IMPACT OF LOW-DOSE HEPARIN ON DURATION OF PERIPHERALLY INSERTED CENTRAL CATHETER AT THE NEONATAL INTENSIVE CARE UNIT: A META-ANALYSIS

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ABSTRACT

OBJECTIVES: To determine efficacy of continuous heparin infusion vs placebo on maintenance of peripherally inserted central catheter line among neonates admitted at the NICU.

METHODS: This is a meta-analysis of randomized controlled trials reported in accordance with PRISMA checklist. Cochrane Risk-of-bias tool was used in assessment of reporting biases. Pooled risk ratios were estimated using random- or fixed-effects model.

RESULTS: Of 4519 studies identified, 4 studies were included, and all have low risk of bias. Meta-analysis showed that continuous heparin infusion on PICCs had significantly higher duration of catheter patency compared to the placebo group (MD=2.22, 95%CI=1.03-3.14, p-value<0.00001). Heparin group also had decreased risk of occlusion (RR=0.47, 95%CI=0.94, p-values=0.03) compared to control. The risk for other adverse events such as thrombosis, infection, IVH progression, and mortality was comparable between the two groups.

CONCLUSION: Continuous heparin infusion in PICC fluids can prolong duration of catheter patency by 2.2 days and reduce risk of catheter-related occlusion by 50%, without having significant effect on incidence of other adverse events.

RECOMMENDATIONS: Continuous heparin infusion on PICC fluids should be part of maintenance and care policy at the NICU, but precautions should be followed to prevent adverse outcomes. Systematic review of intermittent heparin flushing can be a window of opportunity.

KEYWORDS: heparin, peripherally inserted central catheter, patency, neonates.

INTRODUCTION

Intravenous access is an important and crucial part of the neonatal intensive care unit; however nothing can be more difficult, time-consuming and frustrating than obtaining and maintaining a reliable vascular access in newborns. Peripheral intravenous catheters are the easiest and safest means of achieving vascular access. As newborn veins are very tiny, the frequency of cannula change is as high as the incidence of thrombophlebitis. Up to 91% of peripheral lines are removed prematurely due to cannula complications in this population, and peripheral dwell time averages only 27-49 hours (1). Repeated skin breaches expose the vulnerable newborns to infection and painful experiences, which might eventually affect neurodevelopmental outcome. Due to

these factors, maintaining access with peripheral catheters in this population is often difficult and impractical. Therefore, when prolonged support is required, a central line is typically placed. Central venous catheters are considered an indispensable tool in the Neonatal Intensive Care Unit (NICU). Recent technological innovations in catheter size and materials have allowed vascular access in even smaller and sicker infants both for therapeutic and diagnostic purposes, while recognizing its risks to life and limb (2). Preterm and critically ill infants who are slow to tolerate enteral feeds rely highly on venous access for administering fluids, parenteral nutrition, medications, and even blood products, and thus it is vital to their survival. To date, the most frequently used central venous catheters are umbilical vein catheters and peripherally inserted central catheters (PICC).

Peripherally inserted central catheters are routinely used at the NICU, both in term and preterm infants to provide intravenous access for prolonged therapy and parenteral nutrition (3). PICCs are readily available in our setting and can be conveniently inserted at the bedside by trained medical staff without the need for surgical intervention. They are associated with a reduced incidence of complications such as thrombosis, catheter occlusion, and leakage compared to short peripheral catheters (4). Despite these advantages, PICCs are associated with various complications such as occlusion, infection, thrombosis, breakage, migration, and displacement (5). The incidence of PICC-associated complication rates in literature varies from 27-42% (6,7). Collachio stated that most common complication is phlebitis at 32.1%, next is infection at 25.5% and occlusion comes in closely at 17.4%. With regards total parenteral nutrition (TPN) use in the NICU to optimize nutrition for sick neonates, catheter blockage and sepsis are two major complications that have been associated with its administration (8). PICCs have been more prone to possible occlusion and thrombosis than other kinds of central access.

Heparin has been utilized as an antithrombotic agent for maintaining catheters for decades. Anticoagulation effect by heparin is predominantly mediated through antithrombin III in plasma. Due to rapid pharmacokinetics and relatively low cost, heparin is widely and routinely used in clinical practice (9) including among the neonatal population to prevent catheter-related occlusion and malfunction by thrombosis. In some countries and medical facilities, infusion or flushing solutions have become standard procedures. Despite its routine use, several clinical trials studying heparin in catheter maintenance failed to find significance of its efficacy. There are also pressing concerns about the safety of heparin as it has been shown to induce thrombocytopenia, increase bleeding risk, and promote allergic reactions (10). Several randomized trials with inconsistent or conflicting results have been published, prompting further debate on its use for peripherally placed catheter maintenance.

