MonashHealth

Clinicians, Consumers, Evidence
Centre for Clinical Effectiveness

Rapid Review

Levosimendan for the prevention of severe ventricular dysfunction: A rapid review.

Citation Joseph, C. & Melder, A. January 2018. Levosimendan for the prevention of severe ventricular dysfunction: A rapid review. Centre for Clinical Effectiveness, Monash Health, Melbourne, Australia.

Executive Summary

Background

A formulary application has been submitted to the Technology Clinical Practice Committee (TCPC) of Monash Health for the approval of the use of Levosimendan to optimise cardiac function in patients with severe ventricular dysfunction. Upon discussion of the approval of this drug (Meeting 20/12/2018; Agenda item 5.3), it was deemed necessary to have a clearer picture of the most up to date evidence for Levosimendan. More specifically, there was some concern that some large and recent randomised control trials had been published that were not included in the application, and that these findings from newer trials needed to be included in the application, or synthesised with other evidence. Therefore, CCE were asked to provide a report to include the most recent evidence and to undertake a meta-analysis where possible.

Aim

The aim of this Rapid Review was to summarise the most recent literature regarding the use of Levosimendan in patients with severe ventricular dysfunction.

Findings

Two reviews were included[1,2], the most recent systematic review[2] was an update of a previous systematic review[1]. This was of benefit because there were a number of large randomised control trials conducted since the previous review[1] that showed some non-significant findings which may influence the findings of the previous meta-analysis. As a result, the findings of the most recent systematic review with meta-analysis[2] will be reported in this Rapid Review.

- High quality evidence showed levosimendan is not associated with beneficial or harmful outcomes.
- High quality evidence showed no difference in postoperative acute kidney injury compared to placebo, no difference in renal replacement therapy compared to placebo, no difference in myocardial infarction compared to placebo, no difference in ventricular or supraventricular arrhythmias infarction compared to placebo, and no difference in serious adverse events compared to placebo.
- High quality evidence showed that levosimendan led to a higher incidence of hypotension compared to placebo.
- Pooling all trials together, high risk and low risk of bias trials, levosimendan was associated with a lower mortality than placebo and Dobutamine and appeared to be more affective when administered via bolus.
- When pooling all trials together, levosimendan was associated with lower acute kidney injury compared to placebo and Dobutamine, and lower renal replacement therapy when compared to placebo and Dobutamine, standard inotropic or vasopressor treatment, nitroglycerine, intra-aortic balloon pump, or nothing
- Pooled results did not show a difference in the use of levosimendan and serious adverse or ventricular arrhythmias events compared to placebo, Dobutamine or Milrinone, but did reduce supraventricular arrhythmias when administered post-operatively compared to placebo.
- Pooled results also showed that levosimendan is associated with higher hypertension than placebo, but not dobutamine.
- There was no evidence regarding other specific outcomes contained in the formulary application such as, ventilation time, admission time, mechanical circulatory support, hospital stay, myocardial injury, cardiac output state, or inotropic support.

Conclusions

High-quality evidence suggests perioperative levosimendan is not associated with beneficial nor detrimental effects.

Background

Levosimendan is an inodilator developed for the treatment of acute heart failure[1]. A formulary application has been submitted to the Technology Clinical Practice Committee (TCPC) of Monash Health for the approval of the use of Levosimendan to optimise cardiac function in patients with severe ventricular dysfunction. Upon discussion of the approval of this drug (Meeting 20/12/2018; Agenda item 5.3), it was deemed necessary to have a clearer picture of the evidence for Levosimendan. More specifically, there was some concern that some large and recent randomised control trials had been published that we not included in the application, and that these trials had alternate findings to the trials in the application. Therefore, CCE were asked to provide a report to include the most recent evidence.

Objectives

To search the evidence base for high level evidence regarding the use of Levosimendan in cardiac surgery.

Search strategy, data extraction and synthesis

Ovid medline, Pubmed, Cochrane Library and The National Institute for Clinical Excellence (NICE) were searched by one author (CJ). Search terms and filters can be found in Table 1, and study inclusion/exclusion details can be found in Table 2. Titles and abstracts identified from each database were exported to EndNote X7 (Thompson, Reuters, Carlsbad, California, USA). Papers identified were screened using the set inclusion and exclusion criteria established a priori by one author (CJ). Bibliographies and citations were also searched for additional studies that may not have been identified in the initial database search. Data extraction and synthesis was performed by one author (CJ) and summarised below.

Table 1. Database and search terms.

Database	Search terms	Filters
Ovid Medline	levosimendan, and random*	published since 2016, human studies, RCT
Pubmed	levosimendan, and random*	published since 2016, human studies, RCT
Cochrane library	levosimendan	None
NICE	levosimendan	None

Table 2. Inclusion/Exclusion criteria

Population	**Include:** Patients with severe ventricular dysfunction. **Exclude:** All other patients.
Interventions	**Include:** Administration of Levosimendan.
Outcomes	Mortality, morbidity, ventilation time, ICU admission time, requirement for cardiovascular supports, hospital stay time, myocardial injury, cardiac output, requirement for additional inotropic support, end organ failure.
Context	**Include:** Patient undergoing cardiac surgery. **Exclude:** All other contexts.
Types of evidence	**Include:** High level (Level I and II)
Limits	**Date**: Jan 2016- Jan 2018 **Language:** None

Results

Search results

A total of 328 studies were identified through the database searches (Figure 1). Of these, 327 were excluded, and 1 studies included[1]. Furthermore, searching the reference list of the included study[1] yielded one further study for inclusion[2]. Given the identified studies were of Level I evidence[3], and one study[2] included the most recent large randomised controlled trials, no additional randomised controlled trials were included in this review.

