EXECUTIVE SUMMARY
(Adapted from the report by SYFUL AZLIE MD FUZI)

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Background

Cardioplegic arrest represented one of the most important (probably the greatest) achievement of cardiac surgery in the last 40 years because it allow, on one hand, the feasibility of treating all heart pathologies with a stopped and bloodless heart and at the same time, encouraging myocardial protection during the ischaemic period. Choosing a cardioplegic solution, however, is a significant issue in modern cardiac surgery and it remains controversial as debate continues on the ideal or optimal strategy. A traditional blood cardioplegia is widely used as a method of myocardial protection but it is administered repeatedly every 15 to 30 minutes, which cause interruption of cardiac procedure and therefore are considered a drawbacks of this technique. Recently, there has been growing interest among cardiac surgeons in the use of a more simplified solution that offers simplified perfusion technique, prolonged ischaemic tolerance, and minimised disruption during surgery. Histidine-tryptophan-ketoglutarate (HTK) or Bretschneider's or Custodiol solution has emerged as an option, especially in lengthy cardiac procedures as it is simple to use, administered as one single dose, and it is claimed to give sufficient myocardial protection for more than two hours of cardiac arrest. Hence, this technology review was requested by the Office of the Minister of Health, Malaysia following a proposal from a company to introduce the usage of Custodiol HTK as a replacement for blood cardioplegia in cardiac surgery conducted in MOH hospitals.

Objective

To identify evidence evaluating the efficacy, safety, and economic implication of Custodiol HTK solution as compared with those obtained using blood cardioplegia in patients undergoing various type of cardiac surgeries.

Methods

A systematic review was conducted. Review protocol and search strategy was developed by the main author while literature search was conducted by an *Information Specialist* who searched for published articles related to myocardial protection that comparing Custodiol HTK with conventional cardioplegia (either blood or extracellular crystalloid) in patient undergoing cardiac surgery. The following electronic databases were searched through the Ovid interface: MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (R) 1946 to Mar 2021. Parallel searches were run in PubMed, US FDA and INAHTA database while additional articles were retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. The last search was conducted on 22nd March 2021.

Results and conclusion:

Efficacy

There was substantial fair level of retrievable evidence to suggest that a single dose of Custodiol HTK is as effective as repetitive blood cardioplegia in protecting the myocardium in patients (adult and paediatric) undergoing various surgical status (elective, urgent or emergent) and type of cardiac surgeries including coronary artery bypass grafting (CABG), congenital heart, valve repair and/or replacement (aortic/ mitral), and aortic surgery. Both cardioplegia strategies had similar rate for:

i. Myocardial infarction (MI) (2.81% versus 1.62%, risk ratio [RR] 1.72, 95% confidence interval [CI] 0.82 to 3.60; p=0.15).

ii. The release of cardiac enzyme (creatine kinase myocardial band [CK-MB]: mean difference [MD] -4.15, 95 CI -12.41 to 4.10; p=0.32, and troponin-I: MD −1.424 ng/ml, 95% CI −7.747 to 4.898; p=0.659).

iii. Electrocardiographic changes (p=0.176).

iv. Low cardiac output syndrome (LCOS) or inotropes support (risk ratio [RR] 1.3, 95% CI 0.86 to 2.05; p=0.20.

v. Rhythm disturbances (atrial fibrillation [AF] RR 1.36, 95% CI 0.74 to 2.50; p=0.32, and ventricular fibrillation [VF] RR 1.84, 95% CI 0.91 to 3.74; p=0.09).

vi. Blood transfusion or blood product use (57.9% versus 58.9; p=0.514).

vii. Cardiopulmonary bypass (CPB) time (MD 2.103 minutes, 95% CI −2.329 to 6.536; p=0.352).

viii. Aortic cross-clamp time (MD 0.276 minutes, 95% CI −2.569 to 3.120; p=0.849).

Findings also indicated that Custodial HTK compared favourably with blood cardioplegia with regard to:

i. Less severe endothelial injury (postoperative endothelin-1 [ET-1] level which is among the indicators of systemic endothelial dysfunction has a higher trend, and the flow-mediated dilation [FMD] value was lower in blood cardioplegia group; p=0.001 and p=0.043, respectively).

ii. Less incidence of postoperative segmental wall motion abnormalities (SWMA) at postoperative echocardiography (p=0.008).

iii. Shorter mechanical ventilation time (5.97 ± 0.69 versus 9.07 ± 1.27 hours; p<0.001).

Safety

There was substantial fair level of retrievable evidence to suggest that patients receiving Custodiol HTK had a similar risk of mortality as patients receiving blood cardioplegia for myocardial protection in adults (odds ratio [OR] 1.237, 95% CI 0.385 to 3.978; p=0.72) and paediatrics (OR 1.11, 95% CI 0.43 to 2.88; p=0.327). Postoperative complications such as pulmonary, gastrointestinal, reoperation for bleeding, and renal dysfunction or renal failure were also comparable between the two strategies.

Organisational issues

There was substantial fair level of retrievable evidence to suggest that no significant differences were identified between patients receiving Custodiol HTK and blood cardioplegia during cardiovascular surgery in terms of:

i. Length of intensive care unit (ICU) stay for both cardioplegia strategies in adults (42.8 ± 17.4 hours to 5.43 ± 7.00 days versus 46.4 ± 19.7 hours to 5.39 ± 8.00 days) and paediatrics (MD -0.08, 95% CI -1.52 to 1.36 days).

ii. Length of hospital stay for both cardioplegia strategies in adults (5.48 ± 0.94 days to 10.14 ± 7.67 days versus 5.99 ± 0.91 days to 10.45 ± 7.00 days) and paediatrics (weighted mean difference [WMD] 0.13, 95% CI -0.85 to 1.12 days).

iii. Intensive care unit readmission rate (2.4 to 2.8 days versus 3.4 to 5.5 days) in adults.

iv. Hospital readmission rate (5.6 to 14.4 days versus 6.9 to 16.1 days) in adults.

Economic implication

The cost-effectiveness of Custodiol HTK for myocardial protection has not yet been formally evaluated. The first study to look closely at the financial analysis of the solution indicated that there was less hospital readmission within 30 days when using Custodiol HTK cardioplegia which contributed to a significant reduction in patient charge by an average USD 3,103 per patient.