Review Article

Heparin flush vs. normal saline flush to maintain the patency of central venous catheter among adult patients: A systematic review and meta-analysis

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Abstract

Background: Around the globe, protocols for flushing the catheter to maintain the patency of central venous catheter (CVC) vary by institution to institution or by practitioner to practitioner. Therefore, this review was carried out with the aim of evaluating the efficacy of heparin flush vs. normal saline flush to maintain the patency of CVC among adult patients. **Methods:** We followed the guidelines of Cochrane handbook for interventions and searched in MEDLINE, Embase, Cochrane library, Clinical trials database, and reference list of related articles, which were published from Jan. 2012 to 31 Dec. 2018 in English language. We included only randomized controlled trials, and nine studies were included in this review. The pooled standard mean difference and relative risk were calculated by using Rev Man Review Manager 5. **Results:** We identified nine eligible studies with a total number of 3,113 participants. Consolidated results from eight studies conveyed little favorable effect to maintain patency of CVC with heparin when compared with normal saline as evident by risk ratio 0.83, 95% CI 0.50 – 1.40; $P = 0.13$. We also carried out analysis for secondary outcomes, and there was no evidence that heparin was better than normal saline in terms of safety except heparin-induced thrombocytopenia. **Conclusions:** Heparin has little favorable effects to maintain patency of catheter than normal saline but not in secondary outcomes. As the quality of evidence was very low, therefore, results should be comprehend with care.

Keywords: Central venous catheter, heparin, normal saline, patency

Introduction

Central venous catheters (CVCs) are routinely utilized in health care industries, primarily in critically care units.[1] CVC is a device that is temporarily placed into patients for assessing the central veins. It is also known as lines.[2,3] CVCs can be used for monitoring hemodynamic status, administration of parental nutrition, blood and blood products,[2,3] medications or chemotherapy drugs, and performing of hemodialysise ct. when it is not safe to administer through peripheral venous catheters.[4,5]

Presently, four types of CVCs commonly used are tunneled (e.g. Hickman's Catheters), non-tunneled catheter, peripherally inserted central catheters (PICCs), and totally implantable port or totally implantable venous access devices.[5,6]

CVCs are having great use in critical care units and associated with decrease stay of hospitalizations, enhance the patient's safety, and reduction of the hospitalization costs.[7,8] However, CVCs are

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associated with complications. Complications related to CVCs can be mechanical complications, which occur at the time of insertion such as hematoma, arterial puncture; pneumothorax, etc., ranges from 5% to 29%[9,10] and complications related to infections ranges from 5% to 26% and complications related to thrombosis ranges from 2% to 26%.[10,11]

CVCs obstruction may lead to venous thrombosis or develop a fibrin sheath, accounts approximately 40% of catheter-related complications, which are major causes for catheter dysfunctions.[12] Occlusion of catheter can be categorized as partial (able to flush freely but not able to aspirate the blood) and complete (not able to flush freely and aspirate blood).[13,14]

There are various factors like condition of patient, lumen size and position of catheter, insertion site and technique, chemical composition and nature of flushing solution, etc., which are associated with catheter-related thrombosis.[15] Catheter-related thrombosis is an important causative factor for not only morbidity and mortality but also that thrombus acts as a medium for micro-organism growth.[16] Another complication which is associated with CVC-related upper limb DVT is pulmonary embolism, which is a life-threatening situation, occurs near about 15% of patients.[17]

Therefore, to prevent the risk of catheter occlusion, it is very much needed for maintaining patency and prolong functioning of the catheter,[18,19] and to achieve it proper flushing of catheter is deemed necessary and considered as primary intervention.[20,21] To prevent or avoid formation of thrombus in CVCs, the solutions used by clinician to flush the catheter include heparin, 0.9% sodium chloride, vitamin C, lepirudin, sodium citrate, polygelin,[22,23] alteplase, or urokinase.[24]

Heparin flushing has been used and most commonly performed procedure to avoid thrombus formation in CVCs.[25] Heparin flush is the standard guideline to maintain the patency of CVCs.[26-28] However, the effectiveness of this standard practice is still unproven[29] and associated with some complications such as heparin-induced thrombocytopenia (HIT), allergy, and risk of bleeding.[30-32]

It is reported by some studies that utilization of normal saline is as much effective as heparin to maintain the patency of CVC.[33-35] Furthermore, two Cochrane systematic reviews provided inconclusive evidence favoring the application of heparin solution over normal saline for maintaining the patency of central venous and arterial catheters.[36,37]

As such, a number of studies with conflicting results have been published, prompting further debate on which solution is better for CVC maintenance. Therefore, this systematic review and metaanalysis of RCTs was carried out to assess more precisely the effectiveness of heparin in maintaining CVCs when compared with normal saline.

Materials and Methods

We followed PRISMA guidelines for this systematic review and meta-analysis [Additional file 1]. The PICO framework was utilized to address the review question evidently [Additional file 2]. The primary outcome for this review was catheter patency, and secondary outcomes were catheter-related infection, venous thrombosis, HIT, bleeding, and mortality.