STUDY OBJECTIVES

General Objective:

This study aims to determine the efficacy of continuous heparin infusion on maintenance of peripherally inserted central catheter line among neonates admitted at the Neonatal Intensive Care Unit.

Specific Objectives

1. To determine efficacy of continuous heparin infusion vs placebo on PICC lines at NICU to improve: Mean duration of catheter patency; Catheter-related occlusion incidence rate; Catheter-related thrombosis incidence rate; and Catheter-related bacteremia incidence rate.

2. To determine incidence of adverse events with continuous heparin infusion on PICC lines.

METHODOLOGY

This study employed meta-analysis and reporting was accomplished in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Guidelines. We performed a systematic computerized literature search from various publicly accessible scientific journal databases such as PUBMED, MEDLINE, Cochrane Central Registry of Controlled Trials, and Google Scholar. Database of unpublished trials in https://clinicaltrials.gov, Philippine Health Research Registry, and other foreign clinical trial databases were also checked. Keywords used in the literature search were "peripherally inserted central catheter" or "PICC" or "catheters" [MeSH] and "heparin" [MeSH] and "neonates" or "infant/newborn" [MeSH] or "neonatal intensive care unit" or "intensive care units, neonatal" [MeSH] and "occlusion" [MeSH] or "thrombosis". Neonatology experts were asked for possible reference articles or unpublished studies. Reference and citation lists of the eligible studies have been reviewed also to further look for relevant articles. Duplicate studies were removed, and screening of titles and abstracts was done. Studies were excluding using the inclusion and exclusion criteria and remaining studies were screened using their full text.

Eligibility Criteria

Type of Studies: All prospective randomized controlled trials (from year 2001 to present) determining the effect of heparin infusion on patency of PICC line and other outcomes were included in this meta-analysis.

Type of Participants: All included trials involved neonates (both full term and preterm, regardless of diagnosis and clinical status) on peripherally inserted central catheter lines admitted at the intensive care unit.

Two review authors (primary investigator and co-investigator) independently screened the abstracts and titles of yielded studies with reference to the specified eligibility criteria (see Annex A). No disagreements happened between the reviewers.

Assessment for risk of bias was performed using the Review Manager program, and version 2 of the Cochrane risk-of-bias tool for randomized trials tool (RoB 2.0). Each included article was appraised by the primary investigator and co-investigator based on 5 bias domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Co-investigator and research assistant performed data extraction. Extracted data on study design, patient population, facility location, comparator, intervention, and all outcomes measured were recorded and tabulated. The number of central line days, incidence of catheter occlusion, catheter thrombosis, catheter-related infection, and adverse events if any were also recorded on standardized format. Primary outcome pooled in this analysis is the mean duration of catheter patency (in days) for both the intervention group and comparator group. Secondary outcomes collated were the following in each group: incidence of catheter-related occlusion, incidence of catheter-related thrombosis, and catheter-relation bloodstream infection. Adverse events like incidence thrombocytopenia and hemorrhage, if any, were also collated from each study group. The meta-analysis was performed using the Reviewer Manager Software, version 5.3 (Cochrane Collaboration, UK). Relative risk for incidence of catheter-related occlusion, catheter-related thrombosis, and catheter-related bacteremia were estimated, and random effects method was used to estimate the pooled effect. Mean difference for mean duration of catheter patency between the groups was used. Forest plots of the outcomes of interest were generated to display effect estimates and confidence intervals for both individual studies and meta-analysis. The level of statistical significance was set at $p<0.05$, with a 95% confidence interval. To assess heterogeneity between studies for the outcome, chi-squared test was used as included in the forest plot of RevMan program, with $P<0.10$ indicating significant heterogeneity, and I2 with suggested thresholds for low (24-49%), moderate (50-74%) and high (>75%) values. Risk of publication bias was detected with the use of funnel plot.

RESULTS

The initial search through databases and other sources yielded 4,519 references. Most articles were excluded due to different study designs, population, and other outcomes used. Nine full text articles were reviewed for eligibility. Out of the nine, three full text articles were excluded due to a different manner of applying the intervention, one was excluded due to a different catheter used for the patients, and one trial was excluded due to non-availability of study results. A total of four (4) studies were then included in the analysis. A flowchart of study selection is summarized in Figure 1.

This paper included 4 studies, all of which are prospective randomized controlled trials comparing the effect of continuous heparin infusion versus placebo primarily on patency duration of peripherally inserted central catheter amongst neonates admitted at the neonatal

intensive care unit. Two studies were done in 2010 while the other two were done in 2007. For the secondary outcomes, all four studies tested risk for occlusion and bacteremia. Only three studies (Birch, Uslu, and Kamala) analyzed risk for mortality, while only at least two of the four studies tested for the other secondary outcomes like risk for thrombosis, phlebitis, and intraventricular hemorrhage (Table). Risk of bias of the selected articles was judged based on Risk of bias tool (ROB 2.0) and Review Manager 5.0 bias assessment tool. All four included studies in this paper have low risk of bias based on five different domains as summarized in Figure 2.

PRIMARY OUTCOME: Effect of continuous heparin infusion on PICC patency.

Mean duration of catheter patency (in days) for both the intervention group and comparator group was primarily pooled in this study. The overall effect estimate was calculated as mean difference with 95% confidence interval. Pooled summary estimates were derived using the fixed effects method in Review Manager 5.3. Meta-analysis results (Figure 3) indicates that patients with continuous heparin infusion on PICC lines had significantly higher duration of catheter patency compared to the control group (MD=2.22, 95%CI=1.03-3.14, p-value<0.00001). Heparin use can prolong catheter patency by an average of 2.2 days. The level of heterogeneity using I2 is 38% (low).

SECONDARY OUTCOME 1: Relative risk for incidence of catheter-related occlusion and random effects method was used to estimate the pooled effect with 95% confidence interval. Pooled data (Figure 4) showed that there is 50% lower risk for occlusion in the continuous heparin group compared to the control group (RR=0.47, 95%CI=0.94, p-value=0.03). There is moderate heterogeneity (I2 =62%) but visual analysis of the forest plot showed that 3 out of 4 studies leaned more towards heparin than control having less incidence of catheter-related occlusion. Moderate heterogeneity can probably be explained by one study (Birch et al., 2010) leaning more towards control than intervention. A subgroup analysis was done to check for possible causes of heterogeneity by: 1) sample size and 2) heparin dose. Kamala's trial has the smallest sample size and has a different dose of heparin used (1 IU/ml) hence a subgroup analysis excluding this trial was done (Figure 5), however there was even higher heterogeneity (I2 =73%).

SECONDARY OUTCOME 2: Only two of four studies measured risk of thrombosis as their outcome. Relative risk for incidence of catheter-related occlusion and fixed effects method was used to estimate the pooled effect with 95% confidence interval. Pooled data (Figure 6) showed no significant difference between the two groups in terms of risk for thrombosis (RR=0.88, 95%CI=0.51-1.53, p-value=0.65).

SECONDARY OUTCOME 3: All four studies measured risk of sepsis as one of their outcomes. Pooled data (Figure 7) showed no significant difference was observed between the two groups in terms of

risk for catheter-related sepsis or bacteremia (RR=1.01, 95%CI=0.61-1.67, p-values=0.97).

SECONDARY OUTCOME 4: Adverse events noted on the included studies were intraventricular hemorrhage progression, phlebitis, and mortality rate. Two of the four studies measured risk for intraventricular hemorrhage (IVH) (Kamala 2007 and Birch 2010) and risk for phlebitis (Kamala 2007 and Uslu 2010). There was no significant difference in risk for progression of intraventricular hemorrhage (Figure 8, RR=0.52, 95%CI=0.20-1.36, p-value=0.18), and risk for phlebitis (Figure 9, RR=0.80, 95%CI-0.40-1.59, p-value=0.52) between the heparin and control groups.

Three of four studies measured risk for mortality (Kamala 2007, Birch 2010, Uslu 2010), and pooled data shows no significant difference between the intervention and control groups (Figure 10, RR=0.75, 95%CI=0.35-1.64, p-value=0.48). Funnel plot (Figure 11) of the four included studies in this meta-analysis shows a symmetric-shape funnel that indicates publication bias is unlikely.

DISCUSSION

Peripherally inserted central catheters are common in the neonatal intensive care unit for various purposes but is associated with some complications. Most common complications include catheter occlusion prompting its early removal. Heparin is widely used to prevent occlusion however it has also known complications such as allergic reaction, risk of bleeding, and thrombocytopenia. Only a few studies among neonates have been found in literature. Kamala et al. conducted their study on 66 neonates with PICCs used for TPN administration (14). Results showed that the difference in the occurrence of blocked catheters between the two groups was not statistically significant (incidence of 14.3% in heparin group versus 22.6% in no heparin group, p-value= 0.4). A higher percentage (62.9%) of infants in the heparin group received a full course of TPN successfully as compared with those in the no heparin group (48.4%), but this was not statistically significant [relative risk (RR)= 0.6, 95% CI 0.2 to 1.8, p-value= 0.30].

Contradicting results were seen in the study of Shah et al. (19) which compared the usability of PICC when incorporated with heparin amongst a larger sample (201 neonates). The duration of catheter patency was 267 ± 196 hours for the heparin group, while 233 ± 194 hours for the no heparin group (p-value= 0.22). More so, the occlusion rate of the PICC in the heparin group was 6% as compared to the 31% of the no heparin group, which was regarded as statistically significant (p-value= 0.001). Thrombosis and catheter-related sepsis were noted to have no differences (p-value> 0.05), with values of 20% versus 21%, and 10% versus 6%, respectively. The authors concluded that the use of heparin infusion can prolong the duration of peripherally inserted central venous catheter usability, without increasing the incidence of adverse effects. This allows a higher percentage of therapy completion among neonates.

In this meta-analysis, patients who used heparin significantly had longer duration of catheter patency compared to the control group, while the risk for occlusion was also lower. A longer duration of catheter patency for even just +2.2 days will be beneficial for neonatologists as it can make or break the success of their management plan. The risk for other adverse events such as thrombosis, infection, phlebitis, and mortality were comparable between the two groups. The strong evidence shown in this meta-analysis was based on the large effect size (MD=2.22 for duration of catheter patency and RR=0.47 for occlusion), lack of bias in the included studies, and minimal risk for publication bias. These results can be comparable to You's[9] systematic review and meta-analysis which concluded that use of heparin as continuous infusion significantly prolonged the duration of catheter patency (SMD 0.90, 95%CI, 0.48-1.32, $p<0.001$), reduced rates of infusion failure (RR 0.82, 95%CI=0.76-0.92, $p<0.001$) and occlusion (RR 0.82, 95%CI=0.69-0.98, $p<0.05$). But contrary to this meta-analysis, Yao also concluded that risk of phlebitis was significantly decreased with continuous heparin infusion. Studies used in Yao's review were either on intermittent or continuous heparin versus normal saline or placebo on different peripheral intravenous catheters (including PICCs) encompassing all ages (6/32 studies among neonates).

This meta-analysis showed improved outcomes with continuous infusion of heparin; however results must be interpreted with caution since risk for adverse events is still comparable especially among our vulnerable patient population. Recommendation for resuming heparin incorporation to PICC fluids in the NICU is justified but compliance to strict protocols including its dose, manner of preparation, and monitoring is very crucial to achieve target clinical outcomes. This meta-analysis focused on the effect of only one method of heparin incorporation to PICC fluids, which is continuous infusion of heparin. More recent literatures will mention on intermittent heparin incorporation, which is heparin flushing. Important variables like osmolality of fluids or medications infused via PICC, which can be confounding factors in the study results, has not been controlled.

CONCLUSIONS AND RECOMMENDATIONS

Continuous heparin infusion in PICC fluids can prolong duration of catheter patency by an average of two (2) days and reduce the risk of catheter-related occlusion by 50%, without having significant effect on incidence of catheter-related thrombosis, bacteremia, and other adverse events. Catheter occlusion leading to premature removal of PICC has been the unit's primary concern these recent months, and with the overall results of this study, we therefore recommend that continuous heparin infusion on PICC be part of maintenance and care policy at the Neonatal Intensive Care Unit. Just like any other chemical intervention, special precautions should be followed, and subjects monitored for complications to prevent adverse outcomes. Further randomized controlled trials are suggested to explore the benefits of lower dose heparin in discussed outcomes and to study its

economic impact. Systematic review of heparin flushing can also be a window of opportunity.

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Table: Characteristics of Studies Included in the Meta-Analysis

STUDY ID Author, Year, Location	Study Title	Population	Method/Design	Comparator	Intervention (dose)	Study Outcomes
A Kamala, etal. 2007 Kuala Lumpur, Malaysia (Hospital Universiti Kebangsaan Malaysia-NICU)	Randomized controlled trial of heparin for prevention of blockage of peripherally inserted central catheters in neonates	Inclusion: All admitted neonates at NICU with PICC for the purpose of receiving TPN Exclusion: Neonates with clinical evidence of bleeding tendencies, severe IVH Gr3-4, platelet count <100, prolonged APTT	Randomized, double-blind, controlled study	No heparin group	Heparin 1unit/ml	Duration of catheter patency, incidence of catheter blockage, incidence of catheter-related sepsis, IVH, disturbances in lipid metabolism and coagulation studies
B Shah, etal. 2007 Ontario, Canada (4 Tertiary care NICUs)	A Randomized Controlled Trial of Heparin Versus Placebo Infusion to Prolong the Usability of Peripherally Placed Percutaneous Central Venous Catheters (PCVCs) in Neonates:	Inclusion: Neonates requiring percutaneous central venous catheter Exclusion: Grade 3-4 IVH, recent onset presumed/confirmed sepsis, bleeding diathesis, DIC, platelet count <100, preexisting liver disease	Prospective, randomized double-masked, placebo-controlled trial	Placebo (10% or 5% dextrose)	Heparin 0.5 IU/ml	Duration of catheter use, catheter occlusion, catheter-related sepsis, thrombosis, other causes of catheter removal
C Birch, P., etal 2010 New Zealand (Wellington Hospital-NICU)	A randomized, controlled trial of heparin in total parenteral nutrition to prevent sepsis associated with neonatal long lines	Inclusion: Neonates requiring long line for TPN Exclusion: Those with previous long line successfully inserted and utilized	Prospective, randomized, double-blind controlled trial	No heparin	Heparin 0.5 IU/ml	catheter-related sepsis, progression of IVH, Candida line infections, line extravasation OR occlusion
D Uslu, S. etal 2010 Istanbul, Turkey (Diyarbakir Children's Hospital-NICU)	The effect of low-dose heparin on maintaining peripherally inserted percutaneous central venous catheters in neonates	Inclusion: Neonates requiring percutaneous central venous catheter Exclusion: Neonates with bleeding tendencies, Grade 3-4 IVH, recent suspected or confirmed sepsis, thrombocytopenia, DIC, arrhythmia, congenital malformations	Prospective, randomized, controlled, double-blind clinical trial	No heparin	Heparin 0.5 IU/ml	Duration of catheter, phlebitis, infection, blockage, neonatal death

