Review

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Heparin versus normal saline locking for prevention of occlusion, catheter-related infections and thrombosis in central venous catheter in adults: Overview of systematic reviews

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Abstract

Venous access devices are used in health care. To prevent occlusions the evidence confirmed the need for routine catheter flushing before and after infusion as well as at the end of use. To date, the efficacy of heparin has not been demonstrated. The aim of this study was to evaluate the effectiveness of the locking of central venous catheters with heparin versus normal saline in adults to prevent occlusion, catheter-related infections and thrombosis in adults. A literature search using Medline, Embase, Cochrane Library and Cinahl was performed to identify all meta-analyses addressing the effectiveness of heparin versus normal saline in locking central venous catheters in adults. Four reviewers independently selected publications assessed quality and extracted data. Parameter estimates regarding occlusion, catheter- related infections and thrombosis were pooled using an umbrella review. We identified 6356 references. Seven systematic reviews were included in the study. Most of the studies included in the systematic reviews were conducted in oncohaematology departments, intensive care and cardiac surgery units among patients with multiple diseases and chronicity. Most studies report a heparin concentration of 10 to 5000 IU/ml versus normal saline and other solutions. There was no evidence that heparin was more effective than normal saline in reducing complications such as occlusion, catheter-related infections and thrombosis. No statistically significant difference was found between heparin and normal saline in reducing catheter occlusion. Heparin is not superior compared to normal saline.

Keywords

Central venous catheter, heparin, normal saline, flushing, locking, systematic review, complications, occlusion, catheter-related infections, catheter-related thrombosis

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Introduction

A central venous catheter is a device with a tip that reaches anatomically into the proximal third of the superior or inferior vena cava of the right atrium. The devices can be inserted through a peripheral vein (PICC) or a proximal central vein (CICC); the veins generally used are internal jugular, subclavian and femoral vein (FICC).[1] The axillary vein is more and more used in the last decades.[2]

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Venous access devices are used in health care. Central venous catheters (CVCs) are not a big portion of these devices[3] because in Europe and in the USA, the ratio between peripheral venous access devices and central venous access device is 22:1.[4]

The infusion of solutions which are not compatible with peripheral way is the main indication for insertion of the CVCs.

The choice criteria for the insertion of central venous catheter, depend on several factors, among the main ones to be considered ph, osmolarity and type of solution to be infused (vescicants or irritants), as well as in case of parenteral nutrition, haemodialysis or haemodynamic monitoring.[5]

The use of these devices leads to the onset of complications in approximately 15% of patients. Catheter-related infections, occlusions and thrombosis account for approximately two-thirds of the total number of late complications.[6]

To prevent occlusions and increase the patency of the vessel, evidence confirmed the need for routine catheter flushing before and after infusion as well as at the end of use.[5] Flushing an intravascular catheter is defined as the manual injection of a generally normal saline, with push and pause technique, with the aim of cleaning the internal lumen of the catheter by removing the remains of infused substances and maintaining its patency. Locking with pulse positive pressure is generally defined as the intraluminal injection of a limited volume of fluid, after flushing the catheter, during periods when the catheter is not in use, in order to prevent lumen occlusion and/or bacterial colonisation.[5]

Flushing can be performed both using normal saline and heparin; several systematic reviews, however, showed that locking with heparin (10 U/ml) has the same effectiveness as a normal saline in preventing catheter-related complications.[2,7,8]

The Infusion Nursing Society (INS) Guidelines[9] state that the flushing of a central vascular device should be performed using normal saline 0.9% with a volume at least twice the internal volume of the system (using 10 ml syringes); with regards to locking, including peripherally inserted central catheters (PICCs) and Ports,there is insufficient evidence to demonstrate whether one strategy is superior to the other, and this is due to the fact that the outcomes are superimposable.[10]

To date, the efficacy of heparin has not been demonstrated, and various side effects have been linked to its use; normal saline 0.9% is harmless and well-tolerated by patients.[11] To the best of our knowledge, there is only one overview of systematic reviews[12] in this topic. However, this study was published in Italian language and the results were described only through narrative approach.

