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Research Paper

Low-dose heparin for prolonging the patency of peripheral intravenous catheters in adults – a systematic review and meta-analysis

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Abstract

Objective: To assess evidence from randomized controlled trials (RCTs) about the efficacy of low-dose heparin for prolonging patency of peripheral intravenous catheters in adults.
Design: Systematic review and meta-analysis.
Data Sources: We searched MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CCTR) to identify studies up to July 6, 2012. Additional citations were retrieved from the bibliography of the selected articles. No language restrictions were placed.
Eligibility criteria for selecting studies: The eligible studies were RCTs of low-dose heparin, used as continuous infusion or as intermittent flush, through peripheral intravenous catheter as compared to a control; and measured any one of the following outcomes: duration of catheter patency, occlusion rates or local site reactions such as thrombophlebitis.
Results: Eight RCTs were identified (5 testing heparin as continuous infusion and 3 as intermittent flush). Catheters using heparin infusions had longer patency [Mean difference = 13.37 hours, 95%CI (3.37, 23.37), p=0.009], however, no difference in the duration of patency was noted from its use as intermittent flushing solution. Similarly, continuous infusion of heparin resulted in approximately 50% lower rates of infusion failures [rate ratio = 0.50, 95%CI (0.33, 0.76), p=0.001] and phlebitis [rate ratio = 0.47, 95%CI (0.31, 0.73), p<0.001] compared to no difference noted with its use as intermittent flushing solution. Few studies reported treatment related adverse events.
Conclusion: Low-dose heparin used as continuous infusion in PIV catheters resulted in longer catheter patency with lesser episodes of infusion failures and phlebitis. Heparin's use as intermittent flush solutions had no benefit.

Keywords: *Heparin, Patency, Infusion Failure, Phlebitis, Systematic Review*

1. Introduction

Heparin solutions are widely used in central venous and arterial lines for maintaining catheter patency and have become the standard of practice. The benefits demonstrated include reduction in catheter occlusions, catheter-related venous thrombosis and likely reduction in catheter related bacterial infections (Barrington 2000, Randolph et al. 1998, Shah et al. 2008a). However, the benefits of heparin in peripheral intravenous (PIV) catheters continue to be debated.
A previous systematic review of randomized controlled trials (RCTs) showed that while intermittent heparin flushes had no added benefits compared to normal saline, low dose heparin infusions may have benefits in terms of lesser incidence of phlebitis or longer duration of catheter patency (Randolph et al. 1998b). However, this review concluded that further studies would be needed to establish heparin's benefit in peripheral venous catheters. A more recent systematic review in pediatric population showed clinically significant benefits from continuous heparin infusion in PIVs, in terms of longer catheter patency, lesser episodes of infusion failures and a trend towards lower phlebitis rates (Kumar et al. 2013), with minimal benefits noted from heparin's use as intermittent flushing solution for PIVs.
Our objective was to conduct an updated systematic review of the RCTs in adult population to test the efficacy of low dose heparin in maintaining the patency of commonly used non-metallic peripheral intravenous catheters.

2. Methods

2.1. Search strategy

The research librarian in collaboration with the research team conducted structured searches in the following electronic databases- MEDLINE (1946-2012), EMBASE (1980- 2012), CINAHL and Cochrane Central Register of Controlled Trials (until June 6, 2012). The following combination of subject headings and text words were used: [(infusions, intravenous/ OR (infusion* or intravenous) adj2 (infusion* or drip or catheter) OR Catheteriza-

tion, Peripheral/ OR (peripheral adj2 (catheter* or intravenous)] AND [(heparin/ OR (heparin or heparin* or alpha-heparin or liquamin)]. Search results were not limited by language and a date restriction was not applied. Additional citations were retrieved from the bibliography of the selected articles if they appeared to answer the research question. We did not include studies published as abstracts only.

2.2. Study selection

Studies were included in the review if they met the following criteria: randomized sequence generation; comparing low-dose heparin added to the intravenous fluid through PIV catheter versus no heparin added to the similar base fluid in adult population; and, measured any one of the following outcomes: duration of catheter patency, occlusion rates or local site reactions such as thrombophlebitis. Discrepancies regarding inclusion were resolved through discussion among the review team.

We did not include RCTs where the purpose of initiating PIV catheter was to obtain short duration vascular access such as in emergency departments. Other exclusions were: cluster randomized trials and studies where subjects in both groups uniformly received systemic heparin from alternate routes.

2.3. Data extraction

Data were extracted by one reviewer (NM) using a standardized form. All forms were checked for accuracy by a second reviewer (MK) and discrepancies were resolved by discussion between the two reviewers. We extracted the following information: characteristics of the study (e.g., language of publication, year of publication); characteristics of the study population and of the catheter (e.g., reasons for receiving intravenous fluids, catheter size and material); description of the intervention and comparisons (e.g., heparin dose and method of administration); outcome measures and measurements tools; and results.

Our primary outcome of interest was the duration of catheter patency. The secondary outcomes included infusion failure (defined as any reason that resulted in premature removal of the catheter), catheter related phlebitis (defined as one or more of the following: pain, erythema, induration, local tenderness or palpable cord) and any other major adverse effects reported.