Study selection

There were two independent reviewers who read the title and abstract and wherever needed the full text of applicable or probably related references, to select studies which required being more detail examination. When there was any variation of opinions between both reviewers, then first author was consulted to make final conclusion for the study. We also tried to contact the authors of ongoing trials and whose studies needed more clarification. In this review, we included randomized controlled trials (RCTs) compared the efficacy of heparin flush versus normal saline flush to maintain the patency of CVC in adult patients and published in English language only. Studies were excluded when primary researcher uses other methods of randomization like quasi randomization, studies on non-human, case-control, cohort studies, letters and reviews, and age of participants <18 years of age.

Search strategy

Review authors screened the Cochrane library l (last search 31 December 2018). We also searched MEDLINE (Ovid, 2012 to 2018), Embase (Ovid, 2012 to 2018), and clinical trials registers (last search 31 December 2018). We used free-text terms and MeSH terms like CVC, heparin, normal saline, sodium chloride, RCT, catheterization, flushing and patency, etc., [Additional file 3] for searching the studies. We explored all articles related to present review and also used list of references from searched published studies to identify new relevant studies.

Data extraction

There were two reviewers who extracted data and discussed with the third reviewer, who then solved the discrepancies. Data regarding the first author, publication year, country, study type, population, interventions (doses of heparin) outcomes (Primary and Secondary outcomes), and results were extracted. Whenever, it was required to get additional information, we approached the authors of those studies.

Assessment of bias

Risks of bias of studies were evaluated by two authors independently. Evaluation of risk bias was done by using standard guidelines of Cochrane. If there was any discrepancy between two authors, then the third reviewer was consulted to get the final judgment. Risk of bias comprised of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting it was assessed by using funnel plot [Figure 1], and other bias.

Types of outcome

In the included studies, the primary outcomes of interest communicated were maintaining the patency and occlusion of CVC. Secondary outcomes were HIT, risk of bleeding or hemorrhage from any part in the body, infection and thrombosis related to CVC, allergic reaction to heparin, cost of treatment with heparin, and mortality.

Data analysis

Statistical analysis was done as per the statistical guidelines protocol in the current version of the Cochrane Handbook for Systematic Review of Randomized controlled trial. RevMan Manager 5 was used for review production and data analysis. Studies which assessed the effects of heparin flush to maintain the patency of CVC were analyzed for subgroups and secondary outcomes. There were three different types of unit for analysis: six studies (participants), two studies (catheters), and two studies (line access). In this present review, we utilized risk ratio (RR) for dichotomous data. The mean ± standard deviations (SD) were used to express the continuous data and analyzed using standard mean differences (SMDs). As I^2 values were low, which indicates heterogeneity is low. Hence, we are supposed to use fixed-effect model to pool data. However, we planned and used random-effect model (for continuous data) because although the same medication was used to flush or lock the CVC in all studies (heparin), we identified fairly heterogeneity in the study methods involved like different types of patients, distinct settings, dissimilar duration of follow-up, inconsistent amount of concentration of drug (heparin), etc. The fixed model (MantelHaenszel) was used for dichotomous data. The publication bias was assessed by using funnel plot.

Results

Study selection and characteristics

We followed PRISMA guidelines for search and selection of studies, which met the inclusion criteria [Figure 2]. Total 1,157 records were searched through electronic database. Out of them, 762 were found as duplicates because of overlap of the database, remaining 395 references were screened and 357 records were found not relevant and excluded. Further,[38] full-text articles were assessed for eligibility and 29 of them were excluded because they did not meet the inclusion criteria. Finally, there are nine studies which met the pre-specified inclusion criteria and included for systematic review and meta-analysis.

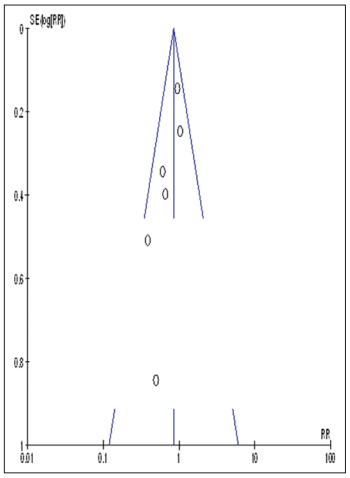

Figure 1: Funnel plot

Baseline characteristics

In total, nine studies were included which originated from Belgium[39] ($n = 1$), Iran[40-42] ($n = 3$), India[43] ($n = 1$), Italy[44] ($n = 1$), and USA[45-47] ($n = 3$) and from those studies, only one study[44] was conducted at multi-centric level, remaining 8 studies were single centric. The concentration of heparin ranged from 10 IU/ml to 1000 IU/ml. The duration of follow-up varied from 1 day to 204 days and 1 day to 294 days in normal saline (NS) group and heparin group, respectively. There were only three studies[40-46] which carried out in non-ICUs setting, whereas remaining six were performed in critical care units, and all studies were reported from 2012 to 2018. The basic characteristics of included studies were presented in Table 1.

