TITLE: Saline versus Heparin for Maintaining Patency of Central Venous Catheters: A Review of Clinical Effectiveness and Safety

DATE: 02 October 2013

CONTEXT AND POLICY ISSUES

Central venous access devices (CVAD) or central venous catheters (CVC) are devices that provide easy access to a patient's circulation and are used to administer medication, provide nutrition, obtain blood samples, and monitor hemodynamic parameters.[1-3] There are several types of central venous catheters (CVCs) such as peripherally inserted central catheter (PICC), tunneled catheter and implanted ports.[3] However, complications may arise with the use of these devices such as occlusion of the catheter and infection. For efficient use of CVCs, maintenance of catheter patency is important. Patency of the catheter depends on several factors such as the catheter material and gauge, connectors used, the infusion solutions, handling protocols, and patient characteristics.[4] After intermittent infusion, blood reflux within the catheter lumen may increase the risk of thrombus formation. Loss of catheter functionality due to thrombus formation may require thrombolytic therapy or catheter removal and replacement.[1] When thrombotic occlusion of CVC occurs, alteplase, a recombinant tissue plasminogen activator, is often administered to lyse the clot and restore patency.[2] To maintain functionality and patency of the catheter flushing is important. Saline or heparin have been used as a flushing solution. It is believed that heparin may prevent blood from clotting in the device.[5,6] However, heparin may be associated with adverse effects, such as risk of heparin induced thrombocytopenia. Furthermore, heparin dosing errors may lead to increased risk of bleeding.[5] There is still debate as to which flushing solution is the best option.

The purpose of this report is to provide evidence on the clinical effectiveness and safety of flushing with saline in comparison to heparin for maintaining patency of central venous catheters.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of saline compared with heparin to maintain patency of non-valved catheters in adult and pediatric patients?

2. What is the safety of saline compared with heparin to maintain patency of non-valved catheters in adult and pediatric patients?

KEY FINDINGS

In adult patients, catheter non-patency or occlusion appeared to be numerically higher with saline compared to heparin in many of the studies however the differences were not statistically significant in most cases. It was unclear whether these differences were clinically meaningful. In the light of this, it remains unclear as to whether saline or heparin is better for maintaining patency. In pediatric patients, catheter occlusion appeared to be higher with saline than with heparin however the differences were statistically significant in two out of three studies and findings need to be interpreted with caution.

In general, adverse effects associated with saline and heparin use were sparsely reported. Moreover, there were some inconsistencies in the findings between studies and definitive conclusions were not possible.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, CINAHL, The Cochrane Library (2013, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2008, and September 4, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, selected potentially relevant articles for retrieval of full-text publications for further investigation and evaluated the full-text publications for final selection, according to the criteria listed in Table 1.

Table 1: Selection Criteria

Population	Adults or pediatric patients with non-valved central venous catheters (CVCs)
Intervention	Flushing with saline to maintain patency of the non-valved, central venous catheters *Peripherally inserted central catheter (PICC) lines included as a type of CVC
Comparator	Flushing with heparin; Studies with no comparator were eligible for inclusion if few comparative studies were identified.
Outcomes	Patency, catheter occlusion, infection, adverse events
Study Designs	Health technology assessment (HTA), systematic review (SR) and meta-analysis (MA), randomized controlled trial (RCT), and non-randomized study

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2008, or included in an included systematic review. Studies which did not specifically mention central venous catheter, central venous access device, or peripherally inserted central catheter were excluded. Studies that were deemed to have incomplete reporting of outcomes, such as not reporting numerical values for outcomes, were excluded. As comparative studies were available, non-comparative studies were not included.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist[7] was used for systematic reviews and the Downs and Black checklist[8] for RCTs and non-randomized studies.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 101 citations. Upon screening titles and abstracts, 82 articles were excluded and 19 potentially relevant articles were selected for full-text review. One potentially relevant article was identified from the grey literature. Of these 20 articles, 12 did not satisfy the inclusion criteria and were excluded. The eight included articles comprised two systematic reviews, four RCTs and two non-randomized studies. No relevant health technology assessment was identified. Details of the study selection process are outlined in Appendix 1.

Summary of Study Characteristics

Characteristics of the included systematic reviews and clinical studies are summarized below and details are provided in Appendix 2.

<u>Systematic reviews</u>

Two relevant systematic reviews[5,9] were identified. One systematic review[9] on neonates was published in 2011 from Canada. It included one RCT comparing heparin with saline and two RCTs comparing heparin with no heparin and reported on occlusion, patency duration and adverse effects. One systematic review[5] on adult patients was published in 2009 from the USA. It included two RCTs and one non randomized study comparing saline with heparin and reported on patency.