2.4. Assessment of bias

We (MK, DB) addressed methodological quality as per the Cochrane risk of bias tool (Higgins et al. 2011), which includes items for adequacy of random sequence generation, allocation concealment, blinding, loss to follow-up, selective reporting, or other biases. Discrepancies were resolved by discussion and consensus.

2.5. Data analysis

The effects of low-dose heparin from infusion and intermittent flush studies were analysed as separate subgroups. Studies were pooled using DerSimonian and Laird random effects model. Since catheter patency was reported differently across studies (e.g., some studies measured time to failure, while others measured total number of failures at various time periods), both continuous and dichotomous outcome data were converted to a common measure of standardized mean difference (SMD) to pool effect size from all the studies as per the methods suggested in the Cochrane handbook (Odds ratios from studies providing dichotomous data was converted into SMD unit using the equation

$$SMD = \frac{\sqrt{3}}{\pi} In\, OR$$

(Chinn 2000). Many studies had more catheters than patients, and thus rate ratios were used to pool some of the outcomes (i.e., infusion failure, phlebitis) with standard errors being estimated through poisson rates, which take into account the multiple catheters. Data was analyzed using RevMan *version 5.1*.

Sensitivity analyses were planned to separately evaluate effect size from studies those provided data from single catheter per subject to avoid concerns that result from dependency of data when same subject is included more than once in a trial.

2.6. Assessment of heterogeneity

I^2 statistic was calculated for each analysis to quantify heterogeneity across studies. If substantial ($I^2 > 50\%$) heterogeneity was detected, the potential causes for its existence were explored and further sensitivity analysis undertaken.

3. Results

Fig. 1 shows the flow of the studies through the selection process. We identified 8 RCTs that met the inclusion criteria; 5 evaluating low-dose heparin as continuous infusion (Daniell 1973, Tanner 1980, Bassan et al. 1983, Messing el al. 1986, Reid et al. 1990) and 3 evaluating heparin as intermittent flush (Hamilton el al. 1988, Shoaf el al. 1992, Mayer el al. 1995). A brief description of salient characteristics of the included trials is presented in Tables 1 and 2 (studies listed by first author and year of publication). While the majority of studies reported results for the first catheter per enrolled subject, three trials, i.e., two infusion studies (Daniell 1973, Reid et al. 1990) and one intermittent flush study(Hamilton el al. 1988), reported results allowing multiple catheter insertions in each study patient. Appendix 1 shows studies that were screened as RCTs but considered ineligible for inclusion upon full-text review.

Table 1: Characteristics of Rcts Evaluating Efficacy of Heparin Used as Continuous Infusion

Study	Population, settings, catheter size and material	Heparin group (N = patient/catheters)	Control group (N=patient/catheters)	Outcomes reported	Comments
Daniell 1973*	Adults, coronary care unitCatheter: 18G, polyethylene	N = 65/88 Dose: 1 U/ml	N =57/86 Saline placebo	Patency Infusion failure Phlebitis	About 50% patients in each group also received other medications
Tanner 1980†	Adults, undergoing surgical procedures Catheter: G not stated, Teflon	N = 36/36 Dose: 1U/ml	N = 36/36 Maintenance IV fluids	Phlebitis Catheter tip culture	Observations censored at 72 hrs. Excluded patients receiving medications
Bassan 1983**	Adults with suspected MI Catheter size and material not stated	N = ~25/25 Dose: ≈2 U/ml (4000 U added to 24 hr fluids)	N = ~25/25 Saline placebo	Phlebitis	Numbers in each group a guestimate (100 patients/4 groups), Observations censored at 48 hrs
Messing 1986#	Adult admitted with various conditions requiring PN Catheter: G not stated, Teflon	N =32 /32 Dose: 1U/ml	N = 33/ 33 PN without heparin	Patency Infusion failure Phlebitis	Observations censored at 48 hrs
Reid 1990**	Adult post-operative patients receiving PN Catheter : 18G, Teflon	N =20/‡ Dose: 1U/ml	N = 20/‡ PN without heparin	Patency Phlebitis score	

PN= Parenteral nutrition, NICU = neonatal intensive care unit

* = Study had a 3rd group of high dose heparin equivalent to therapeutic heparinization, data not presented here
† = Study had a 3rd group of subcutaneous heparin, data not presented here
# the study had a 3rd group of heparin + hydrocortisone, data not presented here
** = Studies had four groups each, data for hydrocortisone and heparin + hydrocortisone groups not presented
‡ =A total of 112 catheters in 4 groups (exact number for each group not provided)

Table 2: Characteristics of Rcts Evaluating Efficacy of Heparin Used as Intermittent Flush

Study	Population, settings, catheter size and material	Heparin group (N = patient/catheters)	Control group (N=patient/catheters)	Outcomes reported	Comments
Hamilton 1988	Adults, medical surgical wards Catheter: most 18-22G, Teflon	N = 80/170 Dose: 100 U/ml Freq: q8h	N = 80/137 Saline placebo	Patency Phlebitis	Catheter routinely changed q48hrs, Catheters not always removed despite evidence of phlebitis
Shoaf 1992	Adults, undergoing cardiac procedures Catheter: G not stated, Teflon	N = 132/132 Dose: 10 U/ml Freq: q8h*	N = 128/128 Saline placebo	Patency Infusion failure Phlebitis	Subjects excluded if receiving streptokinase or heparin drip
Meyer 1995	Pregnant women in labor, requiring blood sampling Catheter: 18G, Teflon	N = 31/31 Dose: 100 U/ml Freq: q6h*	N = 33/33 Saline placebo	Patency Infusion failure Phlebitis	Study terminated at 72 hrs or on detection of non-patency

*= or flushed after medications

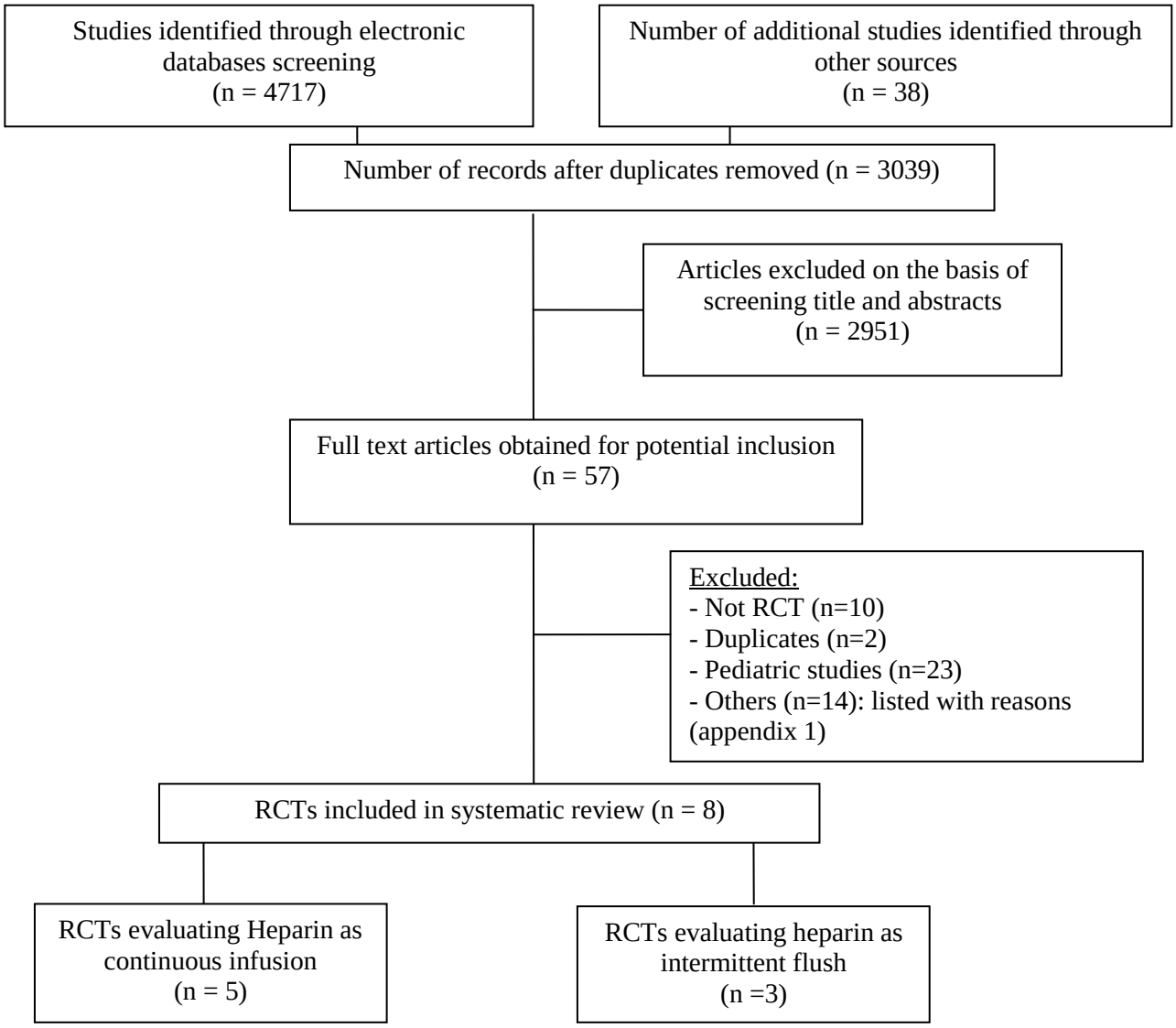


Fig. 1: Flow of Studies through the Selection Process

3.1. Risk of bias assessments

Table 3 shows the risk of bias assessment of the included studies. Four studies did not adequately describe the method that was used

to generate the random sequence for participants. The majority of the included studies had concealed allocations and had satisfactorily masked the interventions (blinding) from the care-givers and assessors. Most studies were listed as 'unclear' for the criterion of free of selective reporting, as it was hard to make this judgement in absence of availability of trial protocols. Four studies had a large proportion of subjects excluded after randomization, mostly for reasons of incomplete participant data and change of treatment plans (discontinuation of PIV and/or early discharge from hospital) (Daniell 1973, Bassan et al. 1983, Hamilton el al. 1988, Shoaf el al. 1992). Where reasons for drop-out were presented, they were similar across heparin and control groups and the post-randomization exclusions did not result in imbalance in numbers for heparin and control groups. Three studies censored observations beyond a fixed period from starting catheters, one at 48 hours (Messing el al. 1986) and two at 72 hours (Tanner 1980, Mayer el al. 1995).

3.2. Outcome of patency

This outcome was reported by six studies included in the review. The studies used variable measures to describe patency outcomes, i.e., mean+/-SD of the duration of patency (in hours) and/or patency at 24, 48 and 72 hours after the start of infusion.

Fig. 2 shows the outcome of patency in the units of standardized mean difference (SMD). The use of the heparin resulted in a significant longer duration of catheter patency in the infusion studies [SMD 0.65, 95%CIs (0.33, 0.97), p<0.001], whereas the difference noted from its use in intermittent flush studies was not statistically significant [SMD 0.29, 95%CIs (-0.13, 0.70), p=0.17]. All three of the heparin infusion studies included in the analysis, also reported patency as a continuous outcome (mean and SD in hours), and the reported SMD was equivalent to 13.37 hours [95%CIs (3.37, 23.37)] of longer catheter lifespan with heparin infusion (Supplementary data 1).

Meta-analysis of the four studies that presented patency outcome at fixed time periods, revealed that the catheters using heparin solutions were twice more likely to be patent at selected time points. The odds ratio for patency at 48 hours was 2.19[95%CIs (1.40, 3.44), p <0.001]. The results for patency at 72 hours were similar; however, lesser studies reported this outcome (Fig. 3). In sensitivity analysis, there were no statistically significant differences in the estimates from the studies providing single catheter/subject data as compared to all catheter data (Supplementary data 2).

3.3. Infusion failure

This outcome was reported by four of the included studies. The use of the heparin resulted in a 50% reduction in infusion failure in the heparin infusion studies [rate ratio 0.50, 95%CIs (0.33, 0.76), p =0.001], however, the difference was not significant for heparin used as intermittent flush [rate ratio 0.73, 95%CIs (0.27, 1.99), p=0.54] (Fig. 4).

3.4. Phlebitis

Meta-analysis was conducted for seven of the included studies that reported phlebitis as a binary outcome (as yes/no). The use of the heparin resulted in a 53% reduction in phlebitis episodes in the heparin infusion studies [4 studies, rate ratio 0.47, 95%CIs (0.31, 0.73), p <0.001]. However, so significant difference was noted for the outcome of phlebitis in the studies using heparin as intermittent flush [3 studies, rate ratio 0.95, 95%CIs (0.36, 2.55), p=0.92] (Fig. 5). The effect size was not statistically different between the studies that provided data for one catheter per subject and multiple catheters per subject.

One study (Reid et al. 1990) that could not be included in the meta-analysis, measured phlebitis on an ordinal scale (Modified Maddox scale with grading between 0 to 6) and showed a trend towards lesser phlebitis in the heparin group (p=0.06).

3.5. Assessment of adverse effects

Few studies reported treatment related adverse events. One study reported one episode of non-major bleeding in a subject receiving low-dose heparin (Daniell 1973). There was no increased risk of sepsis or heparin induced thrombocytopenia reported from the use of heparin in any study.

Table 3: Risk of Bias Assessment of Included Studies

	Adequate sequence generation	Allocation concealment	Blinding of care-givers & assessors	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Description of other bias
				Infusion studies			
Daniell 1973	Unclear	Yes	Yes	No	Unclear	Unclear	Post randomization exclusions(data from 44 catheters)
Tanner 1980	Yes	Unclear	Unclear	Yes	Unclear	Yes	
Bassan 1983	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Post randomization exclusions (31 subjects)
Messing 1986	Unclear	Yes	Yes	Yes	Unclear	Unclear	
Reid* 1990	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Post randomization exclusions (7 subjects)
				Intermittent flush studies			
Hamilton 1988	Yes	Unclear	Yes	No	Unclear	Unclear	Post randomization exclusions (81subjects) for incomplete data, per-protocol analysis
Shoaf 1992	Yes	Yes	Yes	Yes	Unclear	Unclear	Post randomization exclusions (38 subjects) for early discharge/ or discontinued sites
Meyer 1995	Yes	Yes	Yes	Yes	Unclear	Unclear	