This is the first study conducted in the English language that seeks to summarise the results obtained from previous systematic reviews conducted on this topic.

The aim of this overview was to summarise the evidence from systematic reviews on the effects of heparin locking on preventing occlusions, catheter-related infections and thrombosis in adults patients with CVC.

Methods

This overview complies with the recommendation given in Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015.[13]

The protocol was registered in the PROSPERO database (n° ********).

Database search strategy

The PICO framework[14] was used to indicate the clinical questions (Table 1). Searches were performed within the following databases: Medline, Embase, Cochrane Library, and Cinahl. The search strategy was constructed by combining free-terms and Medical Subject Headings (MeSH) terms with Boolean operators. The complete search strategy can be found in Supplemental File 1. No language restrictions were applied.

The reference population is made up of adult subjects (male and female) with central venous catheters. The intervention is characterised by flushing/locking with heparin. The comparison is characterised by flushing/locking with normal saline. The primary outcome of interest was the occlusion of the central venous catheters (defined as the inability to infuse fluids through the catheter due to an obstruction or persistent withdrawal occlusion[7]). The secondary outcomes included were catheter-related infection and catheter-related thrombosis.

Selection study and eligibility criteria

This study included systematic reviews with meta-analysis regarding heparin versus normal saline in the flushing/locking of central venous catheters in adults. Other study designs, such as randomised controlled trials (RCTs) and observational studies, studies with subjects under the age of 18 (paediatric patients) and patients with peripheral venous catheters or catheters for haemodialysis were excluded.

Four reviewers (BB, DC, IS and VT) independently screened titles and abstracts in order to identify relevant systematic reviews. Full texts were also evaluated by these

Table 1. PICO framework.

Population	Adults with central venous catheter
Intervention	Flushing/locking with heparin
Comparison	Flushing/locking with normal saline
Outcomes	Occlusion, catheter-related infections, catheter-related thrombosis

reviewers. Any discrepancies were resolved with a fifth review (MB).

Data extraction

The data were extracted by four independent reviewers (BB, DC, IS and VT). Any disagreements will be resolved by discussions and confrontation with a fifth reviewer (MB).

For each included study, the following information were extracted:

- First author and year of publication
- Title of the review
- Aim of study
- Description of the subjects included
- Number of studies included/number of patients included in the study
- Description of the intervention evaluated (i.e. heparin concentration, type of flushing and locking)
- Description of the control evaluated (i.e. type of solution)
- Setting
- Outcomes (primary and secondary)
- Association estimate/mean difference
- Between studies heterogeneity evaluation (heterogeneity test's, p-value and/or I^2 index).

Assessment of methodological quality

Four reviewers (BB, DC, IS and VT) independently evaluated the methodological quality of the included studies. Any discrepancies were again resolved by discussion with a fifth reviewer (MB).

The assessment of multiple systematic reviews (AMSTAR)[15] tool was used to assess the quality of the included systematic reviews, and it included 11 items.

Each item was evaluated as follows: 'Yes' (definitely done), 'No' (definitely not done), 'Unable to answer' (unclear status) or 'Not applicable'. For each 'Yes' answer, the rating was taken to indicate whether or not the quality was adequate. Systematic reviews were evaluated as high quality (score 8–11), medium quality (score 4–7) or low quality (score 0–3). Systematic reviews were not excluded from the overview based on the AMSTAR score. Exclusion was determined by the potential difference between the quality of the studies was discussed. For each of the considered results, the estimates of the associations deriving from the included meta-analysis were represented by a forest plot.

Data analysis

The concordance among reviewers in the papers' inclusion evaluation was assessed using the Fleiss' kappa.[16] Agreement was considered 'poor' if K was lower than 0, 'slight' if K was between 0.01 and 0.20; if K was between 0.21 and 0.40 'fair agreement', if K was between 0.41 and 0.60 'moderate agreement', if K was between 0.61 and 0.80 'good agreement', and 'almost perfect' if K was greater than 0.8. The association measures between flushing solutions and the risk of the selected outcomes (or mean difference for CVC patency) extracted from the meta-analyses included in the study were graphically represented using forest plots.

Results

We identified 6356 references through the search strategy conducted on April 29, 2021. After the screening conducted by the four aforementioned reviewers, seven systematic reviews were included[17–23] (Figure 1). The PRISMA flow diagram presented in Figure 1 illustrates the review process being conducted.

A very good correlation was observed between the four reviewers (Fleiss' K 0.729).

Description of included reviews

Seven systematic reviews met the inclusion criteria for this overview.[17–23] Overall, participants included in the systematic reviews ranged from 1323 to 7875.

All the included reviews reported a comparison between heparin and normal saline.[17–23] Dal Molin et al.[17] also included studies that compared heparin with other solutions such as urokinase, lepirudin and vitamin C. The heparin concentration ranged from 10 UI/ml from 5000 UI/ml. Occlusion was the most frequently reported outcome (7 out of 7 studies), followed by catheter-related infections (4 out of 7 studies).

All reviews included populations from hospital settings, particularly oncology patients and/or critical patients.

Low heterogeneity affects the specific pooled estimates of the meta-analyses with I^2 index values lower than 50%; the exception to this was in the outcomes of the Wen et al.[23] and Lopez et al.[19] study regarding catheter-related infections and heparin-induced thrombocytopenia.

Further details of the included reviews can be found in Table 2.

Methodological quality of included reviews

The methodological quality of the included systematic reviews was independently assessed by each of the four authors (BB, DC, IS and VT) using the AMSTAR checklist.[15]

The methodological quality of the seven studies included in this review is moderate-high.

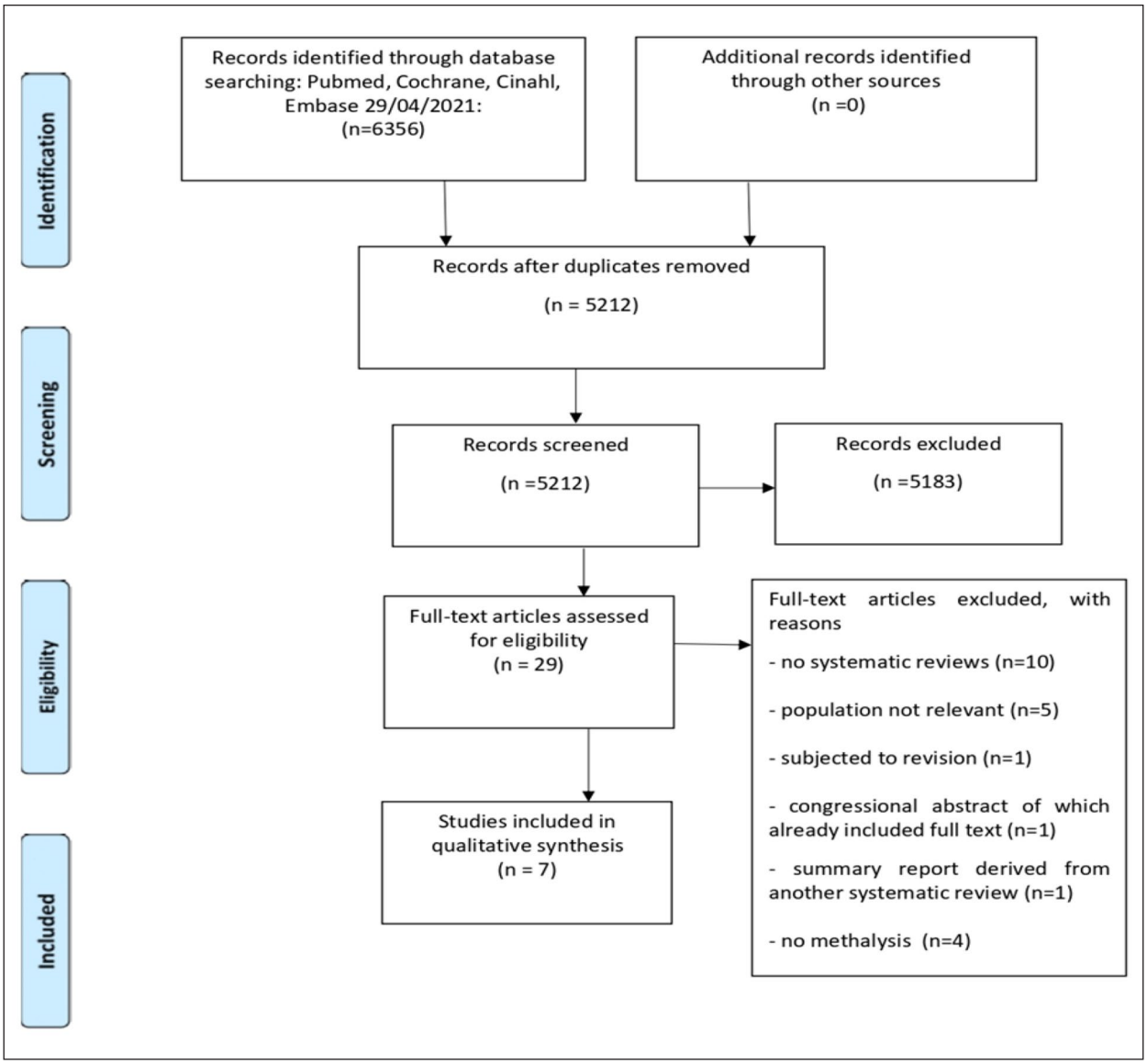

Figure 1. PRISMA flow diagram.

Effect of intervention

Through the overview of the systematic reviews, insufficient evidence was found to determine the effects of heparin locking versus normal saline locking, specifically in preventing occlusion in central venous catheters in adults. There is no evidence that heparin is more effective than normal saline in reducing catheter-related infections and catheter-related thrombosis.

Occlusion. All systematic reviews[17–23] evaluated the effect of heparin, at different concentrations versus normal saline in CVC locking, determining occlusions as the primary outcome. With regard to the risk of occlusions, most studies have shown no differences between locking with heparin and locking with normal saline with RR ranging from 0.55 Dal Molin et al.[17] to 1.58 Wen et al.[23] (Figures 2 and 3). The only meta-analysis reporting a statistically significant result is that of Lopez et al.[19] which showed that locking with heparin reduces the risk of occlusion by 30% compared to normal saline; this is not the case when only studies with good allocation concealment are considered.

Catheter-related infections. Four studies[18–21] analysed catheter-related infections. The results showed that catheter-related infection rates were not statistically significant (Figure 4).

Catheter-related thrombosis. Three studies[19–21] reported on the incidence of CVC-related thrombosis. There was no evidence of a differential effect between heparin and normal saline groups. Two studies have equal estimates as they are based on the same original study (Figure 5).

Data on cvc patency (defined as ability to infuse normal saline and withdraw a blood sample[24]) and heparin-induced

Table 2. Characteristics of study included.

Firts authors	Titles of the reviews	Aim of study	Subject	n°study/ n°subject	Interventions	Control	Settings	Outcomes	Estimates	Heterogeneity assessment (Heterogeneity test's p-vale and/or I2 index)
Dal Molin et al.[27]	Flushing the central venous catheter: is heparin necessary?	To compare the effectiveness of heparin over other solutions in catheter flushing among adult patients with central venous catheter	Adults > 18 years with CVC	8/1323	Heparin (from 10 to 5000 IU/ml)	Normal Saline 0.9%	Onco-haematology, Intensive care	N° occlusions Venous thromboembolismcatheter-related infections, heparin-induced thrombocytopenia.	0.55 (0.12;1.37) NA	I^2 = 30%
Dos Santos et al.[22]	Effectiveness of heparin versus 0.9% saline solution in maintaining the permeability of central venous catheters: a systematic review	Determining the effectiveness of heparinized flush solutions compared to 0.9% saline flush in the permeability of central venous catheters in adults.	Adults > 18 years with CVC	9/2645	Heparin (from 10 to 5000 IU/mL)	Normal Saline 0.9%	Haemodialysis, Oncohematology, Intensive care	N° occlusions	0.68 (0.41–1.10)	p = 0,35 I^2 = 9%
Wen et al.[23]	Flushing effects of normal saline and heparin saline after central venous catheterisation: a meta-analysis	To evaluate the flushing effects of normal saline (NS) and heparin saline (HPS) after central venous catheterisation.	Adults > 18 years with CVC	12/2092	Heparin (from 10 to 1000 IU/mL)	Normal Saline 0.9%	\	N° occlusions Patency of the CVC in days	1.58 (0.79; 3.14) −7.24 (−22.90; 8.41)	$p < 0.0001$ I^2 = 74% $p < 0.00001$ I^2=93%
Zhong et al.[21]	Normal saline versus heparin for patency of central venous catheters in adult patients – a systematic review and meta-analysis	To assess the efficacy of NS versus HS in the maintenance of the patency of CVCs in adult patients.	Adults > 18 years with CVC	10/7875	Heparin (from 10 to 5000 IU/mL)	Normal Saline 0.9%	House assistance Cardiac surgery Oncohematology Oncology Intensive care	N° occlusions Heparin-induced thrombocytopenia Haemorrage Catheter-related thrombosis Catheter-related infections Catheter-related infections	1.21 (0.91; 1.61) 1.33 (0.09; 18.54) 0.75 (0.32; 1.74) 0.81 (0.50; 1.31) 0.84 (0.11; 6.71) 0.84 (0.11; 6.71)	p = 0.299 I^2 = 16,6% p = 0.231 I^2 = 30.4% p = 0.851 I^2 = 0.0% p = 0.872 I^2 = 0.0% p = 0.126 I^2 = 51.7% p = 0.126 I^2 = 51.7%
Lòpez-Briz et al.[19]	Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults	To assess the effectiveness and safety of intermittent locking of CVCs with heparin versus normal saline (NS) in adults to prevent occlusion.	Adults > 18 years with CVC	11/2392	Heparin (from 10 to 5000 IU/mL)	Normal Saline 0.9%	Hospital setting	N° occlusions Patency of the CVC in days Catheter-related infections Site haemorrage Catheter-related thrombosis Heparin-induced thrombocytopenia Allergic reactions to heparin, n°of added CVC insertions and altered coagulation profile	0.70 (0.51; 0.95) **0.74 (0.51; 1.05) 0.44 (−0.10;0.99) 0.74 (0.03; 19.54) 1.32 (0.57; 3.07) 1.24 (0.77; 2.02) 0.21 (0.01; 4.27) NA	p = 0,32 I^2 = 14% p = 0.23 I^2 = 31% p = 0.95 I^2 = 0% p = 0.05 I^2 = 74.77% p = 0.85 I^2 = 0% p = 0.87 I^2 = 0% $p < 0.0001$ I^2 = 100%
Sharma et al.[20]	Heparin flush vs. normal saline flush to maintain the patency of central venous catheter among adult patients: A systematic review and meta-analysis	To evaluate the efficacy of heparin flush vs. normal saline flush to maintain the patency of CVC among adult patients.	Adults > 18 years with CVC	9/ 3113	Heparin (from 10 to 1000 IU/mL)	Normal Saline 0.9%	Oncohematology, Cardiology	N° occlusions Heparin-induced thrombocytopenia Haemorrage from any part of the body Catheter-related infections Catheter-related thrombosis	0.83 (0.65; 1.06) 0.21 (0.01; 4.27) 3.10 (0.13; 75.55) 0.67 (0.08; 5.92) 1.24 (0.77; 2.02)	p = 0.6 I^2 = 8% NA NA p = 0.10 I^2 = 56% p = 0.87 I^2 = 0%
Wu et al.[18]	Heparin versus 0.9% saline solution to maintain patency of totally implanted venous access ports in cancer patients: A systematic review and meta-analysis	Systematically evaluate whether NS can replace HS in the locking of total implantable venous accesses.	Adults > 18 years with CVC	4/2652	Heparin (from 50 to 100 IU/mL)	Normal Saline 0.9%	Oncology	N° occlusions Catheter-related infections Catheter-related thrombosis	1.02 (0.77; 1.35) 0.83 (0.45; 1.53) NA	p = 0.23 I^2 = 30% p = 0.36 I^2 = 3%

CVC: Central venous catheters; NS: Normal saline; HS: Heparin saline; IU: International Unit.
**good allocation concealment.