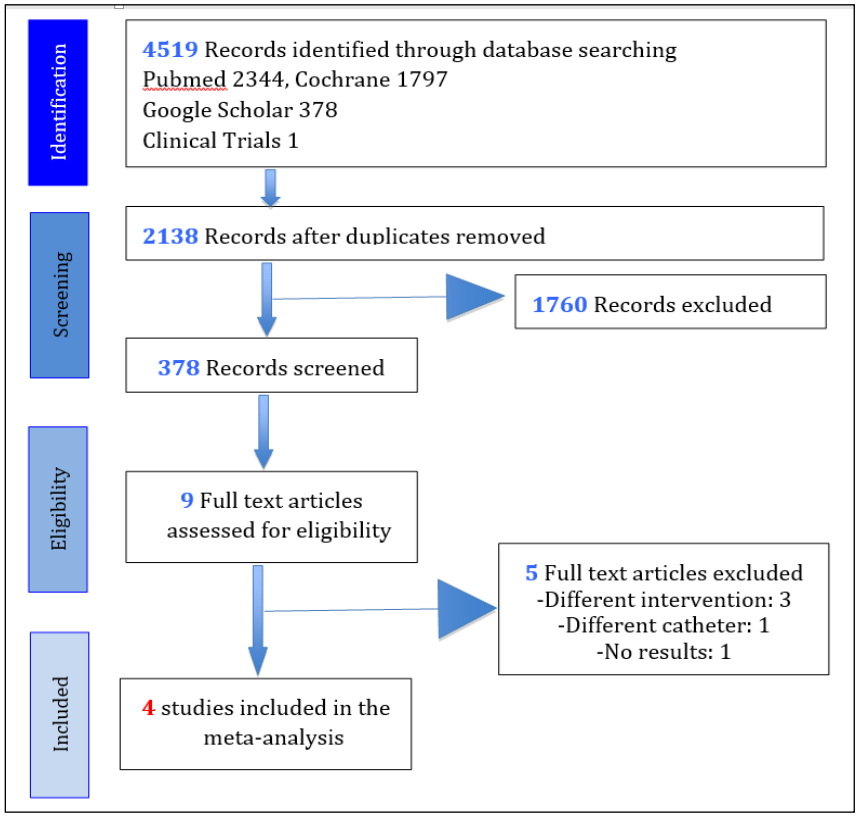

Figure 1: PRISMA Flowchart of Literature Search

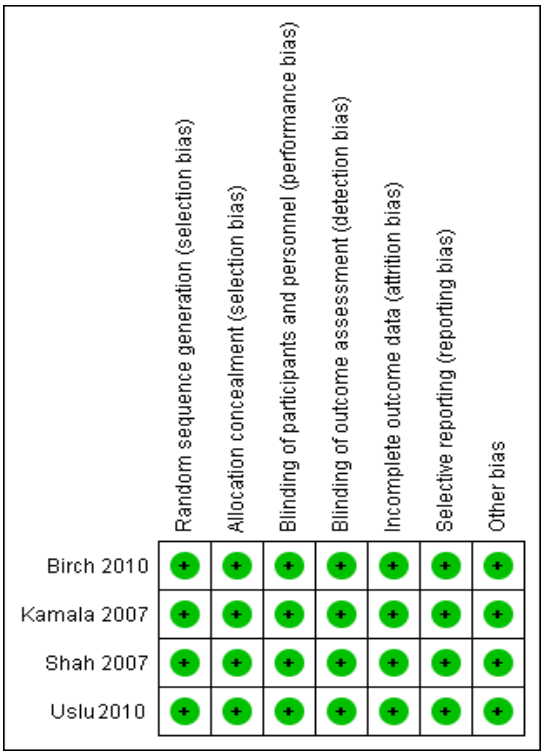

Figure 2. Risk of bias summary of included studies

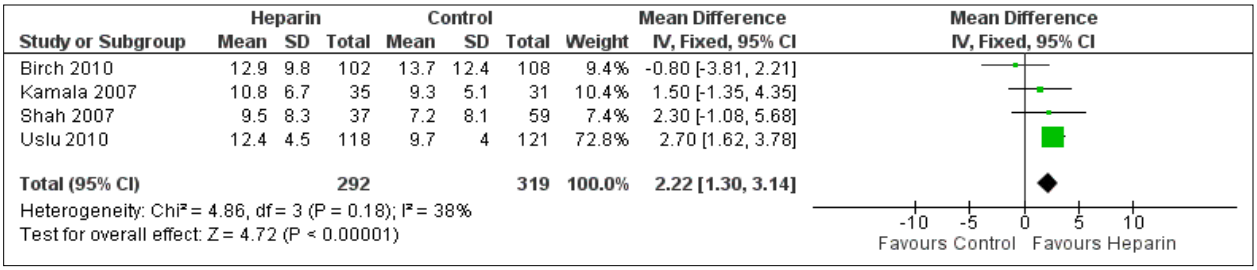

Figure 3: Effect of Heparin on Duration of Catheter patency