* Some subjects in each group received subcutaneous heparin for DVT prophylaxis

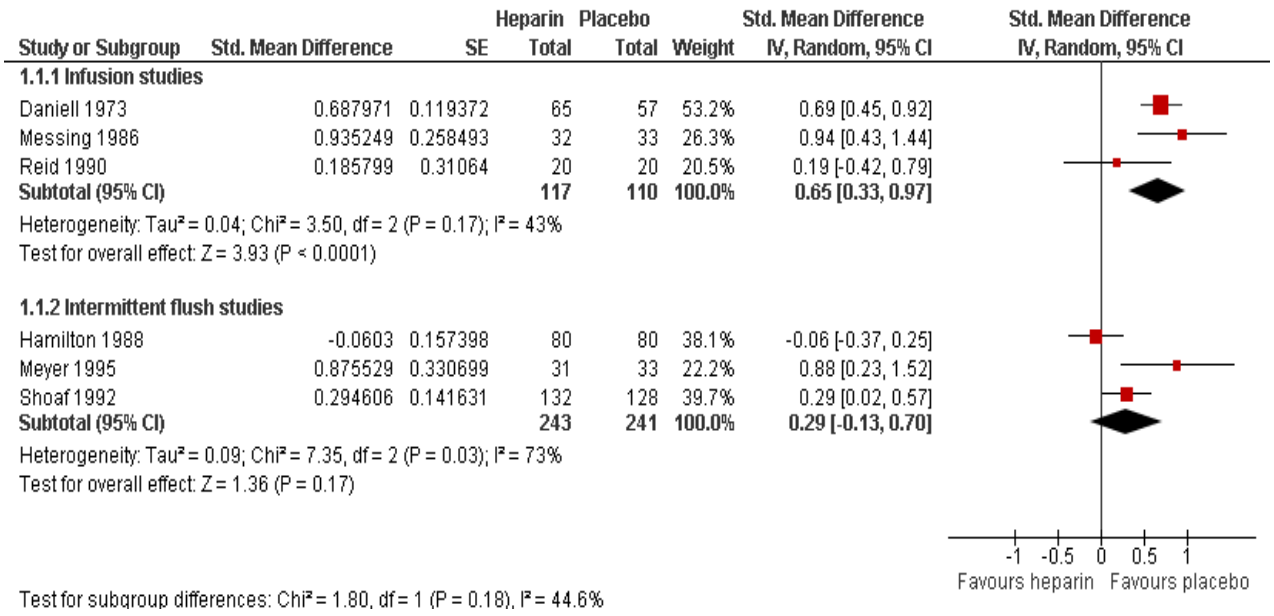


Fig. 2: Heparin versus Control. Meta-Analysis of Data for Catheter Patency in Standardized Mean Difference (SMD) Units

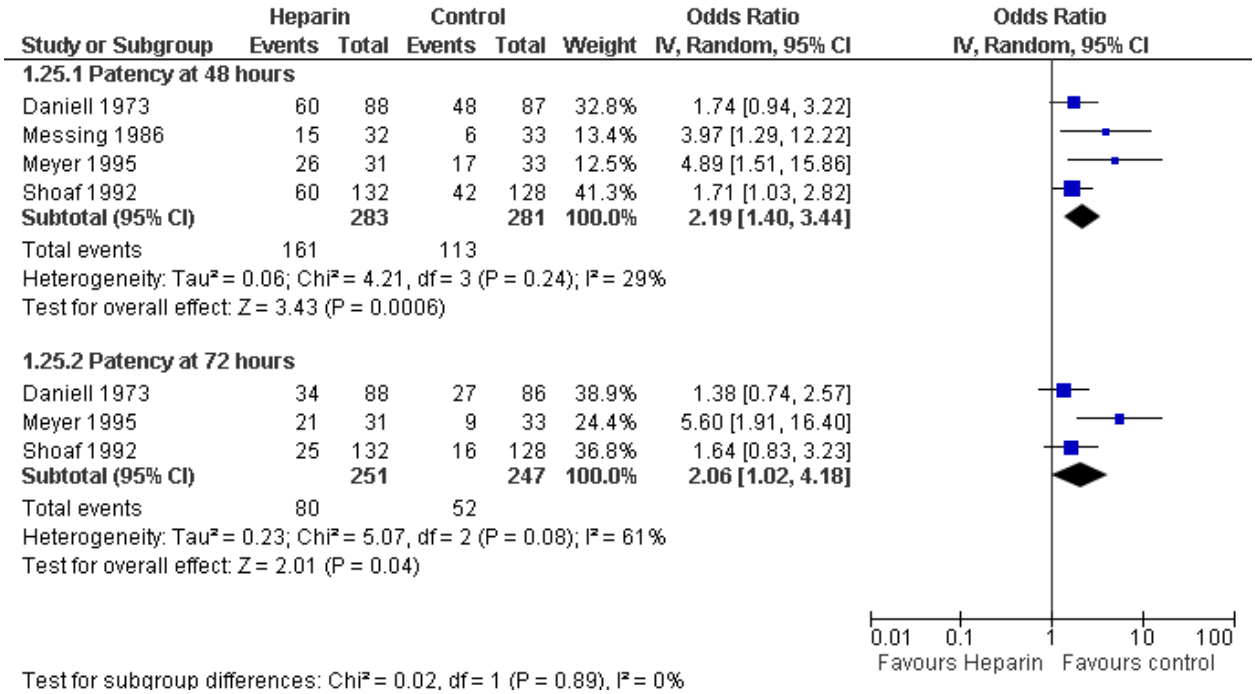


Fig. 3: Catheter Patency at Fixed Time Points (as Reported in Studies)