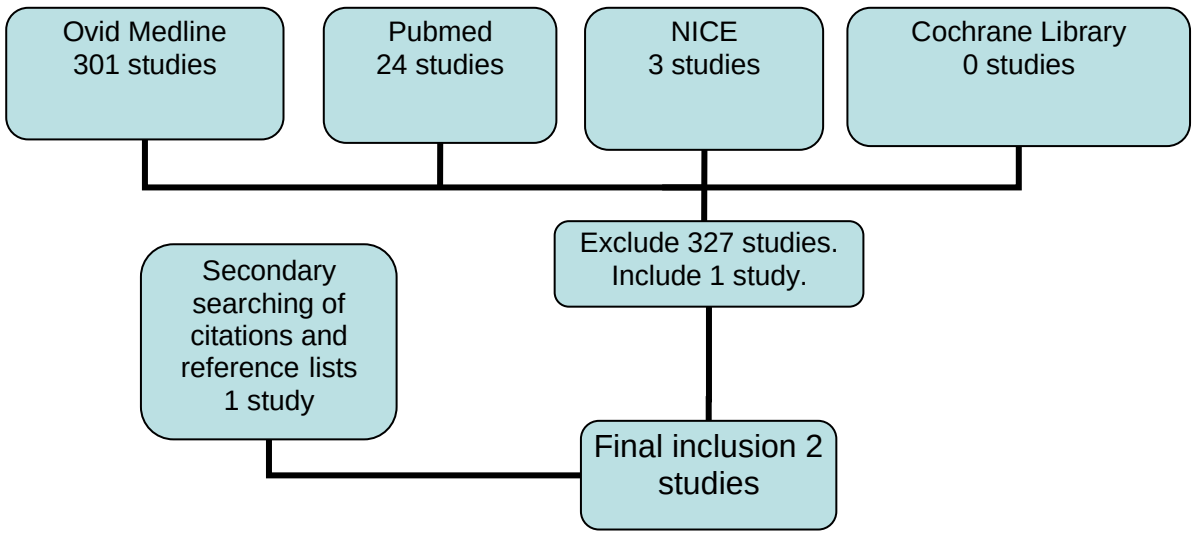

Figure 1. Flow chart showing the inclusion of studies from the search results.

Quality Appraisal

Publication bias is present in the results, showing there were more studies published that reported positive effects of levosimendan than those that did not report positive findings. Publication bias was evident for mortality, need of RRT, MI, ventricular and supra-ventricular arrhythmias. Furthermore, of the 35 trials included in the systematic review[2], only 5 were judged as having a low risk of bias.

Summary of Findings

Upon reading the two included studies[1,2], it was clear that the most recent systematic review[2] was an update of a previous systematic review[1]. This was of benefit because there were a number of large randomised control trials conducted since the previous review[1] that showed some non-significant findings which may influence the findings of the previous meta-analysis. As a result, the findings of the most recent systematic review with meta-analysis[2] will be reported in this Rapid Review.

Based on high quality trials with a low risk of bias, levosimendan is not associated with beneficial or harmful outcomes compared to placebo. However, higher incidence of hypotension and supraventricular arrhythmias could be present when compared to placebo. Upon pooling high quality and low quality trials, levosimendan does decrease postoperative mortality compared to placebo, Dobutamine, or other control, but caution is to be taken around this finding given the small size of the studies and poor quality methodology. Pooled results also suggest levosimendan appears to be more affective when administered via bolus.

Studies with a low risk of bias showed no difference in postoperative acute kidney injury, no difference in renal replacement therapy, no difference in myocardial infarction, no difference in ventricular or supraventricular arrhythmias, and no difference in serious adverse events when compared to placebo. However, studies with a low risk of bias did show that levosimandan led to a higher incidence of hypotension compared to placebo.

The authors did not find any high level evidence regarding other specific outcomes contained in the formulary application such as, ventilation time, admission time, mechanical circulatory support, hospital stay, myocardial injury, cardiac output state, or inotropic support.

Conclusions

The main finding is that, according to high-quality randomized trials, perioperative levosimendan is not associated neither to beneficial nor detrimental effects on some crucial postoperative outcomes.Given the small amount of high quality evidence, it is not clear if the use of levosimendan will benefit or harm patients.

References

1. Pollesello, P., Parissis, J., Kivikko, M., & Harjola, V. P. (2016). Levosimendan meta-analyses: Is there a pattern in the effect on mortality? *International Journal of Cardiology*, *209*, 77-83.
2. Putzu, A., Clivio, S., Belletti, A., & Cassina, T. (2018). Perioperative levosimendan in cardiac surgery: A systematic review with meta-analysis and trial sequential analysis. *International Journal of Cardiology*, *251*, 22-31
3. National Health and Medical Research Council (NHMRC). 2009. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf