A META-ANALYSIS ON THE USE OF HEPARIN AND HYDROCORTISONE IN THE PREVENTION OF PHLEBITIS IN PATIENTS WITH INTRAVENOUS NUTRITION

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Background and Objectives:

Peripheral intravenous nutrition is an alternative to patients who cannot feed enterally. A common complication is the development of phlebitis. Additives such as heparin and hydrocortisone have been used to prevent phlebitis, but has conflicting results on literature. This meta-analysis was done to determine its true benefits.

Methods:
A comprehensive literature search was done for trials investigating the use of heparin and hydrocortisone in the prevention of phlebitis. The investigators extracted the relevant data and performed a meta-analysis to determine the ability of heparin and hydrocortisone to prevent phlebitis. Cochrane Risk of bias tool was used to determine the quality of the studies used.

Results:

Three placebo controlled clinical trials were included in the analysis. All three trials assessed the use of heparin and hydrocortisone in the prevention of phlebitis, while two trials assed the rate of occlusion and infection in patients given heparin and hydrocortisone during parenteral feeding.

Heparin and hydrocortisone reduced the rate of phlebitis OR 0.31 [95% CI 0.17, 0.56, p=0.0001]. The rate of occlusion between heparin and hydrocortisone versus control is similar OR1.01 [95% CI 0.14,7.44 p=0.99].. Likewise, rate of infection is similar OR 1.01 [95% CI 0.14,7.44 p=0.99]. The risk of adverse events were not assessed in this study since all the studies included did not investigate this endpoint.

Conclusion:

The addition of heparin and hydrocortisone reduced the rates of phlebitis. However, the rate of line occlusion and infection was similar. The use of heparin and hydrocortisone extended the total duration of feeding attainable.

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Background

Peripheral intravenous nutrition is an important therapeutic modality in many clinical situations particularly as an alternative to patients who cannot feed enterally. In the US, the number of patients receiving peripheral intravenous infusions has been increasing throughout the years, peaking at 43,350 patients in 2012. [1]

The most important complication in the use of Peripheral intravenous nutrition is thrombophlebitis. The osmotic content as well as the infusion rate greatly affects the incidence of thrombophlebitis. [2] Heparin is a common anticoagulant which has antithrombotic properties. Heparin inhibits fibrin and eventually clot formation both in vitro and in vivo. [3] Hydrocortisone is a potent anti inflammatory agent due to its ability to biosynthesis of prostaglandins and leukotrienes. [4]

Additives such as heparin and hydrocortisone have been used to prevent phlebitis, but has conflicting results on literature. This meta-analysis was done to determine its true benefits.

Methods

A comprehensive literature search was done for trials investigating the use of heparin and hydrocortisone in the prevention of phlebitis. The investigators extracted the relevant data and performed a meta-analysis to determine the ability of heparin and hydrocortisone to prevent phlebitis. Cochrane Risk of bias tool was used to determine the quality of the studies used.

Criteria for considering studies for this review

The authors included all clinical trials comparing the effect of heparin and hydrocortisone to control on the rate of phlebitis.

Types of studies

Clinical trials comparing the effect of the effect of heparin and hydrocortisone to control on the rate of phlebitis.

Types of participants

Participants in the trials considered were adults needing intravenous nutrition for whatever reason

Types of interventions

Trials included used heparin and hydrocortisone versus control

Outcomes

The primary outcome analyzed is the rate of phlebitis. Other outcomes assessed was the rate of occlusion, rate of line infection and duration of use of the IV access.

Search methods for identification of studies

The investigators conducted a comprehensive literature search for trials investigating the effect of heparin and hydrocortisone vs control on the rate of phlebitis. The investigators searched MEDLINE, EMBASE, and the Cochrane database for trials published on the aforementioned subject from inception to November

2017. The following search terms were used in free text and MeSH: heparin, steroids, phlebitis, intravenous nutrition, parenteral nutrition. The investigators also examined the references of the included trials to identify additional studies that may be related to the subject.