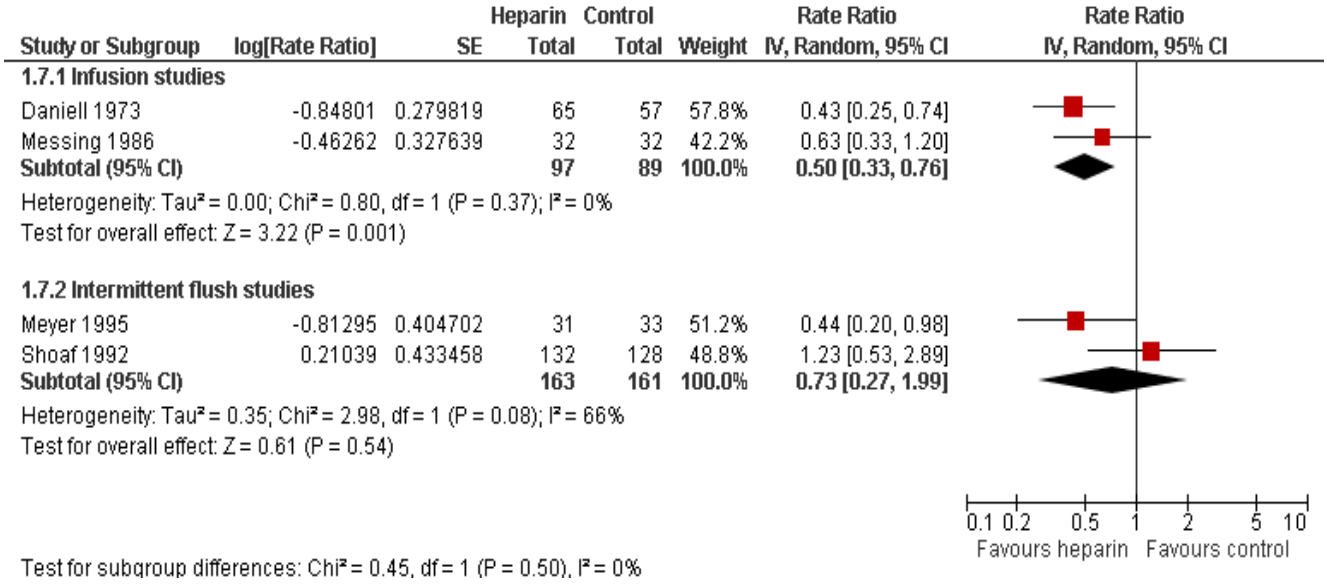


Fig. 4: Meta-Analysis for the Outcome of Infusion Failure

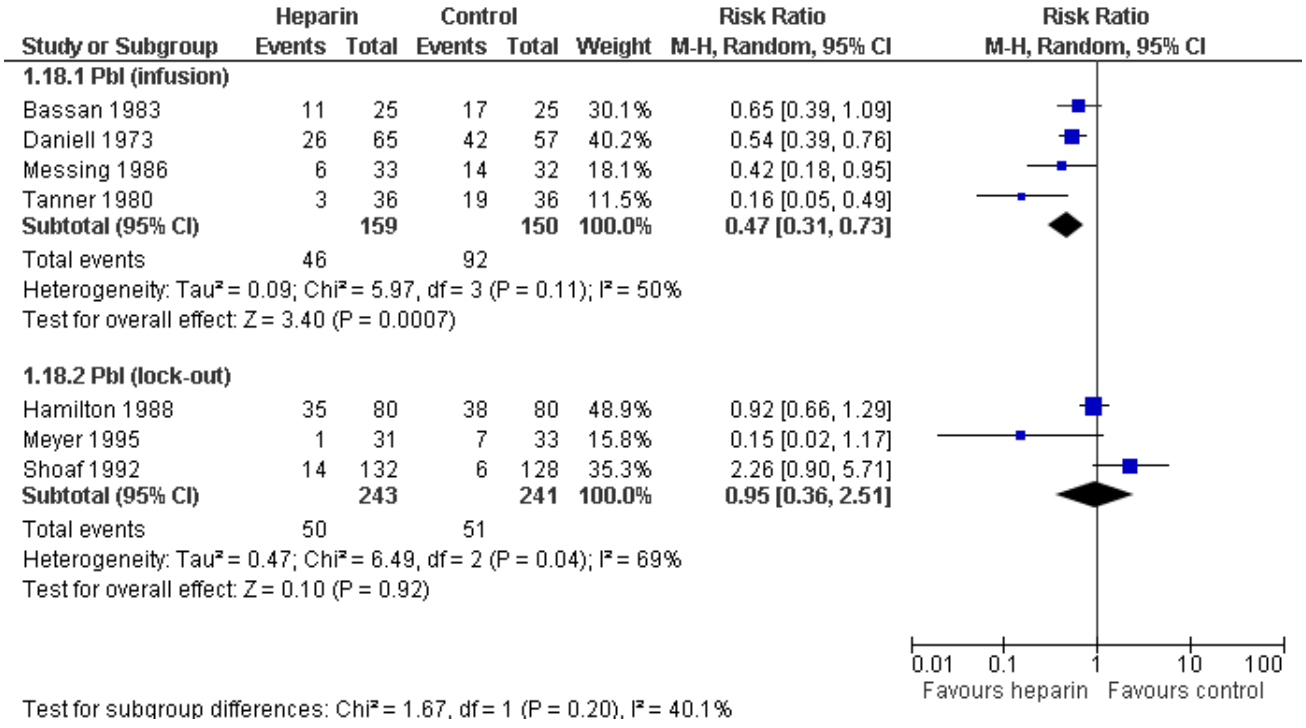
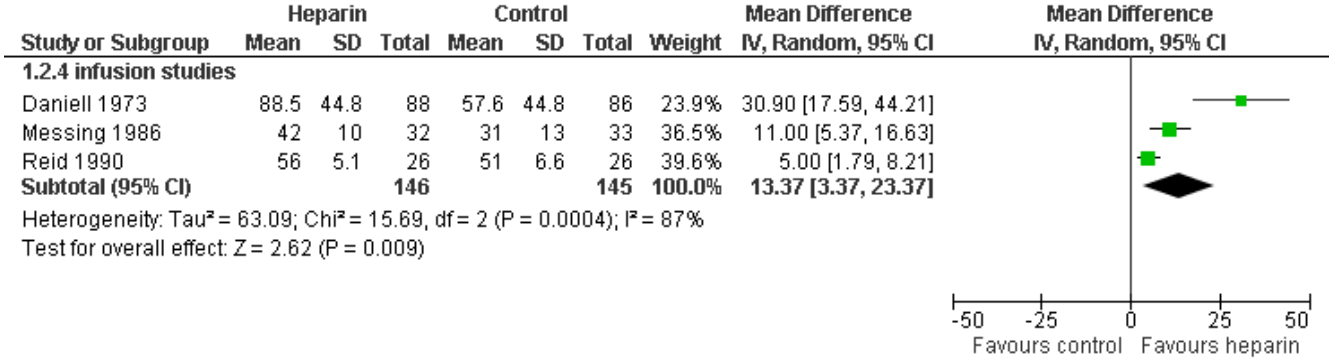