Methodological quality

Most of the studies expressed a low or unclear level of risk of bias, except in performance and detection bias as display in Figure 3. There were only two studies[43,45] that did not clearly explain about method of randomization. In terms of allocation concealment, 4 trials[39,44,46,47] discussed properly, whereas the remaining 5 trials were unclear about this. Furthermore, there were only two studies[41,42] reported an appropriate method of blinding, one trial[46] was unclear and remaining all others have high risk for performance and detection bias. With regard to incomplete outcome data, only one study[39] had unclear risk, remaining others described drop-out information. In terms of selective reporting, only one study[43] had

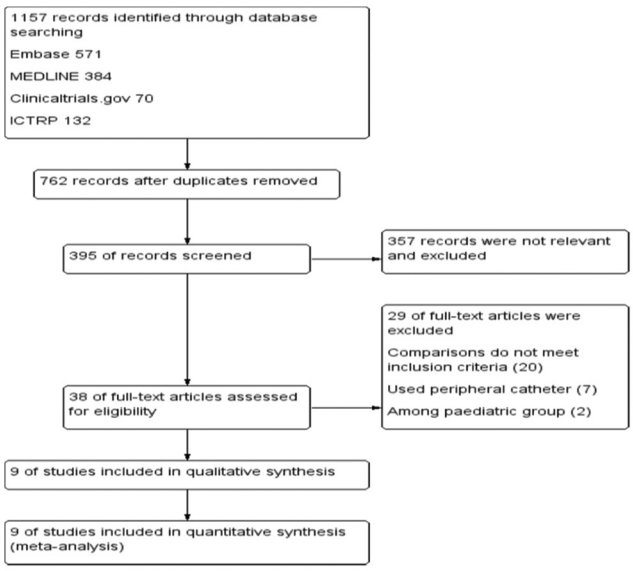

Figure 2: Selection of studies as per PRISMA guideline [ICTRP = International Clinical Trials Registry Platform (WHO database)]

Table 1: Basic characteristics of included studies

Study ID	Study design	Participants	Intervention	Results
Beigi 2014, Iran (S)	Single-blinded, RCT	129 patients with chronic kidney disease *n*=100 randomized *n*=50 NS group *n*=50 heparin group	1000 IU heparin Versus 0.9% saline solution	Catheter thrombosis No one in both groups Required manipulation to maintain patency Heparin group=2 (4.2%) 0.9% NS group=3 (6.1%) Bleeding experience Heparin group=4 (8.5%) 0.9% NS group=3 (6.1%)
Dal Molin 2015, Italy (M)	RCT , Open Label	430 patient with cancer Randomized *n*=203 NS group *n*=212 Heparin group	Normal saline solution versus heparin 5 cc (50I U/ml)	Withdrawal occlusion Heparin group=10 (4.71%) NS group=14 (6.90%) Total occlusion Heparin group=0 (00%) NS group=1 (.49%) Infection Heparin group=1 (0.49%) NS group=1 (0.49%) Venous thrombosis and Extravasation Heparin group=1 (0.49%) NS group=0 (00%)
Goossens, 2013, Belgium (S)	RCT , Open Label	802 patient with cancer Randomized *n*=398 NS group *n*=404 Heparin group	Normal saline solution versus Heparin 3 ml (100 IU/ml)	Easy injection, impossible aspiration incidence Heparin group=3.92% NS group=3.70% Catheter-related blood stream infection Heparin group=0.10/1000 catheter days NS group=0.03/1000 catheter days
Heidari, 2015, Iran (S)	Double Blind, RCT	802 patient with various diseases Randomized *n*=42 NS group *n*=42 Heparin group	Normal saline solution versus Heparin 3 ml (100 IU/ml)	Duration of CVC flushing Heparin group=15.47±3.9 NS group=14.45±5.56 Taking blood from CVC Heparin group=15.23±4.09 NS group=13.8±5.94
Kiein, 2018, Florida (S)	RCT, Open Label	30 patients with cancer (698 observations) Randomized *n*=15 NS group *n*=15 Heparin group	Standard Flush (NS+Heparin) 10 or 1000 IU/ml versus Normal saline	Rate of patency of CVC Standard group=313 (91%) NS group=325 (92%) Use of tPA Standard group=06 (25%) NS group=07 (27%) Occurrence of CLABSI Standard group=00 NS group=01
Lyons, 2014, USA (S)	RCT, Single Blinded	90 patients without cancer randomized *n*=30 NS group *n*=30 SASH (High) *n*=30 SASH (low)	Normal Saline versus Heparin (High) heparin 3 ml (100 IU/ml) Heparin 5 ml (100 IU/ml)	Rate of occlusion of catheter Heparin (High) = 9 (32.2%) Heparin (Low) = 8 (26.7%) NS group=9 (32.2%) Catheters needed alteplase SASH (High) = 3 (9.4%) SASH (Low) = 3 (10.0%) NS group=7 (25.0%)
Mahesh, 2014, India (S)	RCT, Open Label	100 patients with respiratory disease *n*=50 NS group *n*=50 Heparin group	0.9% NS solution versus Heparin 3 ml (10 IU/ml)	Non-patency of CVC Heparin group=2 (4%) NS group=4 (8%) Thrombocytopenia No incidence in both group
Schallom, 2012, St. Louis (S)	RCT, Open Label	341 patient with various diseases 295 pt. randomized *n*=150 NS group *n*=145 heparin group	0.9% NS solution versus Heparin 3 ml (10 IU/ml)	Lumen non-patency Heparin group=12 (3.8%) NS group=25 (6.3%) Rate of heparin-induced thrombocytopenia Same between groups Catheter-related blood Stream infection Similar in both groups

Contd...

