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The efficacy and safety of complete pericardial drainage by means of intrapericardial fibrinolysis for the prevention of complications of pericardial effusion: a systematic review protocol

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ABSTRACT

Introduction: Intrapericardial fibrinolysis has been proposed as a means of preventing complications of pericardial effusion such as cardiac tamponade, persistent and recurrent pericardial effusion, and pericardial constriction. There is a need to understand the efficacy and safety of this procedure because it shows promise.

Methods and analysis: We aim to assess the effects of intrapericardial fibrinolysis in the treatment of pericardial effusion. We will search PubMed, the Cochrane Library, African Journals online, Cumulative Index to Nursing and Allied Health Literature, Trip database, Clinical trials.gov and the WHO International Clinical Trials Registry Platform for studies that evaluate the efficacy and/or safety of complete pericardial fluid drainage by intrapericardial fibrinolysis irrespective of study design, geographical location, language, age of participants, aetiology of pericarditis or types of fibrinolytics. Two authors will do the search independently, screen the search outputs for potentially eligible studies and assess whether the studies meet the inclusion criteria. Discrepancies between the two authors will be resolved through discussion and arbitration by a third author. Data from the selected studies shall be extracted using a standardised data collection form which will be piloted before use. The methodological quality of studies will be assessed using the Cochrane Collaboration's tools for assessing risk of bias for experimental studies and non-randomised studies, respectively. The primary meta-analysis will use random effects models due to expected interstudy heterogeneity. Dichotomous data will be analysed using relative risk and continuous with data mean differences, both with 95% CIs.

Ethics and dissemination: Approval by an ethics committee is not required for this study as it is a protocol for a systematic review of published studies. The results will be disseminated through a conference presentation and peer-reviewed publication.

Strengths and limitations of this study

- The planned review will shed light on the evidence to date regarding the efficacy and safety of intrapericardial fibrinolysis in preventing complications of pericardial effusion, and guide future research on this theme.
- This manuscript is prepared according to the recent Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) Statement.
- Unbiased selection of many studies conducted in different settings will strengthen the validity of the review results.
- The main limitation of the planned review will be the heterogeneity of the settings and designs of included studies.

Review registration number: PROSPERO, CRD42014015238.

BACKGROUND

The era of HIV has seen an increase in the incidence of pericarditis.[1] The main cause of pericarditis in Africa is tuberculosis.[2] Pericarditis may complicate to tamponade in the short term, and chronic effusive pericarditis and constrictive pericarditis in the long term. Cardiac tamponade and constrictive pericarditis lead to death if not treated in time. The definitive management of constrictive pericarditis involves pericardiectomy, which is associated with a mortality of up to 14%[3] and is an expensive procedure.[4] Imazio *et al*[5] have shown that tuberculous and purulent pericarditis are more likely to progress

to constrictive pericarditis than pericarditis due to other causes. Ntsekhe *et al*[6] found a 10.9% incidence of constrictive pericarditis over a 6-month period in patients with pericardial effusions that were presumed to be tuberculous. These findings highlight the importance of efforts to prevent progression of pericarditis to constrictive pericarditis.

Various strategies have been used to prevent progression of acute pericarditis to constrictive pericarditis. Early diagnosis and prompt treatment of pericarditis, including treating the underlying cause and draining of effusions, are a major step in this direction. The use of colchicine as adjunctive treatment to prevent recurrent and persistent pericarditis, and thereby reducing the risk of constriction, showed promise in a randomised clinical trial conducted by Imazio *et al*.[7] Corticosteroids have been found to be useful in several trials; however, the findings of Mayosi *et al*[8] have shown that corticosteroids could increase the risk of cancers in patients coinfected with HIV.

Intrapericardial fibrinolysis has been proposed as a way of stemming the development of cardiac tamponade and constriction in patients with effusive pericarditis. The objective of fibrinolysis is to target fibrin formation, to optimise evacuation of a thick fluid, and therefore to prevent both persistent purulent pericarditis and constrictive pericarditis.[9] The procedure is also minimally invasive. A clinical review conducted by Augustin *et al*[9] concluded that intrapericardial fibrinolysis may be useful for prevention of constrictive pericarditis. Cui *et al*[10] investigated the efficacy of intrapericardial fibrinolysis in preventing constrictive pericarditis in patients with infective pericardial effusion, 60% of which were of tuberculous origin. They found that the early employment of fibrinolysis optimised complete evacuation of the pericardial effusion, significantly reduced progress to pericardial constriction and was safe.

In view of the promise held by intrapericardial fibrinolysis, there is currently a need to better understand the safety and efficacy of the procedure. We propose, therefore, to conduct a systematic review to assess the efficacy and safety of intrapericardial fibrinolysis in the prevention of complications of pericardial effusion such as cardiac tamponade, recurrent or persistent effusion, constrictive pericarditis, hospitalisation and death.

OBJECTIVES

1. To determine whether complete pericardial drainage by intrapericardial fibrinolysis reduces the incidence of cardiac tamponade, persistent or recurrent pericardial effusion, constrictive pericarditis, hospitalisation and death in patients with pericardial effusion.
2. To determine whether complete pericardial drainage by intrapericardial fibrinolysis can be performed safely with respect to the incidence of haemorrhage, procedure-related cardiac tamponade, allergy and serious and non-serious adverse events.
3. To determine the appropriate timing, dose and volume of intrapericardial fibrinolysis.

METHODS

Types of studies

We will consider primary studies with the following designs:

- Intervention studies: randomised controlled trials (RCTs), and quasi-RCTs.
- Observational studies: case reports, cohort studies, case–control studies and cross-sectional studies.

Types of participants

People of all ages requiring intrapericardial fibrinolysis for evacuation of pericardial effusion due to any cause.

Study settings

We will include studies that evaluate the efficacy and/or safety of intrapericardial fibrinolysis for preventing constrictive pericarditis irrespective of geographical location.

Types of interventions

All types of fibrinolytics will be considered including (but not limited to) urokinase, streptokinase and tissue plasminogen activator.

Types of outcome measures

The efficacy outcomes of interest to this review are cardiac tamponade, persistent or recurrent pericardial effusion, constrictive pericarditis, hospitalisation and death in patients with pericardial effusion.

The safety outcomes will be the incidence of haemorrhage, procedure-related cardiac tamponade, allergy, serious and non-serious adverse events.

Search methods for identification of studies

We will develop a comprehensive strategy to search for all eligible studies available up to the search date, regardless of language or publication status. For published literature we will search the electronic databases PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE)), African Journals online (AJOL), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Trip database. We will use a combination of the following search terms and tailor them appropriately to the different databases: 'Pericarditis', 'tuberculous pericarditis,' 'purulent pericarditis,' 'pericardiocentesis', 'therapeutic pericardiocentesis,' 'fibrinolytics,' 'intrapericardial fibrinolytics,' 'urokinase,' 'streptokinase' and 'tissue plasminogen activator'. Box 1 below gives the provisional search strategy for PubMed, which will be adapted for each electronic database. To avoid selection bias, two authors will do the search independently. To access unpublished literature, we will

Box 1 Provisional search strategy for PubMed

(((((((pericardiocentesis) OR 'pericardial drainage)' OR 'intrapericardial fibrinolysis)' OR fibrinolysis)) OR ((((('tissue plasminogen activator)' OR urokinase) OR streptokinase) OR fibrinolytics))) AND ((((((((((pericarditis) OR 'tuberculous pericarditis)' OR 'pericardial effusion)' OR 'TB pericarditis)' OR 'purulent pericarditis)' OR 'complicated pericarditis)' OR 'complications of pericarditis)' OR 'complications of pericardial effusions)' OR 'constrictive pericarditis)' OR 'recurrent pericardial effusions)' OR 'persistent pericarditis)' OR 'cardiac tamponade)'.

contact experts in the field of therapeutic pericardiocentesis and search Clinical trials.gov, and the WHO International Clinical Trials Registry Platform.

Data collection and analysis

Two authors will independently screen the search outputs for potentially eligible studies, compare their results and resolve disagreements by discussion and consensus. The two authors will then independently go through the full text of all potentially eligible studies to assess whether the studies meet the inclusion criteria defined by the study design, setting, intervention and outcomes. Discrepancies in the list of eligible studies between the two authors will be resolved through discussion and consensus. A structured and standardised data collection form shall be developed for extracting data from the selected studies. The form will capture key study characteristics, including study design, participants, methods used for diagnosis of pericardial effusion (eg, echocardiography), aetiology of effusions, interventions, risk of bias and outcomes. Prior to use, the extraction form will be piloted on at least three studies identified randomly from the list of included studies.

The methodological quality of studies will be assessed using the Cochrane Collaboration's tool for assessing risk of bias for experimental studies[11] and the 'Cochrane risk of bias assessment tool for non-randomised studies of interventions' for other study designs.[12]

All eligible studies will be summarised and analysed using the Cochrane Review Manager software.[11] Two authors will extract the data, one author will enter the data and the second author will recheck the entries. In the event of discrepancy, the authors shall discuss and resolve the disagreement by discussion and consensus, and if this fails to resolve the disagreement a third author will arbitrate. If the studies are sufficiently similar, we will combine the data using the random effects model. We will examine statistical heterogeneity between study results using the χ^2 test of homogeneity (with a significance α-level of 0.1). We shall quantify statistical heterogeneity between study results using the inconsistency index (I^2).[13 14] When studies cannot be combined for meta-analysis due to diversity of interventions, narrative syntheses will be conducted.

We will stratify analysis by aetiology of pericardial effusion (eg, tuberculous, bacterial), type of pericarditis (eg, effusive, effusive constrictive), modality for diagnosis of pericardial effusions and constriction (eg, use of echography, echography not used) and study design (eg, controlled trials, observational studies). For any meta-analysis involving 10 or more studies, we will use funnel plots to assess the possibility of publication bias. In addition, we will apply the GRADE system to assess the strength of the evidence from the review.[15]

Reporting of protocol and systematic review

We plan to report the findings of the review as recommended in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[16] In addition, we prepared the review protocol according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) statement.[17]

Ethics and dissemination

The planned systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42014015238. Systematic reviews draw on data available in the public domain, and do not need formal ethical review and approval. The findings of this systematic review will be disseminated through peer-reviewed journal publications and conference presentations. To our knowledge, no systematic review on intrapericardial fibrinolysis for the prevention of complications of pericardial effusion has been performed to date. Our discussion of the findings shall be in the light of the relevance of these data in clinical decision-making, and the future research design and direction on this topic.

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Contributors BMM conceived the study, and AK and EAO wrote the first draft of the protocol. AK, CW, EO, AA, AR and BM critically revised successive drafts of the manuscript and approved the final version for publication. CW prepared the final version and is the guarantor of the manuscript.

Competing interests None declared.

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