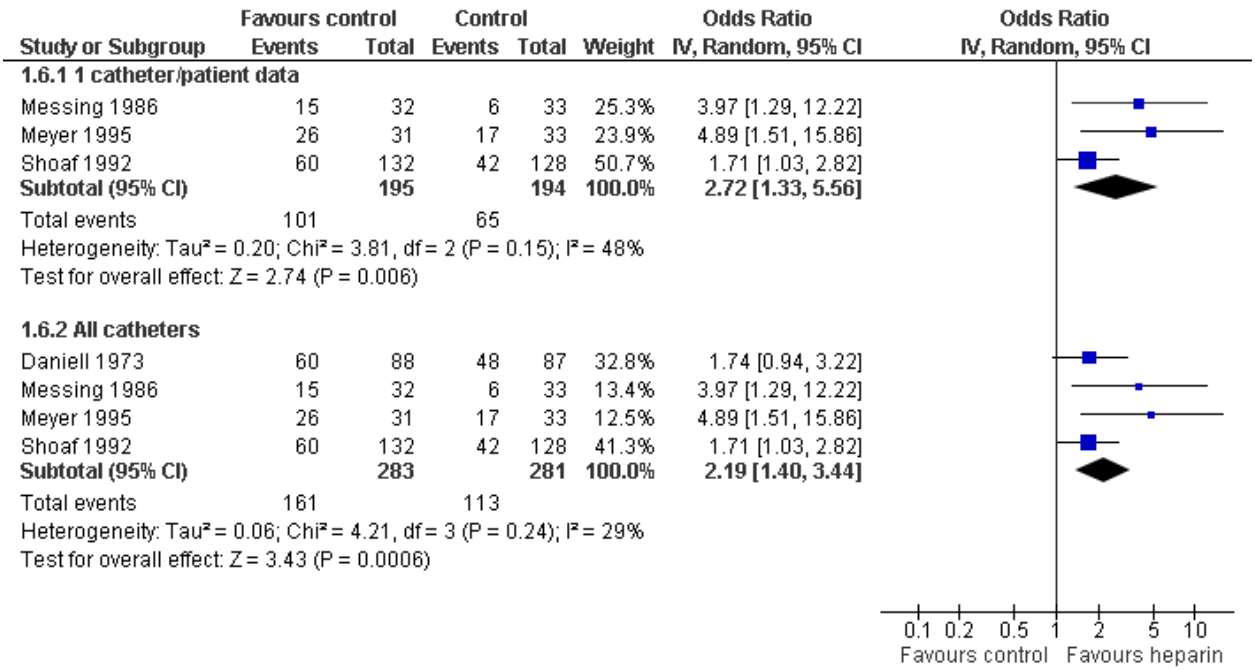


Fig. 5: Meta-Analysis for the Outcome of Phlebitis



Supplementary Data 1: Meta-Analysis of Catheter Patency Data for Infusion Studies in actual units (Hours)