Table 1: Contd...

Study ID	Study design	Participants	Intervention	Results
Ziyaeifard, 2015, Iran (S)	RCT, Double-blinded	100 patients with cardiac surgery Randomized *n*=50 NS group *n*=50 Heparin group	NS solution versus heparin 5 ml (10 IU/ml)	CVC occlusion No occlusion in both groups Catheter manipulation and displacement (3rd day) Heparin group=14 (28%) NS group=17 (34%)

S=Single center; M=Multi-centers; NS=Normal saline; RCT=Randomized control trial

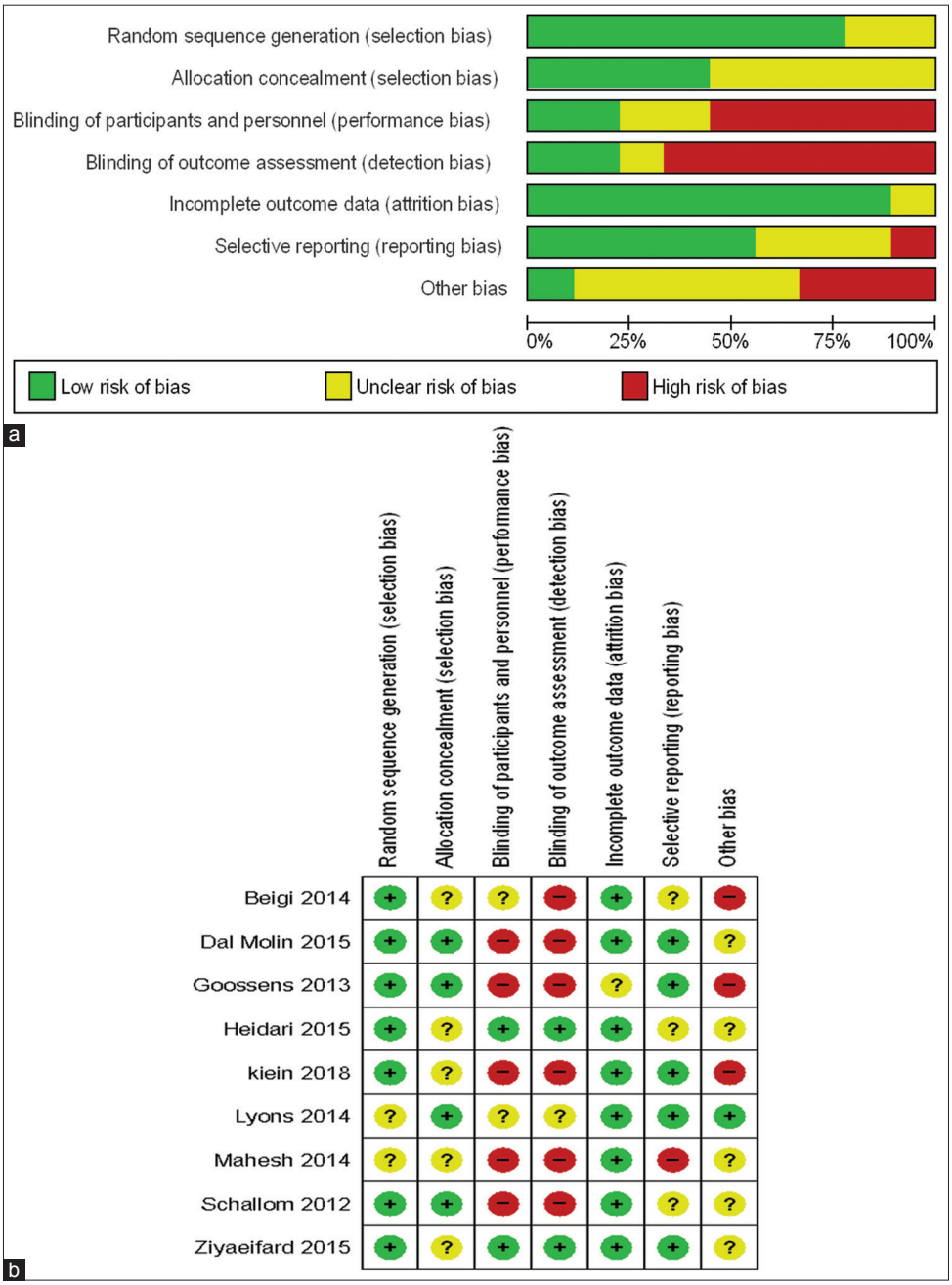

Figure 3: (a) Risks of bias graph. (b) Risks of bias summary

high risk of reporting bias, and three[40,41,47] were unclear risk and remaining low risk as they reported as per pre-specified protocols. There were five studies[40-42,44,46] which had a small sample size. The risk of bias was presented in Figure 3a and b.

Meta-analysis

We identified nine eligible studies for present review and meta-analysis with a total number of 3,113 participants with different disease conditions. We identified variation in methods

used by the included trials and difference in heparin strength (10 to 1000 IU/mL), duration of follow-up (1 to 294 days), participants with disease (participants with cancer or without cancer), and the unit of analysis which was used (participants, catheter, and catheter line access).

