Adding Blood to St Thomas Solution Does Not Improve Mortality in Pediatric Cardiac Surgery; A Meta-analysis of a Homogenous Population

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Abstract

Background: Cardioplegia is the gold-standard for providing ideal operating conditions while effecting myocardial protection. Some studies suggest that the addition of blood to cardioplegia improves efficacy; this is generally accepted as true. However, the few meta analyses conducted on children have pooled heterogeneous populations, this raises concern about the validity of their conclusions. **Method:** PUBMED, the Cochrane Library and Google scholar were searched systematically until March 2019 using the search terms "cardioplegia"; "myocardial protection"; "pediatric" "paediatric"; "children"; "infants"; "neonates". Full text articles were examined if abstracts revealed that the studies possibly contained a blood cardioplegia arm and a crystalloid cardioplegia arm. Studies were included in the meta-analysis if they had a 4:1 blood cardioplegia arm and a St Thomas solution arm. Meta-analysis was conducted using Meta-Mar. **Results:** The search retrieved 423 articles; 5 were included in the meta-analysis; representing 324 patients. The risk ratio for operative mortality was 0.77(95% CI 0.24-2.5; p=0.66). There was little evidence of heterogeneity of the pooled patients. **Conclusion:** Adding blood to St Thomas cardioplegia solution did not improve In-hospital operative mortality; this may have implications for blood cardioplegia use.

Key words: Myocardial protection/cardioplegia, Pediatric, Congenital heart surgery, Mortality
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Introduction

In Optimal cardiac surgical results require the heart to be still, flaccid, lying in a bloodless field and protected from irreversible ischaemic damage. The gold standard for achieving this is the use of cardioplegia which employs three principle concepts for myocardial protection: chemical arrest, hypothermia and additional protection such as manipulating ionic imbalance (1). The merits and demerits of the use of various types of cardioplegia have been examined, however, ambiguity still remains regarding which is best (2,3). Although the exact mechanism of action remains unknown, the addition of blood to a crystalloid cardioplegia base is thought to improve myocardial protection by prolonging aerobic metabolism (4). With respects to the comparison of clinical outcomes between blood and non-blood cardioplegia, the majority of randomised clinical trials have been on adult patients; there are a few paediatric trials (2). Some systematic reviews with meta analyses have been conducted, however, the populations included have been significantly heterogeneous (5). Meta-analysis is a powerful and useful tool when correctly applied; elemental to proper application is the analysis of populations that are as homogenous as possible (6). It has been suggested that available studies examining surgical outcomes related to cardioplegia type, are too heterogeneous for conduction of meta analyses (3). To optimise homogeneity, the answers to the following questions may guide decisions on which studies to include in a meta-analysis:

1. Is the study on pediatric or adult patients?
2. Did cardioplegia achieve depolarized or hyperpolarized arrest?
3. Was Blood added to the cardioplegia solution?
4. Was warm or cold cardioplegia used?
5. What cardioplegia dosing regimen was used?
6. Were other modifications to or variants of cardioplegia used?

Studies for inclusion should differ in as few parameters as possible, preferably in only one (6). The current study aimed to determine whether blood based cardioplegia was associated

with a lower in-hospital operative mortality than non-blood based cardioplegia in paediatric cardiac surgery. The results of this study may have implications for the use of blood cardioplegia in general.

Methodology

Search strategy and selection criteria

In accordance with PRISMA-P checklist (7), PUBMED, the Cochrane Library and Goggle Scholar were searched systematically until March 2019 using the search terms "cardioplegia"; "myocardial protection"; "pediatric" "paediatric"; "children"; "infants"; "neonates". Table 1 shows the search strategies.

Table 1: Search Strategy

Search Step	Search Strategy		
	PUBMED	Google Scholar	Cochrane Library
1	*"cardioplegia" OR "myocardial protection"*	*"Pediatric OR Paediatric" AND "Cardioplegia" AND "Thomas"*	*"cardioplegia" in Abstract AND "pediatric" in Abstract*
2	*"pediatric" OR "paediatric" OR "children" OR "infants" OR "neonates"*		
3	*Results of search 1 and search 2 combined using "AND"*		

Titles and abstracts were interrogated and full-text articles were obtained when the abstract indicated that there was a possibility that the study included a group of pediatric patients exposed to blood cardioplegia and a group of pediatric patients exposed to non-blood cardioplegia (St Thomas Solution). The outcome of interest was in-hospital operative mortality. Non-English language studies and non-human studies were excluded. Only randomised clinical trials were included. The six questions mentioned above were used to refine the choice of studies for inclusion: only studies that utilised intermittent cold cardioplegia (blood or non-blood) were included and only after all authors were in agreement about their inclusion. Two reviewed performed the search and data extraction; when necessary, discrepancies were resolved by discussion and consensus with a third reviewer. Figure 1 shows the search flow.

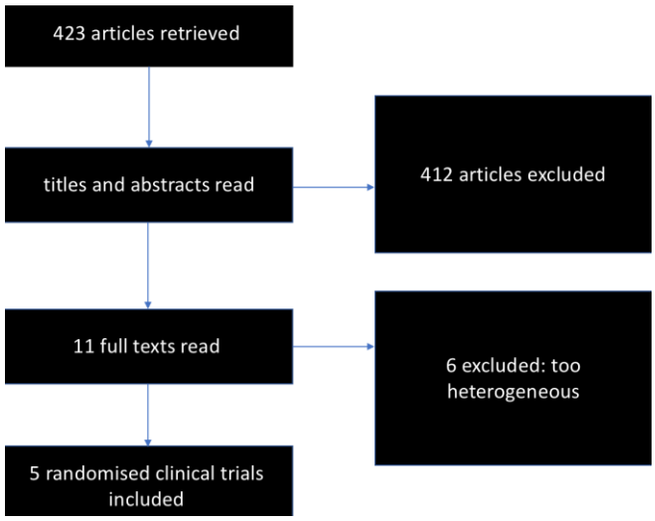

Figure 1: Search flow diagram

Statistical analysis

The meta-analysis was performed using Meta-Mar free online meta-analysis service (V1.8.0)8; risk ratio (RR) was used for analysis. Both fixed and random effects models were employed; I2-statistic was used to assess for heterogeneity (6).

Results

The search yielded 423 articles; 11 relevant full-texts were obtained after examining titles and abstracts. Six full-text articles were rejected on grounds of unacceptable clinical heterogeneity (in accordance with the six questions mentioned above). The important details of the 5 studies included in the meta-analysis are shown in table 2 and the full text articles rejected are listed in table 3.

Table 2: Studies included on meta-analysis

Study	N (324)	CP type	Dose timing
Young 1997 (9)	138	B: St-Th-1(4:1)	20-30 mins
Caputo 2002 (10)	40	B: St-Th-1(4:1)	20-30 mins
Modi 2004 (11)	46	B: St-Th-1(4:1)	20-30 mins
Amark 2005 (12)	30	B: St-Th-1 OR	20-30 mins
Romolo 2019 (13)	70	2(4:1)	20 mins
		B: St-Th-1(4:1)	

. B=blood; CP=cardioplegia; mins=minutes; N=number of patients; St-Th= St Thomas

Table 3: List of rejected full text papers

Authors	Year
1. Sobieraj et al (14)	2018
2. O'Brien et al (15)	2009
3. Sinha et al (16)	2008
4. Zhu et al (17)	2006
5. Modi et al (18)	2006
6. Toyoda et al (19)	2003

The key findings of the meta-analysis are shown in table 4 and the forest plot is shown in figure 2.