Data collection and analysis

All investigators reviewed the abstracts independently, and identified articles meeting the inclusion criteria. Study eligibility was determined by consensus among the authors.

Selection of studies

All investigators independently performed the literature search to identify the relevant studies. Trials were selected from the search results based on the specified inclusion criteria. Any disputes were resolved via consensus.

Data extraction and management

Data from the included trials were extracted by independently using the Cochrane Data Extraction Template. The following information were obtained from each study: total number of included and excluded participants, total number of feeding episodes, participants lost to follow-up and the reasons for being lost to follow-up, baseline characteristics of the populations, dose and duration of treatment heparin and hydrocortisone, treatment with other agents aside from heparin and hydrocortisone, rate of phlebitis, and as applicable, rate of occlusion, duration of IV access, dislodgement and completion of feeding rate.

Assessment of risk of bias in included studies

Methodological quality of included trials was assessed independently by the investigators. The investigators used the Cochrane Assessment of Risk of Bias Tool to appraise the trials obtained.

Based on the aforementioned tool, trials were rated as low risk for bias if all domains were rated as low risk and bias is unlikely to alter the results. Trials were rated as unclear risk for bias if at least one domain is rated as unclear risk. Trials were rated as high risk for bias if at least one domain is rated as high risk for bias and this may weaken the confidence in the results. Any disputes were resolved via consensus.

Measures of treatment effect

Dichotomous outcomes were analyzed by calculating the relative risk and 95% confidence interval. Trials were combined and Forest plots were generated using the Review Manager for Windows, version 5.3.

Dealing with missing data

In circumstances where data was missing, the investigators derived some of the data by computation using statistical methods described in the Cochrane handbook.

Assessment of heterogeneity

Heterogeneity was assessed using the I-squared statistic. A value of less than 25% was classified as minimal heterogeneity, less than 50% as moderate heterogeneity and greater than 50% as significant heterogeneity. Heterogeneity was also assessed using the chi-squared test with a $p<0.10$ indicating heterogenous results.

Assessment of reporting biases

Publication bias was assessed using visual inspection of Funnel plot and the method proposed by Begg and Egger.

Results

Trial characteristics

A total of 68 articles were identified from the literature search. After doing an abstract review, the investigators identified five trials**.** Sixty three out of the sixty eight studies found in the database search were excluded because they did not meet criteria set by the authors.

Two trials were not included due to lack of availability of the article on the different journals, leaving three articles in total. All three trials included in this analysis were published from 1985 to 2006 and were experimental-controlled trials. One trial was randomized but open label, while one trial was non randomized but blinded. One trial was randomized and blinded.

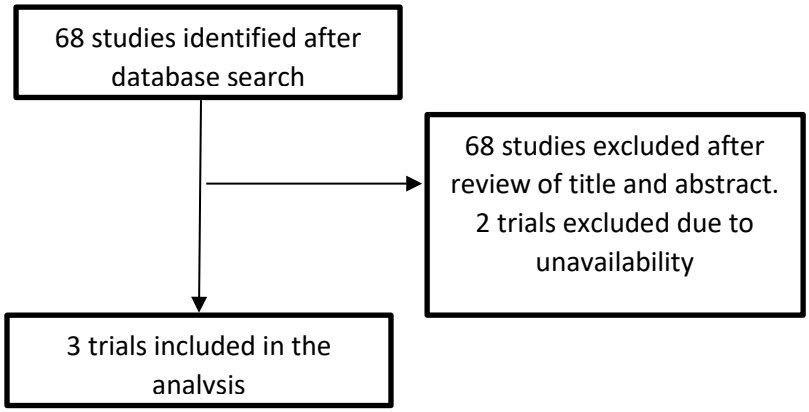


Figure 1. Flow chart of literature search and trial selection.