Consolidated results from eight studies (six studies used participants as unit of analysis with 1,622 participants and two studies used catheter as unit of analysis with 1,407 catheters) conveyed little favorable effect to maintain patency of CVC with heparin when compared with normal saline as evident by RR 0.83, 95% CI 0.50 to 1.40; $P = 0.13$.

We performed subgroup analysis on the basis of unit of analysis. When we used participants (1,622 participants from six studies) as unit of analysis, results reveal little favorable effect to maintain CVC patency with heparin than NS (RR 0.76, 95% CI 0.52 to 1.12; $P = 0.16$), whereas subgroup analysis was performed to use catheter as the unit of analysis exhibit no clear difference in maintaining patency of CVC between heparin and NS (RR 0.83, 95% CI 0.50 to 1.40; $P = 0.49$; 1407 catheters of two studies). When we used line access as unit of analysis, results reveal no clear difference in CVC patency between heparin and NS (RR 1.08, 95% CI 0.84 to 1.40; one study) Figure 4.

We also carried out subgroup analysis on the basis of kinds of participants, numbers of lumens, and strength of heparin concentration and duration of follow-up. We found no clear difference in catheter patency between participants without cancer and those with cancer (test for subgroup difference $P = 0.72$), and subgroup analysis to identify relationship between number of lumen (one lumen and two or more lumen) and catheter patency showed no clear difference between both group (test for subgroup difference $P = 0.79$). While subgroup analysis was performed between catheter patency and heparin strength (less or more than 1000 IU/ml) showed little difference. As less than 100IU/ml strength showed little favor to maintain patency (test for subgroup difference $P = 0.47$). Finally, we did analysis to detect the effect of follow-up duration and catheter patency and found that less than one-month follow-up had favorable effect when compared with the duration of follow-up was more than one-month (test for subgroup difference $P = 0.23$).

We studied to assess the difference of duration of CVC patency in three studies with 886 participants and 709 catheters and results reveal that there were no clear differences in duration of CVC patency between heparin and NS [Mean Difference (MD) 0.42 days, 95% CI –0.21 to 1.01; $P = 0.16$].

We also carried out analysis for secondary outcomes, and results show that except HIT, which was assessed in two studies with 395 participants showed there is no clear difference in the following outcomes: infection related to CVC in two studies with 1,097 participants (RR 0.74, 95% =0.03 to 19.54; $P = 0.86$), bleeding from

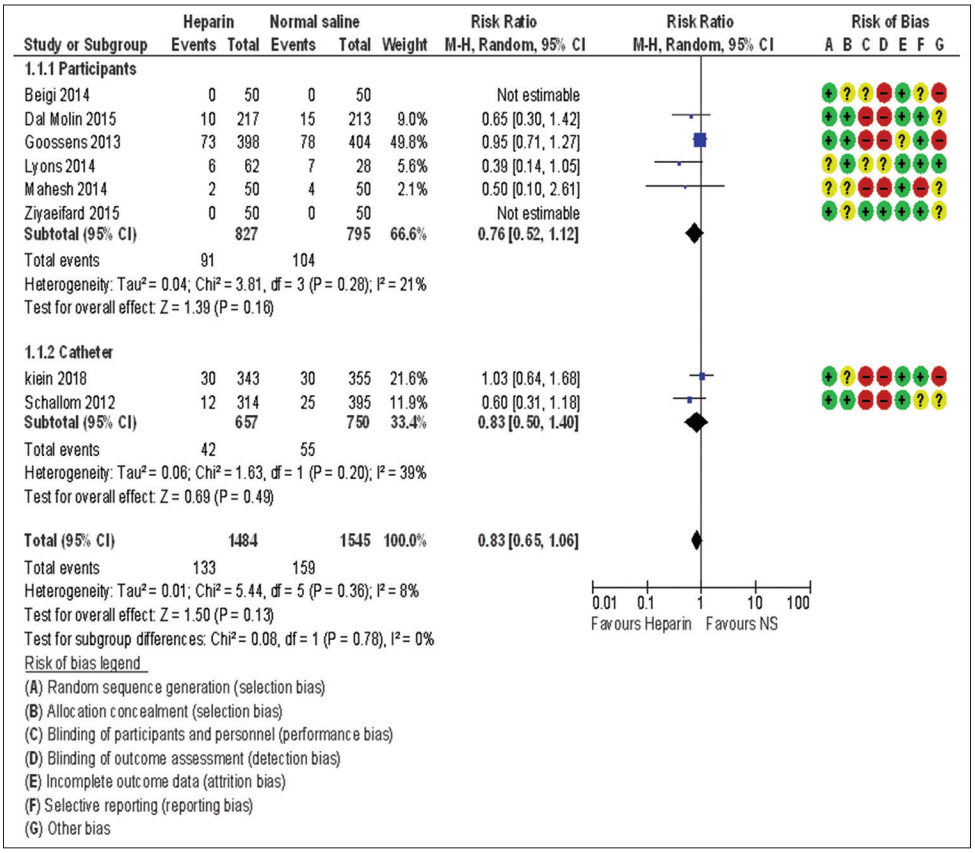

Figure 4: Forest plot of comparison between normal saline (NS) vs. heparin flush and the patency of catheter

any site in the body in three studies with 1,197 participants (RR 0.62, 95% =0.03 to 12.87; $P = 0.76$), CVC related thrombosis in three studies with 1,527 participants (RR 1.25, 95% =0.77 to 2.03; $P = 0.37$) and mortality in one study with 802 participants (RR 0.73, 95% =0.42 to 1.27; $P = 0.26$). Only one secondary outcome (HIT) in two studies with 395 participants show the contradictory effect with heparin (less cases of HIT in heparin group than NS group; RR 0.21, 95% =0.01 to 4.27; $P = 0.31$) Figure 5.