Table 4: Meta-analysis results

Model	Risk Ratio	SE	95%CI	P-value	I^2
Fixed effect	0.77	0.6	0.24-2.5	0.66	0%
Random effect	0.51	0.59	0.16-1.63	0.25	0%

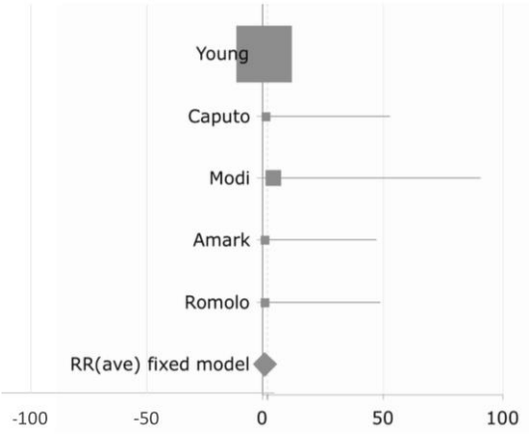

Figure 2: Forest plot

Discussion

The Del Nido solution is composed of 1 part of blood and 4 parts of base solution (i.e. it is 20% blood). It is generally administered as single dose and delivers arrest for up to 90 minutes. It, and blood cardioplegia in general, has emerged as the preferred option for some practitioners in pediatric cardiac surgery based on evidence such as that provided by a relatively recent randomised clinical trial by Talwar et al. This study found that the del Nido solution improved postoperative outcomes with respects to cardiac output, duration of mechanical ventilation, troponin-1 release and electron microscopic evidence of myocardial damage (20). Although these are probably more sensitive outcome measures, we choose not to examine metabolic markers of myocardial protection as they were not measured in a homogenous fashion; for similar reasons we did not examine postoperative inotrope use. Simplicity improves efficiency and reduces the chance of error. In this regard, minimising the steps required to execute any stage of cardiac surgery has a cumulative effect and marginal gains such as these, have been shown to result in significant improvements in outcomes in other disciplines (21). If adding blood to cardioplegia does not improve outcomes, it should not be added. Pragmatically speaking, the ultimate measure of the success of cardiac surgery is long term mortality. Before long term mortality can be considered, operative mortality must be examined; although outcomes such as postoperative cardiac index and release of metabolic markers are considered to be more sensitive markers of the degree of myocardial preservation, they cannot be assumed to translate into improvements in the ultimate outcome. Furthermore, the best quality evidence with respects to the effect of adding blood to cardioplegia, on operative outcome, must be documented. Our work endeavours to document the available evidence of the highest quality in paediatric cardiac surgery. As we worked to achieve this, we remained cognisant of the fact that the immature heart responds differently to ischaemia and that the transition phase is around 3 months of age (22).

Results of clinical studies should be easily applied to patient care; we choose to examine risk ratio (RR) as opposed to odds ratio (OR) as it is a more intuitive parameter for clinicians (23). We found that there was no significant difference, with respects to in-hospital operative mortality, between blood and non-blood (St Thomas crystalloid solution) cardioplegia in pediatric cardiac surgery. A relatively large meta-analysis examining 5576 patients from 36 RCT's found that blood cardioplegia was not superior to crystalloid (non-blood) cardioplegia for myocardial protection with respects to in-hospital operative mortality (2). However, the meta-analysis included a very heterogenous group of patients; no distinction was made between children and adults; use of warm cardioplegia and cold cardioplegia; use of continuous cardioplegia delivery, intermittent delivery and single dose delivery. Two relatively recent meta analyses (5,24) comparing blood and non-blood cardioplegia in paediatric cardiac surgery found no difference in clinical outcomes following the use of either strategy. Of particular interest to us was that Mylonas et al found no difference in 30-day mortality (5). Fang et al examined metabolic markers of myocardial protection, length of postoperative ventilation and length of intensive care unit (ICU) stay; they found that these outcomes were essentially the same irrespective of strategy used (18). The study by Mylonas was solely on paediatric patients, however, it included studies utilising warm cardioplegia, cold cardioplegia, intermittent dosing, single dosing and it also included studies with other significant potential confounders. For example, it included a study by Mimic et al which had a high concentration of glucose in one arm (25). The study by Fang et al was more clinically homogenous but it included a study that compared warm blood cardioplegia with cold non-blood cardioplegia (24). The heterogeneity in these two meta analyses could have affected the pooled outcome. When the six questions mentioned above are used to assess study inclusion in these two meta analyses, it could be argued that

the studies included were too heterogeneous for meta-analysis. This sentiment was echoed recently by Drury et al who concluded that cardioplegia studies in paediatric patients were too heterogeneous for meaningful meta analyses (3).

