

Is there evidence to support the use of thiamine for the prevention or treatment of post-bypass vasoplegia in children?

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INTRODUCTION

Vasoplegia is a high-output shock state and recognised complication of Cardio-Pulmonary Bypass (CPB).

Thiamine plays a key role in cellular respiration and has attracted interest in recent years a potential adjuvant to the management of severe sepsis and septic shock, as well as its potentially protective role in adults undergoing CPB.

There is no evidence for the use of thiamine in children following CPB.

HYPOTHESIS AND AIMS

We hypothesised that strong evidence, including that extrapolated from the adult population, for the use of thiamine in the vasodilatory state of sepsis/ septic shock and/ or following CPB would support its consideration as an adjuvant treatment for vasoplegia in children following CPB.

We undertook a *systematic review* of the evidence base for thiamine in sepsis and in CPB.

METHODS

Two systematic searches of *Embase* and *Medline* were undertaken using the following search terms. Journal articles (excluding conference papers and case series/ reports) in English were considered and manually screened.

SEARCH 1 CRITERIA – SEPSIS

(SIRS OR sepsis OR systemic inflammatory shock syndrome OR vasoplegia OR vasoplegic OR vasodilation OR hypotension) AND (thiamine OR vitamin B1 OR aneurin)

SEARCH 2 CRITERIA – CARDIAC SURGERY

(Cardiac OR cardiothoracic OR bypass OR by-pass) AND (thiamine OR vitamin B1 OR aneurin)

RESULTS OF SEARCH 1 – SEPSIS

23 papers were identified: 9 RCTs (5 single-centre, one 2-centre, 3 multi-centre), 1 post-hoc analysis of RCT, 11 retrospective studies, 2 observational studies.

An early 2-centre RCT of thiamine “metabolic resuscitation”: no benefit to vasopressor dependence or lactate. A post-hoc analysis of this study suggested that thiamine may reduce RRT requirement, but this has not been replicated in subsequent RCTs.

2017 before-after retrospective analysis: improvement in mortality (40.4 vs 8.5%), RRT and vasopressor requirement and 72-hour SOFA for patients treated with HAT (hydrocortisone, ascorbic acid, thiamine).

Subsequent *retrospective studies*: Patchy benefit from HAT. One demonstrated improved survival, but also longer vasopressor requirement in the treatment arm. Others demonstrated, in isolation, shorter ventilation duration/ ICU LOS without improved survival or vasopressor requirement improvement. Most demonstrate no benefit.

3 retrospective/ observational studies: Improved mortality with thiamine use in septic adults with Alcohol Use Disorder/ clinical suspicion of low thiamine levels.

3 single-centre RCTs: Marginal changes to vasopressor requirements/ lactate reduction/ serial SOFA score. None demonstrated improved mortality or LOS and the majority of primary and secondary outcomes were negative for single-centre RCTs.

Multi-centre RCTs: “ACTS” demonstrated an increase in “shock free days” of 1 day, but no other benefit. “VITAMINS” and “VICTAS” demonstrated no benefit from HAT, including to mortality, length of stay, or vasopressor requirement.

RESULTS OF SEARCH 2 – CARDIAC SURGERY

3 single-centre RCTs of adults undergoing planned CPB were identified.

2 studies confirmed that perioperative thiamine levels could be increased, one describing reduced pyruvate dehydrogenase activity and higher oxygen consumption in treatment arm, but without any proven clinical benefit.

A third is described as a pilot study, with no clinical benefit found.

DISCUSSION

Thiamine forms part of the HAT regimen that apparently conferred huge benefit to patients in a 2017 before-after study.

Thiamine and HAT were thereafter subject to multiple retrospective studies, intrinsically vulnerable to confounding and bias, that generally demonstrated no significant benefit. A few single-centre RCTs demonstrated debatable improvements to ICU parameters but no mortality benefit.

Increasingly large, complex and robust RCTs have in one case shown fewer (by 1) “shock free days”, a finding of uncertain clinical significance, and no other benefit.

The strongest evidence for the use of thiamine in the adult population is in patients with known/ suspected thiamine deficiency and this might prompt us to more closely consider the nutritional status of children at risk of vasoplegia.

Thiamine around the time of planned CPB in adults has not been shown to provide any clinical benefit. We look forward to reading the outcomes of the resulting upcoming RCTs following the published pilot studies.

Based on this review, we cannot support the routine use of thiamine to prevent or treat post-bypass vasoplegia in children.

SUMMARY AND KEY POINTS

- Vasoplegia may complicate CPB and we sought to establish the evidence base for IV thiamine in septic shock and CPB populations.
- There is limited evidence to support the routine use of thiamine in sepsis/ septic shock and only feasibility studies in cardiac bypass.
- No subsequent work, including large RCTs, has been able to match the findings of an unblinded, single centre, before-after study of HAT in sepsis.
- There is insufficient evidence to support the use of IV thiamine to prevent or treat vasoplegia in children following CPB.