We downgraded the quality of evidence because of mainly unclear allocation concealment, imprecision, and doubt of publication bias.

Discussion

CVC is used in clients with critical illness for the prevention of infection, injection of medications, and parenteral nutrition. Nurses along with other health care workers deal with such patients as a part of daycare routine, and if prevention of infection is done at an early stage, then it can reduce the risk of lung infection and other serious complication. Heparin and normal saline flush is used to keep the tubing patent until the administration of next medication and speedy recovery happens if used cautiously as primary prevention.

The use of CVC is common in critical care units for various purposes, but it is associated with some complications.[1,2,4] One of the major complications is catheter occlusion, and heparin is a widely used solution to prevent occlusion of catheter.[10,11] However, complications such as allergic reaction, risk of bleeding, and HIT are associated with heparin flush.[25,30,31] While some studies provided evidence that NS is as effective as heparin for maintaining CVC patency and

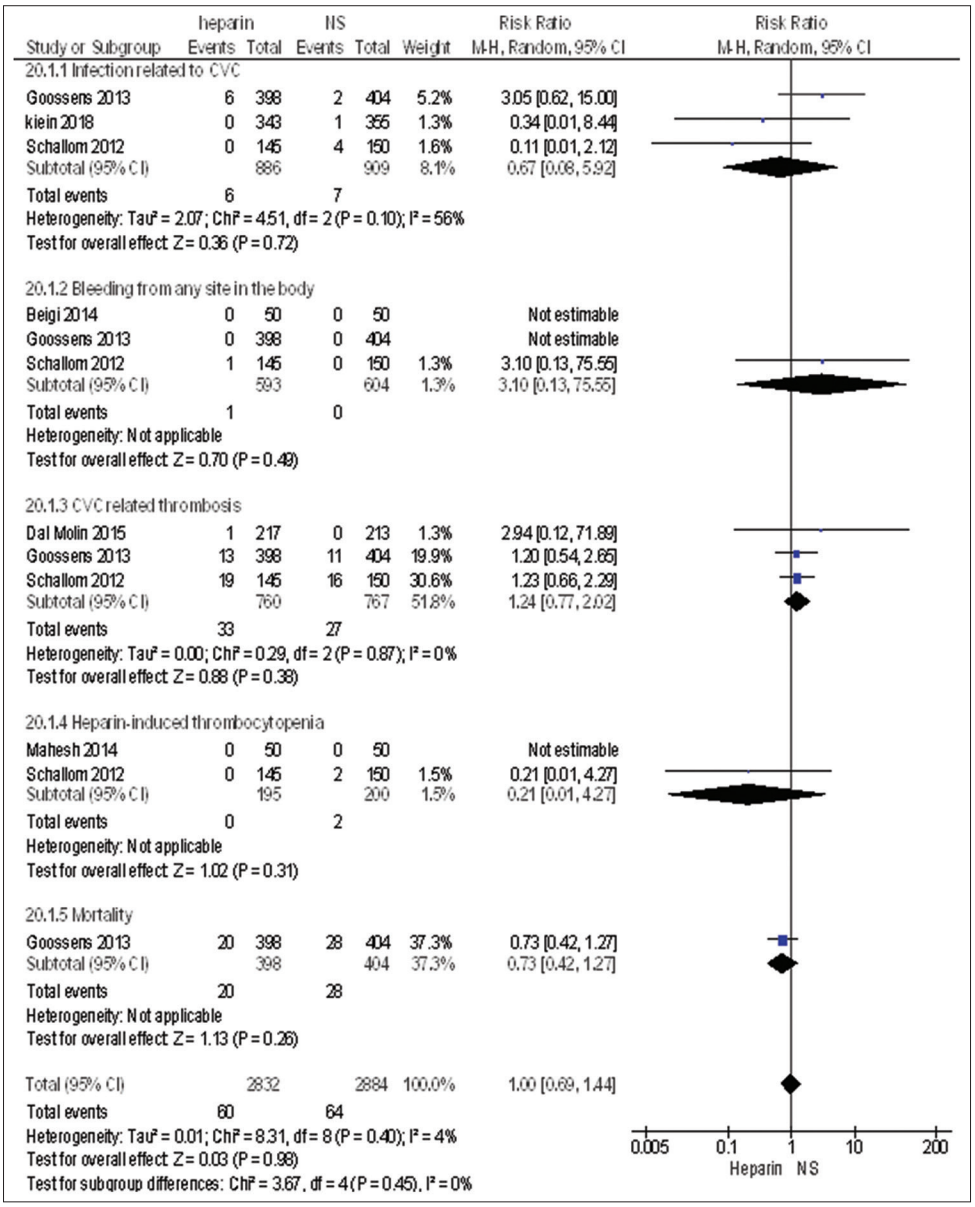

Figure 5: Forest plot of comparison between normal saline (NS) vs. heparin flush and secondary outcomes

have some potential benefits like less complication and cost than heparin.[33,34]

Therefore, the present review is carried out to identify which solution is better than other and results of our study revealed that heparin flush had a little favorable effect to maintain the patency of CVC when compared with NS, but there was no clear evidence of an effect on secondary outcomes between the groups.

There are few RCTs which compared heparin flush vs. normal saline flush for maintaining the patency of catheter in adults. One of the studies concluded that heparin was better than normal saline particularly in terms of catheter survival rate.[22] While some other studies showed that there is no difference in patency of catheter when heparin was compared with normal saline.[39,40] Another report from a multicenter RCT[43] consisted with[39,40] and concluded that heparin is not more effective than normal saline for maintaining CVCs patency, and there was no statistical difference was present.

Results of our review and meta-analysis are consistent with other reviews,[2,3] explained that heparin was associated with fewer occlusion rate of CVC than NS, but quality of evidence was very low. They also concluded that there was no evidence of differences in secondary outcomes (infection, bleeding, thrombosis, HIT, and mortality).

The results of other reviews[36,46] concluded that there is no evidence of a difference between the groups to maintain the patency of CVC. Another meta-analysis[47] revealed that there is no evidence of different effectiveness between heparin flushing and normal saline or other solutions in reducing catheter occlusion.

There are some systematic reviews that used heparin in CVCs but have different inclusion and/or exclusion criteria from this review as one review[48] was carried out among adults and pediatrics participants and concluded that there was a trend toward a decrease in catheter and venous thrombosis significantly when heparin is used. Another review[49] in adults participants with CVCs or PICCs and compared heparin locking, continuous heparin perfusion, NS locking, and urokinase locking versus any other protocol, concluded that there is clear evidence that heparin is more effective than NS. Furthermore, two similar systematic reviews[5,50] carried out in pediatrics and concluded that it is still unclear whether heparin is required to maintain the patency of CVCs.

There are various factors like types of catheter, strength, amount, and frequency of heparin used for flushing, physical condition of patient, and puncture site that are associated with patency of CVC.[51,52] Therefore, well-designed RCTs are required to identify the effect of these factors on the primary outcome.

We found some potential limitations in this review. First, although there was low statistically heterogeneity but methodological heterogeneity likes different kinds of participants, use different strength of heparin concentration, and duration of follow-up in included studies. Second, we explored MEDLINE, Embase, and Cochrane library but could not search CINHAL. In this review, most of the included studies were single centric and had a small sample size.

Conclusion

As per the evidence of this review, there is little or no effect of heparin to maintain patency of catheter when compared with normal saline but no clear evidence between heparin and normal saline flush in secondary outcomes. Moreover, the quality of evidence was very low; therefore, we are not sure whether heparin flush is better to maintain CVC patency than NS flush and results should be comprehended with cautiously. Therefore, further, it is needed to carry out large scale RCTs with standard methodology and at a multi-centric level to produce clear evidence which solution is better in terms of maintaining the patency, cost-effectiveness, and safety of the patients.

Additional Files

Additional file 1: The PRISMA checklist.
Additional file 2: PICO framework.
Additional file 3: The search strategy and search results

Abbreviations

CI: confidence interval; CRBSI: catheter-related bloodstream infection; CVCs: central venous catheters; HIT: heparin-induced thrombocytopenia; ICUs: intensive care units; NS: normal saline; RCTs: randomized controlled; RR: relative risk.

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Conflicts of interest

There are no conflicts of interest.

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Additional file 1: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 Additional file 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2, Additional file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Additional file 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2,5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2,5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6,7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3 Figure-1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4,5 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5 Figure 2 (2 (a), 2 (b))
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6,7 Figure 4 and 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6,7 Figure 4 and 5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8

Contd...

Additional file 1: Contd...

Section/topic	#	Checklist item	Reported on page #
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Additional file 2: PICO FRAMEWORK

Population	Adult patients with central venous catheter
Intervention	Heparin solution (any strength) for flushing the catheter
Comparison	0.9% sodium chloride for flushing the catheter
Outcome	Primary- catheter patency Secondary- catheter-related infection, venous thrombosis, bleeding from any site in the body, HIT, allergy, mortality etc.

Medline search

Additional file 3: Search strategy

("central venous catheters"[MeSH Terms] OR ("central"[All Fields] AND "venous"[All Fields] AND "catheters"[All Fields]) OR "central venous catheters"[All Fields] OR ("central"[All Fields] AND "venous"[All Fields] AND "catheter"[All Fields]) OR "central venous catheter"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

("central venous catheters"[MeSH Terms] OR ("central"[All Fields] AND "venous"[All Fields] AND "catheters"[All Fields]) OR "central venous catheters"[All Fields] OR ("central"[All Fields] AND "venous"[All Fields] AND "catheter"[All Fields]) OR "central venous catheter"[All Fields]) AND ("saline solution"[MeSH Terms] OR ("saline"[All Fields] AND "solution"[All Fields]) OR "saline solution"[All Fields] OR ("normal"[All Fields] AND "saline"[All Fields]) OR "normal saline"[All Fields]) AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