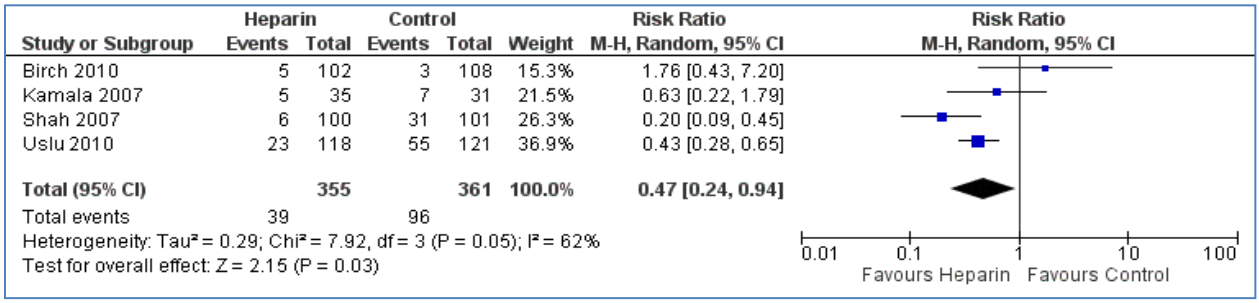

Figure 4: Effect on Heparin on Incidence of Catheter-related occlusion

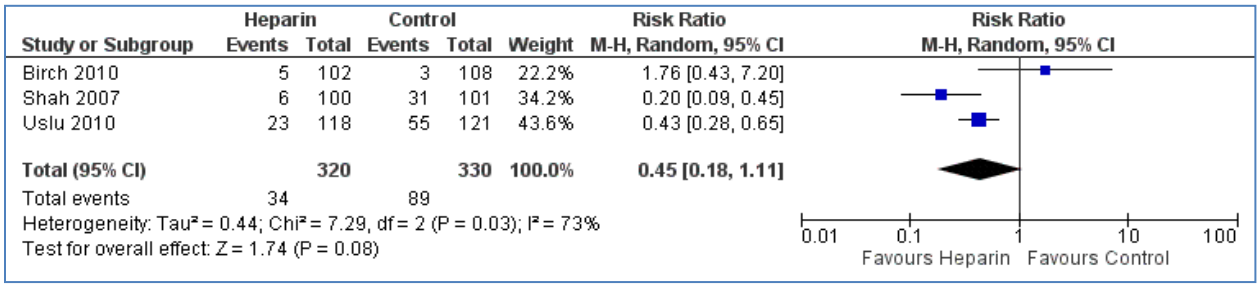

Figure 5: Effect of Heparin on Incidence of Catheter-related occlusion (Subgroup analysis)