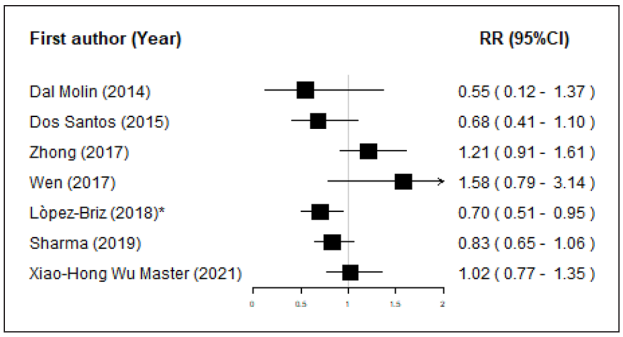

Figure 2. Occlusions.
*All studies.

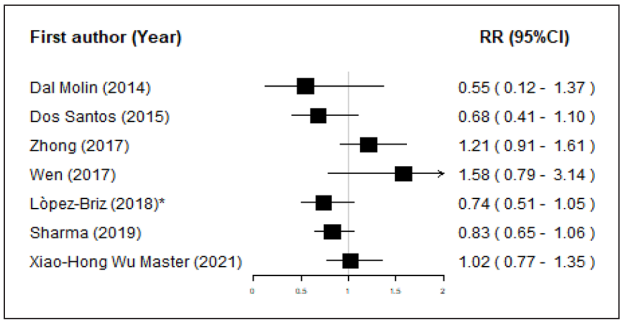

Figure 3. Occlusions.
*Studies with good allocation concealment.

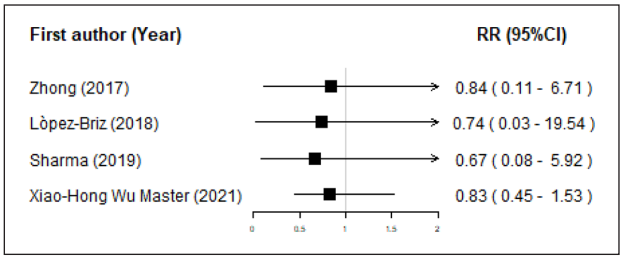

Figure 4. Catheter-related infection.

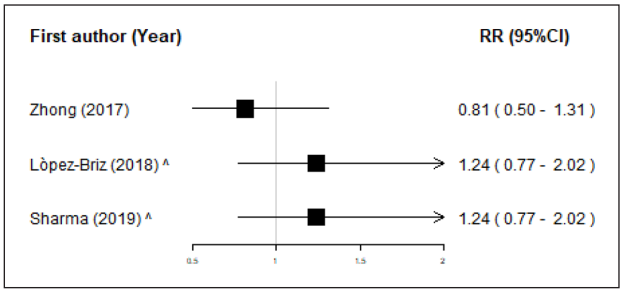

Figure 5. Catheter-related thrombosis.
^Equal estimates because based on the same original studies.

thrombocytopenia (defined as a clinicopathological syndrome that occurs when heparin dependent IgG antibodies bind to heparin/platelet factor 4 complexes to activate platelets and produce a hypercoagulable state[25]) are reported in the Supplemental File 2.

Discussion

We observed that the use of heparin in flushing/locking of CVC has been considered for several years as a traditional and useful practice in maintaining the CVC. However, the management of central venous catheters from this point of view has not yet been fully standardised.

The aim of this overview of systematic reviews was to evaluate the effectiveness of heparin with regards to the central venous catheter. In this review, we did not decide to include studies conducted on paediatric patients and patients with haemodialysis and peripheral catheters.

Our overview indicated that heparin is no more effective than normal saline in catheter locking. The results are consistent with the overview conducted by Re et al.[12] In our overview four new systematic reviews with meta-analysis were included. The systematic reviews conducted by Mitchell et al.[8] and Encarnação et al.[3] were not considered in our study because the authors did not perform a meta-analysis.