("central venous catheters"[MeSH Terms] OR ("central"[All Fields] AND "venous"[All Fields] AND "catheters"[All Fields]) OR "central venous catheters"[All Fields] OR ("central"[All Fields] AND "venous"[All Fields] AND "catheter"[All Fields]) OR "central venous catheter"[All Fields]) AND ("saline solution"[MeSH Terms] OR ("saline"[All Fields] AND "solution"[All Fields]) OR "saline solution"[All Fields] OR ("normal"[All Fields] AND "saline"[All Fields]) OR "normal saline"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

("central venous catheters"[MeSH Terms] OR ("central"[All Fields] AND "venous"[All Fields] AND "catheters"[All Fields]) OR "central venous catheters"[All Fields] OR ("central"[All Fields] AND "venous"[All Fields] AND "catheter"[All Fields]) OR "central venous catheter"[All Fields]) AND ("saline solution"[MeSH Terms] OR ("saline"[All Fields] AND "solution"[All Fields]) OR "saline solution"[All Fields] OR ("normal"[All Fields] AND "saline"[All Fields]) OR "normal saline"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND patency[All Fields] AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

CVC[All Fields] AND ("saline solution"[MeSH Terms] OR ("saline"[All Fields] AND "solution"[All Fields]) OR "saline solution"[All Fields] OR ("normal"[All Fields] AND "saline"[All Fields]) OR "normal saline"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND patency[All Fields] AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

CVC[All Fields] AND ("saline solution"[MeSH Terms] OR ("saline"[All Fields] AND "solution"[All Fields]) OR "saline solution"[All Fields] OR "0 9 nacl"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND patency[All Fields] AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

CVC[All Fields] AND ("saline solution"[MeSH Terms] OR ("saline"[All Fields] AND "solution"[All Fields]) OR "saline solution"[All Fields] OR "0 9 nacl"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND patancy[All Fields] AND RCT[All Fields] AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT]

("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND ("catheterisation"[All Fields] OR "catheterization"[MeSH Terms] OR "catheterization"[All Fields]) AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND ("catheterisation"[All Fields] OR "catheterization"[MeSH Terms] OR "catheterization"[All Fields]) AND PATENCY[All Fields] AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

Contd...

Additional file 3: Contd...

("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND ("catheterisation"[All Fields] OR "catheterization"[MeSH Terms] OR "catheterization"[All Fields]) AND PATENCY[All Fields] AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields]) AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND (("catheterisation"[All Fields] OR "catheterization"[MeSH Terms] OR "catheterization"[All Fields]) AND PATENCY[All Fields]) AND ("2012/01/01"[PDAT] : "2018/12/31"[PDAT])

International Clinical Trials Registry Platform

- 125 records for 119 trials found for: Heparin AND Catheter
- 7 records for 6 trials found for: Heparin AND cvc

Embase search

1	('**central venous catheter**'/exp OR '**central venous catheter**' OR (('**central**'/exp OR **central**) AND **venous** AND ('**catheter**'/exp OR **catheter**))) AND ('**heparin**'/exp OR **heparin**) AND ('**normal saline**'/exp OR '**normal saline**' OR (**normal** AND ('**saline**'/exp OR **saline**)))	175
2	('**central venous catheter**'/exp OR '**central venous catheter**' OR (('**central**'/exp OR **central**) AND **venous** AND ('**catheter**'/exp OR **catheter**))) AND ('**heparin**'/exp OR **heparin**) AND ('**normal saline**'/exp OR '**normal saline**' OR (**normal** AND ('**saline**'/exp OR **saline**))) AND **patency**	49
3	('**central venous catheter**'/exp OR '**central venous catheter**' OR (('**central**'/exp OR **central**) AND **venous** AND ('**catheter**'/exp OR **catheter**))) AND ('**heparin**'/exp OR **heparin**) AND ('**normal saline**'/exp OR '**normal saline**' OR (**normal** AND ('**saline**'/exp OR **saline**))) AND **patency** AND ('**adult**'/exp OR **adult**)	18 **9**
4	('**heparin**'/exp OR **heparin**) AND ('**0.9 % sodium chloride**' OR (**0.9** AND **%** AND ('**sodium**'/exp OR **sodium**) AND ('**chloride**'/exp OR **chloride**))) AND **patency** AND ('**adult**'/exp OR **adult**)	15
5	('**heparin**'/exp OR **heparin**) AND ('**0.9 % sodium chloride**' OR (**0.9** AND **%** AND ('**sodium**'/exp OR **sodium**) AND ('**chloride**'/exp OR **chloride**))) AND ('**occlusion**'/exp OR **occlusion**) AND ('**adult**'/exp OR **adult**)	14
6	('**heparin**'/exp OR **heparin**) AND **normal** AND **saline**	944
7	('heparin'/exp OR heparin) AND normal AND saline AND central AND venous AND catheter	53
8	('central'/exp OR central) AND venous AND ('catheter'/exp OR catheter) AND ('heparin'/exp OR heparin) AND normal AND ('saline'/exp OR saline) AND patency	20
9	('central'/exp OR central) AND venous AND ('catheter'/exp OR catheter) AND ('heparin'/exp OR heparin) AND normal AND ('saline'/exp OR saline) AND patency AND adult	09