that gave at least 1 of the following clinical outcomes: all-cause mortality within 30 days, morbidity of transient neurologic dysfunction (TND) (defined as postoperative confusion, agitation, delirium, prolonged obtundation, or transient parkinsonism), permanent neurologic dysfunction (PND) (ie, presence of permanent neurologic deficits that were focal or global in nature and persisting at discharge from the hospital), and stroke (defined as a serious illness caused when a blood vessel in the brain suddenly breaks or is blocked, diagnosed by computed tomography or magnetic resonance imaging).[9]

Two authors (Drs Zhipeng and Hongbing) independently identified trials for inclusion and extracted information on demographics, interventions, and outcomes. Disagreements were resolved by consensus. For dichotomous and continuous variables, risk ratios (RRs), 95% confidence intervals (CIs), and odds ratios (ORs) were calculated. And for continuous variables, mean difference and 95% CIs were calculated. Statistical heterogeneity was measured using the Q statistic and I^2 test ($Q < 0.10$ or $I^2 > 50\%$ was considered an indication of statistically significant heterogeneity). For each outcome, the fixed effect model (Mantel-Haenszel test for dichotomous variables and inverse variance for continuous variables) or random effects model (DerSimonian and Laird method for dichotomous and continuous variables) was used when the Q statistic suggested lack or presence of heterogeneity, respectively. The sensitivity analyses were used to assess the relative influence of each study on pooled estimates by omitting 1 study at a time. Finally, we assessed the publication bias by using funnel plots. All analyses were done with Stata software (version 12, StataCorp LP, College Station, Tex).

RESULTS

Included Studies

Of 1843 potentially relevant studies, 15 comparative studies met the selection criteria and were included[10-24] (Figure 1). No randomized controlled trial is available. The included studies encompassed a total of 5060 patients

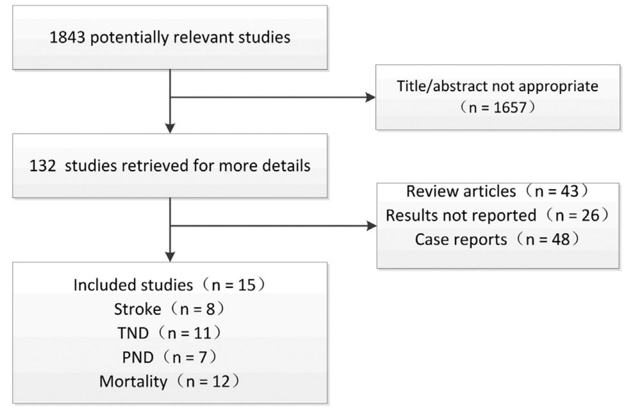

FIGURE 1. Flow diagram of study selection. *TND,* Transient neurologic dysfunction; *PND,* permanent neurologic dysfunction.

of whom 3156 were treated with DHCA + ACP and 1904 were treated with DHCA + RCP. Baseline patient characteristics and main intraoperative details are shown in Table 1. A significant difference only exists in the comparison of the central neurologic event's history before surgery between the 2 groups ($P < .01$). Unfortunately, some important information about proportions of acute and/or chronic dissections, of redo procedures, the extent of the aortic replacement, and the type of cannulation were only presented by part of the studies and could not be compared. Quality assessment of each comparison was done by the GRADE system and the quality of each comparison is only from very low to low (Table 2).[25-27] That may be due to the low quality of the original studies (Figure 2).

Neurologic Complications

Stroke. Postoperative strokes were observed in 8 trials comprising a total of 222 events among 3429 patients. Meta-analysis of these studies using a fixed-effects model ($P = .40$; $I^2 = 3.9\%$) revealed that ACP accounts for higher morbidity of stroke. (Mantel-Haenszel fixed RR, 1.86; 95% CI, 1.30-2.65; $P = .001$) (Figure 3). A funnel plot showed significant publication bias existed (Figure 4).

TND. Postoperative TND was observed in 11 trials comprising a total of 316 events among 4417 patients. The incidence of postoperative TND was 7.50% in the ACP group and 8.7% in the RCP group. No significant difference existed (Mantel-Haenszel fixed RR, 0.89; 95% CI, 0.72-1.1; $P = .275$). There was no heterogeneity between the 2 groups ($P = .154$; $I^2 = 29.8\%$) (Figure 5). The funnel plot showed no evidence of publication bias (Figure 6).

PND. Postoperative PND was reported in 2904 ACP patients and 1583 RCP patients from 7 studies. There was no evidence of heterogeneity ($P = .525$; $I^2 = 0\%$). Difference in postoperative PND incidence was not significant between the 2 groups (6% vs 4.7%, Mantel-Haenszel fixed RR, 1.02; 95% CI, 0.75-1.37; $P = .911$) (Figure 7). The funnel plot showed no evidence of publication bias (Figure 8).