All three trials investigated the rate of phlebitis, and the lifespan of the IV access. Only two studies investigated the rate of occlusion and rate of infection. The quality of the trials included was assessed using the Cochrane Risk of Bias Tool. All included studies did not report allcation concealment. While all but one studies were double blind. Overall the studies were still deemed valid and was included in the analysis

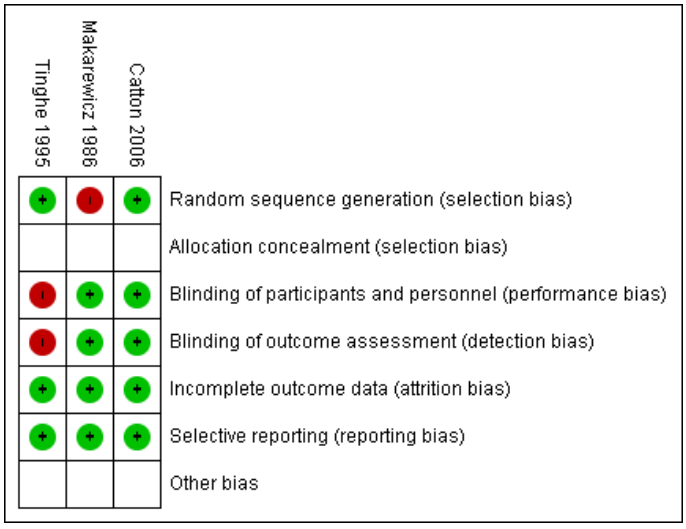


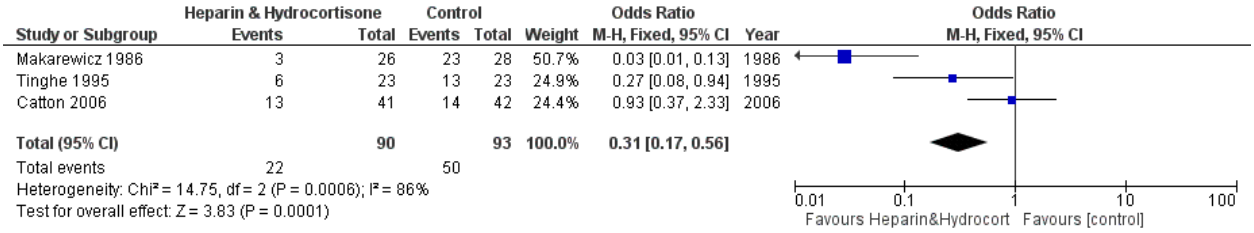
Figure 2. Cochrane assessment of risk of bias tool

Table 1. Characteristics of each trial included

	Makarewicz 1986	Tinghe 1995	Catton 2006
Study type	Non randomized, Double blind	Randomized, Open label	Randomized, double blind
N	54 patients	46 patients	130 episodes of PVN (113 patients)
TPN	2400 ml per day 5 percent dextrose and 3.5 percent amino acid solution with a pH of 5.7 and an osmolarity of 780 mOsm/liter.	TPN 2500 mL provided 1800 kcal nonprotein energy per day 800 kcal from a solution of 200 g of glucose with 120 mmol sodium and 80 mmol potassium and 1000 kcal in the form of 20% lipid	2400 ml per day 2500 mL provided 1800 kcal nonprotein energy per day 800 kcal from a solution of 200 g of glucose with 120 mmol sodium and 80 mmol potassium and 1000 kcal in the form of 20% lipid
Inclusion	All patients requiring nutritional support	Present of an adequate peripheral vein in the proximal forearm of antecubital fossa	Presence of an adequate peripheral vein in the antecubital fossa Nutritional support more than 7 days
Intervention	Heparin 1000, hydrocortisone 5mg, NaOH 1.8meqs per liter of 1L of peripheral parenteral nutrition	Heparin 1500 + hydrocortisone 15mg + glyceril trinitirate patch 5mg	Heparin 1500 or hydrocortisone 15mg or both
Outcomes	Peripheral vein thrombosis Duration of access	Peripheral vein thrombosis Occlusion Infection Duration of access	Peripheral vein thrombosis Occlusion Dislodgement Infection Completion of feeding Duration of access