Study heterogeneity may be fundamentally classified as heterogeneity caused by chance and heterogeneity caused systematic factors; the degree of heterogeneity may simply be assessed clinically or statistically (6). Ensuring clinical homogeneity is a pragmatic method for appropriately selecting studies for inclusion in meta analyses; the six questions mentioned above facilitate this for cardioplegia strategy comparison (26). It is standard practice to assess statistical heterogeneity when conducting meta analyses. In the current study, we sought to minimise the clinical heterogeneity as much as possible by only including studies utilising intermittent cold cardioplegia. For the same reason, we excluded studies that looked at endpoints other than mortality. By doing so, we endeavoured to reduce any confounding resulting from differences in cardioplegia dosing, cardioplegia temperature, cardioplegia additives other than blood. In particular, we only included studies that had a blood cardioplegia ratio of 4:1; blood to crystalloid. Statistically, our studies heterogeneity was low ($I2 = 0\%$). The validity of this finding is strengthened by the similar RR results obtained by the fixed and random effect models in our study (27).

Meta analyses are susceptible to bias, of particular concern are selection bias and small study bias (28). Although it is impossible to determine with certainty the extent to which bias has affected pooled results, a sensible attempt to quantify bias using a funnel plot is performed when appropriate (29). We did not construct a funnel plot as its benefit is questionable when less than ten studies are included in the analysis (29). We used the meta-mar online calculator which has been validated against RevMan and is significantly easier to use (30). Four out of five of the studies that we included had no mortality (zero-event) in at least one of their arms; three studies had no mortality in both arms. A continuity correction is usually used for analysis when there is no event (e.g. mortality) in an arm. It has been shown that a continuity correction of 0.5 reduces bias when there is no event (e.g. mortality) in both arms, particularly if there is a greater likely hood of there being no significant difference in outcomes between arms (27). A large observational study of over seven thousand paediatric patients (greater than three thousand patients in each arm) found no difference in in-hospital operative mortality between del Nido (single dose blood based cardioplegia) and St Thomas II solution (crystalloid cardioplegia) (31); in view of this we opted to use a continuity correction of 0.5. It has been recommended that zero-event studies be included in meta analyses when it is likely that there is no difference between interventions. We think that the findings of this large observational study provide further justification for including zero-event (i.e. no mortality) studies in our meta-analysis (27). Modi et al suggested that blood cardioplegia offers better results in cyanotic patients (11). There was no significant difference in the proportion of cyanotic patient, in our study, when all cases, except those in the study by Romolo et al (13), were pooled together. Although Romolo et al did not indicate the proportion of cyanotic patients in each arm, their study was on patients with tetralogy of Fallot. The mean arterial oxygen saturation was less than 90% in both arms and was not significantly different; the operative mortality was the same in both arms. When this fact, and the fact that the combined proportions of cyanotic patients in the other four studies were not significantly different in the two arms, it would seem that there is no advantage of using blood cardioplegia in cyanotic patients.

Conclusion

Our results suggest that the in-hospital operative mortality associated with the addition of blood to St Thomas I or II solution in pediatric cardiac surgery, is not significantly different from that associated with the use of non-blood (St Thomas solution I or II) cardioplegia. Appropriately conducted meta analyses on well-designed RCT's remain the highest form of evidence with respects to clinical practice. We conducted a meta-analysis, in accordance with best practice guidelines, of available RCTs that were pragmatically clinically homogenous. We ensured that both cardioplegia arms used cardioplegia that caused depolarized arrest and that the only difference between the two arms was the addition of blood in equal concentrations to one arm. Our results may have implications for the use of blood cardioplegia. RCT's with larger populations are required to confirm our finding. We recommend that additional well designed RCT's be conducted to systematically and robustly examine the role of adding blood to cardioplegia.

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