On its own, heparin is not a thrombolytic agent. Its use prevents the progression and formation of new clots. To date, there is no evidence in the literature to support heparin concentration correlates with improved CVC patency rates.[26]

Several clinical studies[26–28] published in the literature as far as non-dialysis catheters (NDCVA) are concerned, the standardised use of normal saline solution is to be preferred to anticoagulant solutions and, in particular, to heparinized saline solutions.

The efficacy of heparin was evaluated by Dal Molin et al.[27] in a multicentre randomised trial where 415 patients were enrolled in this study. A total of 24 occlusions were observed: 10 observed in the heparin group and 14 in the normal saline group. No significant difference was found between the hazards of occlusion.[27]

The efficacy of this solution was also evaluated by some observational studies such as one retrospective study by Bertoglio et al.[26] conducted in 610 patients with a port showed no statistically significant differences for occlusive events between the group where the catheter was flushed with heparin solution and that of normal saline 0.9%.[26]

In the retrospective study conducted by de Oliveira Brito et al.[28] a total of 862 patients were enrolled.[28] The patients were divided into two groups: the heparin group (Hep group), whose lock was composed heparin (100 IU/mL) with saline solution 0.9% and the SS group (saline solution), whose lock was composed of saline solution 0.9%. The Heparin group (group 1) consisted of 270 patients (31%),

and the SS group (group 2) consisted of 592 patients (69%). Regarding occlusion, it was evident in eight cases in group 1 (2.96%) and in eight cases in group 2 (1.35%; $p = .11$).[28]

The use of heparin may cause some severe complications,[11,29,30] such as, heparin – induced thrombocytopenia[30] that we not considered in the protocol review, but it was included during the systematic analyse of the literature. Also, data about cvc patency (not considered in the protocol review) are presented in the Supplemental file 2; even these results indicate the no superiority of heparin. However, this results mush be considered with caution.

The prevention of catheter-related occlusion is based on a correct flushing protocol with 'push/pause' technique, before and after each solution. Next to this good flushing practice, it's also advisable to lock it with pulse positive pressure, with normal saline.[5] Therefore, adequate flushing and locking protocols are recommended for the prevention of catheter-related occlusion.

One systematic review conducted by Clari et al. founded no significant difference between standard and prolonged flushing schedule terms in of complications, concluding that a prolonged flushing and locking interval is feasible and safe.[31]

The use of normal saline 0.9% in flushing/locking cvc prevents exposure to complications arising from the use of heparin such as thrombocytopenia, occlusion, bleeding and catheter-related infections.[32]

This review has some limitations. We performed a search in MEDLINE, Cochrane Library, EMBASE and CINAHL, but grey literature was not included in the search. However, they are considered the main medical/nursing databases and we did not establish any language constraints.

In studies included there is no uniformity between the concentrations of heparin and the hospital protocols for its management are lacking.

When comparing the current study with others in the literature, several caveats should be borne in mind. Other studies may include multiple methods of heparin perfusion, they may have different inclusion and exclusion criteria and, in some cases, it may not be possible to perform separate analyses of the adult and paediatric populations, all of which may impact comparability and generalisability. In future studies, it is suggested that adult data be presented separately from paediatric data to address at least one of these issues, and it would be helpful if all primary studies were to follow a standardised procedure for lock CVC and use dosages as recommended by the guidelines. Anyhow, we feel that our search provides an acceptable overview of the studies.

Conclusions

In conclusion, we performed our review based on 7 meta-analysis summarising the evidence on the efficacy of locking heparin versus normal saline solution on catheter-related complications up to 2021. These results suggest that there is no evidence that heparin is more effective than normal saline in reducing occlusion, infections, and catheter-related thrombosis as reported in the single meta-analyses included in this review.

The normal saline appears to be a solution free from complications and can also be used in hospital and out-of-hospital settings.

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Declaration of conflicting interests

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Consent for publication

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Supplemental material

Supplemental material for this article is available online.

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