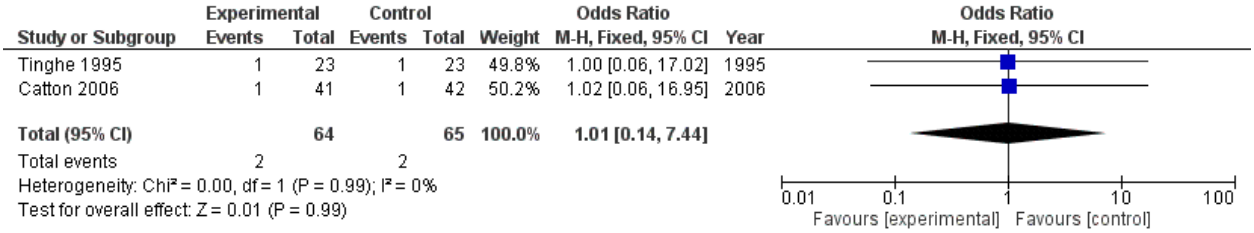
Trial results

Primary outcome: rate of phlebitis



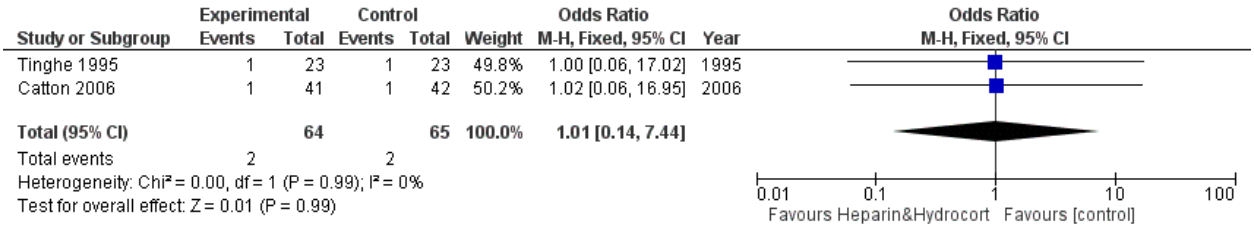
Pooled data on the use of the combination of heparin and hydrocortisone reduced the rate of phlebitis compared to placebo with an odds ratio of 0.31 [95% CI 0.17, 0.56, p=0.0001]. The heterogeneity among studies was however high.

Primary outcome: occlusion rate



Pooled data on the use of the combination of heparin and hydrocortisone versus control showed that the rate of occlusion was similar between groups similar with an odds ratio of 1.01 [95% CI 0.14,7.44 p=0.99]. The heterogeneity was small.

Secondary outcomes: adverse events – infection rate



Pooled data on the use of heparin and hydrocortisone versus control showed that the rate of infection between these groups is similar with an odds ratio of 1.01 [95% CI 0.14,7.44 p=0.99]. The heterogeneity was likewise small.

Discussion

Analysis of the trials showed that the addition of the combination of heparin and hydrocortisone reduced the rates of phlebitis although the rate of line occlusion was similar. Furthermore, this analysis showed that the rate of infection when heparin and hydrocortisone was added was no different from control. Furthermore, the usual duration of the peripheral access in the control arms of the included studies was approximately two days compared to five to seven days in the treatment arm.

The studies included did not explore the interaction of heparin with the components of the parenteral nutrition. ASPEN cautions in the addition of heparin in parenteral nutrition due to its possible influences on the integrity of the emulsion [2]. However most of the cited articles are outdated. Studies cited by ASPEN that showed instability of heparin in parenteral nutrition were done in the 1980s. These formulations may be significantly different from our present formulations available.

In 2014, Foinard et al in did an in vitro study exploring the effects of heparin on parenteral nutrition and have concluded that there is no loss of activity of heparin when it is mixed with parenteral nutrition and furthermore there was no interaction with other nutrient components seen [10]. Ultimately, it is till prudent to check the product insert of parenteral nutrition formulas to check for compatibility with non-nutrient additives.

Ultimately, there are many ways to prevent phlebitis during parenteral nutrition therapy and the addition of heparin and hydrocortisone is a possible addition to the available armament of physicians.

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