Supplementary Data 2: Patency at 48 Hours - Sensitivity Analysis for One Catheter/Subject Data and All Catheter Data

4. Discussion

We have presented here an updated systematic review of RCTs in adult population of the effects of low-dose heparin in peripheral intravenous catheters. The results of this review show that the use of low-dose heparin as continuous infusion significantly prolongs the average duration of patency for PIV catheters by 13.37 hours, with over 50% reduction in the rates of infusion failures and phlebitis. There was no significant heterogeneity noted for any of the beneficial effects noted with low-dose heparin infusion. On the other hand, heparin's use as intermittent flushing solution did not result in significance difference for any of the above outcomes. It is unlikely that we missed an important study that could have altered the main results of our review, as our search strategy, undertaken with the help of a research librarian, was broad and sensitive.

We explored whether the difference in effect size noted between the two modes of heparin use could be related to the heparin dose used for intermittent flush. However the meta-analysis of the two studies using higher concentration of heparin (=100 units/ml) for intermittent flushes did not result in significant benefit either (Hamilton et al. 1988, Meyer et al. 1995).

We were unable to analysis dose-response relationship here as the majority of the infusion studies used 1unit/ml solutions. However, data from a pediatric study that compared benefits from various concentrations of heparin infusion within its study design (Moclair et al. 1995) showed comparable results for using heparin in concentration of 0.5unit/ml or 1 unit/ml in the infusion fluids.

The results of this review are comparable to the results noted in the recently published systematic review in pediatric population (Kumar et al. 2013). However, the implications of the beneficial results presented here may not be similar to those in the pediatric population, due to many considerations. First, the magnitude of benefit noted for difference in patency here is much lower than in pediatric population (13.37 hours versus 26.51 hours). Second, obtaining a PIV access is generally easier in adults than in children; thus use of heparin for prolonging the patency of PIVs may have lesser value for the clinicians looking after adult patients. Third, the risk of heparin-induced thrombocytopenia is much higher in adult population (especially in surgical patients) than in infants and children (Klenner et al. 2003, Klenner et al. 2004, Arepally et al. 2006). We suggest the above factors be taken into consideration while assessing the risk-benefit of using low-dose heparin infusion for an adult patient.

Our review is not without limitations. *First*, several of the studies included in this review pre-date some of the recent advances in the area of intravenous fluid therapy such as use of in-line filters (Ball 2003), newer catheter materials with lesser incidence of thrombophlebitis (Maki el al. 1991), the practice of regular change of intravenous tubing sets (Maltow et al. 1999) and positive pressure flushing technique (RCN IV Therapy Forum 2010). *Second*, we made some assumptions for our analysis where appropriate data was not available, e.g. for one study (Daniell 1973), the mean duration of catheter patency was provided without estimates of standard deviation (SD), we imputed the largest standard deviation that was available from existing RCTs on heparin. We believe that these assumptions were conservative and their impact is more likely to bias towards nil effect. *Third*, for our primary analysis of the outcome of patency, we decided to pool the results under a common measure of SMD due to variability in methods used to describe this outcome across studies, as those measured same clinical construct. This is consistent with the current literature in systematic review methodology and the development of appropriate methods to carry out such analyses. A separate meta-analysis according to each method of reporting an outcome, could result in loss of information and be misleading (Chinn 2000, Ioannidis et al. 2008). *Fourth*, a few multi-group studies also tested low-dose intravenous heparin in combination with other active treatment such as hydrocortisone (Messing el al. 1986, Reid et al. 1990) or with subcutaneous heparin (Tanner 1980). We did not evaluate for the efficacy of these comparisons. *Lastly*, some studies reported large drop-out rates post-randomization (Daniell 1973, Bassan et al. 1983, Hamilton el al. 1988, Shoaf el al. 1992), which could have biased the results of this review.

5. Conclusion

The results of this updated systematic review of RCTs demonstrate that the continuous infusion of low-dose heparin in PIV catheters prolongs catheter life, with clinically significant reduction in rates of infusion failure and phlebitis. These effects are aligned with beneficial effects of low-dose heparin seen when used in central lines or in peripherally inserted central catheters. There were no significant benefits observed with use of heparin as intermittent flushing solution in PIVs.

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Authors' contribution

BV provided statistical support and helped with data analysis. DB helped with risk of bias assessment and was involved with planning at various stages. NM helped with search selection and data abstraction. MK was involved in all stages of the review and wrote the first draft. All provided comments to the draft until its final form. MK is guarantor for the content of this report.

Conflict of interest statements

None of the authors have any conflicts to declare. Corresponding author will submit Unified Competing Interest form for all authors on request.

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Appendix 1

List of excluded RCTs (along with the reasons for their exclusion)

[1] Epperson EL. Efficacy of 0.9% sodium chloride injection with and without heparin for maintaining indwelling intermittent injection sites. Clinical Pharmacy 3(6) () (pp 626-629), 1984 Date of Publication: 1984 1984 ;(6):626-9. (Probably pediatric population)

a. Reason for exclusion: Allocation of interventions by hospital units, instead of randomizing individual patients

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