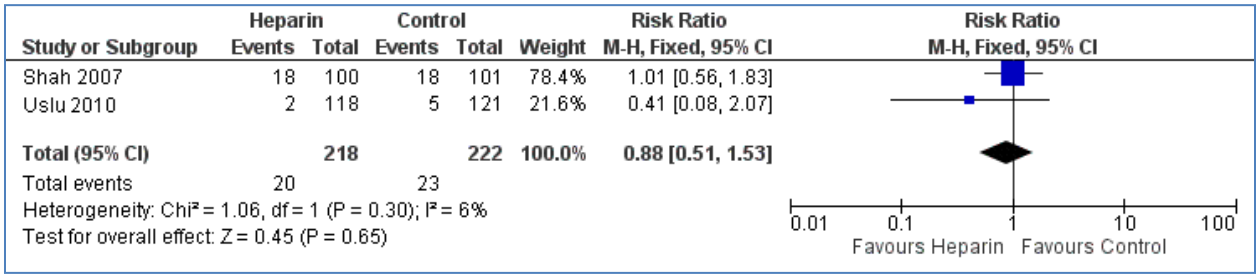

Figure 6: Effect of Heparin on Incidence of Catheter-related thrombosis

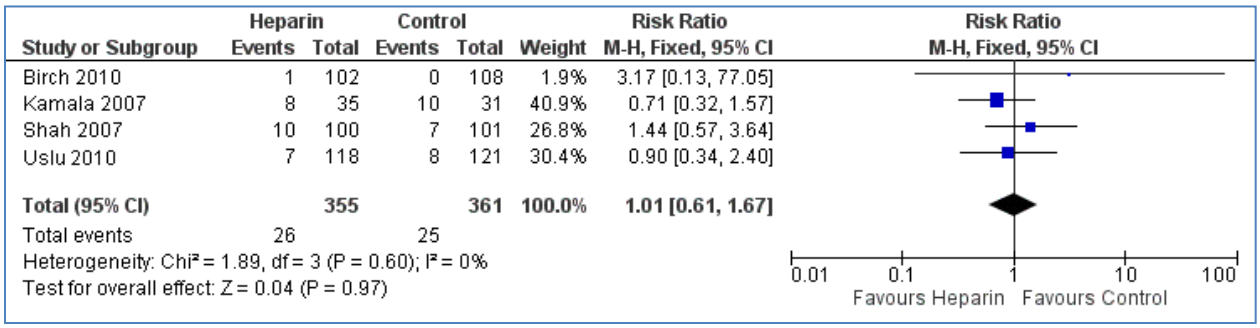

Figure 7: Effect of Heparin on Incidence of Catheter-related bacteremia

Figure 8: Effect of Heparin on risk for IVH progression

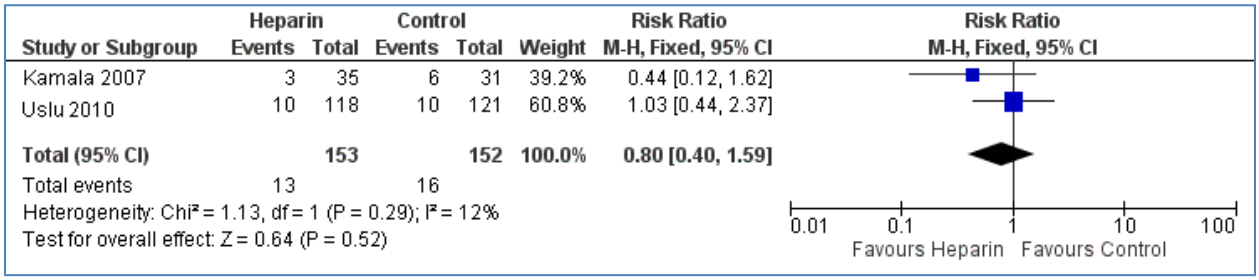

Figure 9: Effect of Heparin on risk for phlebitis

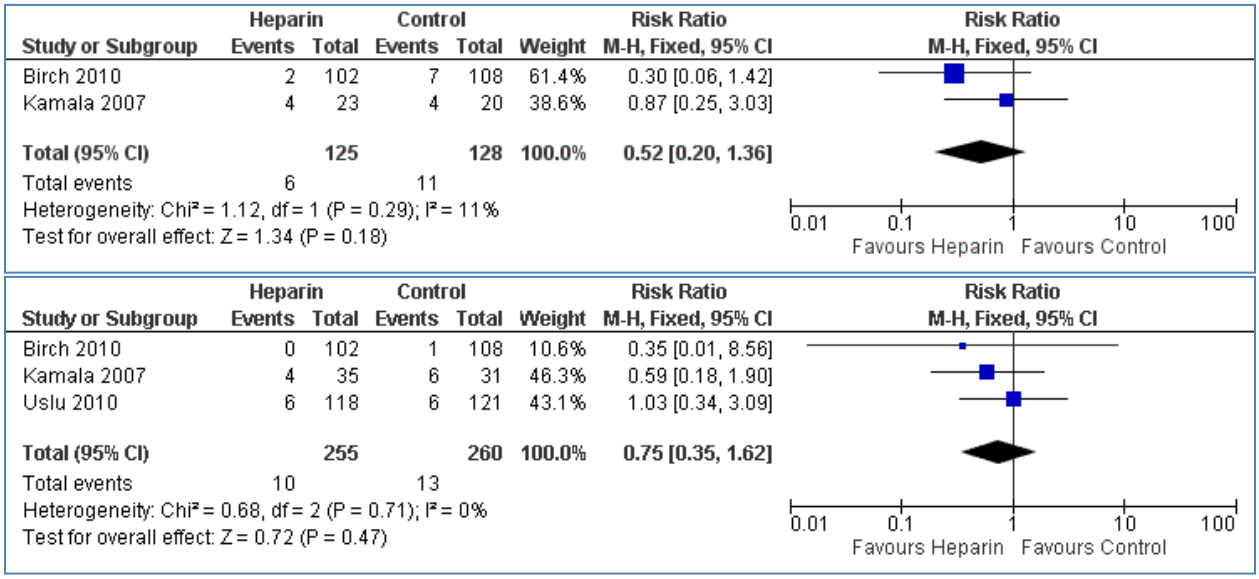

Figure 10: Effect of Heparin on risk for mortality

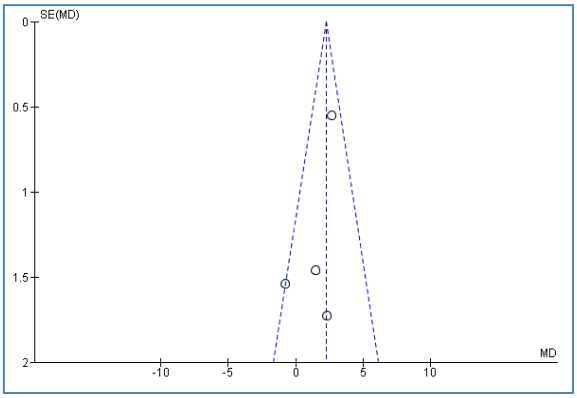

Figure 11: Funnel plot of the included studies