<u>Randomized controlled trials</u>

Four relevant RCTs comparing saline with heparin[1,4,10,11] were identified. One RCT[10] was published in 2013 from Belgium, one RCT[1] was published in 2012 from USA, one RCT was published in 2010 from Brazil, and one RCT[11] was published in 2009 from Italy. Two RCTs[1,10] involved adult patients and two RCTs[4,11] involved pediatric patients. The number of patients

ranged between 133 and 802. Three RCTs[1,4,11] reported on occlusion and one RCT[10] reported injection and aspiration problems. All four RCTs reported on adverse effects.

Non-randomized studies

Two relevant non-randomized studies[2,6] comparing saline with heparin in adult patients were identified. One study[6] was published in 2012 from Italy and one study[2] was published in 2010 from USA. One study[6] included 610 patients and one study[2] did not report patient number and instead reported patient days per month. One study[6] reported on occlusion and adverse effects and one study[2] reported on alteplase use for CVAD occlusion.

Summary of Critical Appraisal

Strengths and limitations of individual studies are provided in Appendix 3.

Systematic reviews

Both systematic reviews[5,9] clearly stated the objective and inclusion/exclusion criteria, conducted a comprehensive literature search, described characteristics of the included studies, and performed quality assessment of the included studies. In one systematic review,[9] article selection and data extraction were done in duplicate and in one systematic review[5] it was unclear if article selection and data extraction were done in duplicate. Neither systematic review explored publication bias. Conflict of interest was stated in both systematic reviews and there appeared to be none.

Randomized controlled trials

All four RCTs[1,4,10,11] clearly stated the objective and the inclusion and exclusion criteria and described patient characteristics, interventions and outcomes, except one RCT[11] that did not explicitly state the exclusion criteria. All four RCTs were open label studies. Sample size calculation was provided in three RCTs[1,10,11] and not in one RCT.[4] Discontinuation or loss to follow up was mentioned in three RCTs[1,10,11] and not in one RCT.[4] All four RCTs provided P values though not always for all outcomes. Generalizability was limited as it was uncertain as to whether the study patients were representative of all patients.

Non-randomized studies

Both of the non-randomized studies[2,6] were retrospective studies. Patient characteristics were described in one study[6] and not in one study.[2]. Both studies described the interventions and outcomes. Both studies provided P values though not always for all outcomes. Generalizability was limited as both were single center studies and it was uncertain as to whether the study patients were representative of all patients.

Summary of Findings

The overall findings are summarized below and detailed findings from the systematic reviews and individual clinical studies are provided in Appendix 4.

What is the clinical effectiveness of saline compared with heparin to maintain patency of non-valved catheters in adult and pediatric patients?

Adult patients

Data on patency or injection and aspiration problems were available from one systematic review,[5] two RCTs[1,10] and two non-randomized studies.[2,6] The systematic review reported findings from individual studies and there was no pooling of data from the different studies.

In the systematic review,[5] which included adult in-patients with CVC, one RCT showed that with saline catheter patency was numerically lower than that with heparin, though not statistically significant, one RCT showed patency was similar in both groups, and one non-randomized study showed that with saline there was a statistically significant lower catheter patency than that with heparin.

One RCT[1] showed that in adult patients with CVC, the occlusion rate was numerically higher with saline than with heparin (6.3% with saline and 3.8% with heparin), though not statistically significant. In this RCT, patients received alteplase for lumens meeting the non-patency criteria and alteplase use was found to be statistically significantly higher in patients in the saline group compared with those in the heparin group (6.3% for saline and 2.8% for heparin). In one RCT[10] with mostly adult patients (3.5% being younger than 18 years) with CVC, injection and aspiration problems were numerically lower with saline than with heparin, however P-values to determine statistical significance were not reported (injection problems were 0.4% and 0.8% for saline and heparin respectively and aspiration problems were 5.4% and 5.8% for saline and heparin respectively).

One non randomized study[6] in adult cancer patients with CVAD, reported that the occlusion rate was numerically lower with saline than with heparin, though not statistically significant (5.7% for saline and 6.7% for heparin). One non-randomized study[2] did not directly report on occlusion rate but showed that with saline there was a statistically significant higher number of patients receiving alteplase for CVAD occlusion than with heparin (92 for saline and 58 for heparin).

Overall findings are summarized in Table 2 and details are available in Appendix 4.

Table 2: Comparison of saline versus heparin in adult patients

Study	Study type	Device	Outcome		
			Occlusion	Alteplase use	Injection/ aspiration problems
Mitchell[5]	SR (2 RCTs, 1 nRCT)	CVC	↑(NS), ↔(NS), ↑(S)	NR	NR
Goossens[10]	RCT	TIVAD	NR	NR	↓(NR)
Schallom[1]	RCT	CVC	↑(NS)	↑(S)	NR
Bertoglio[6]	nRCT	CVAD	↓(NS)	NR	NR
Jonker[2]	nRCT	CVAD	NR	↑(S)	NR

CVAD = central venous access device, CVC = central venous catheter, nRCT = non randomized study, NR = not reported, NS = not statistically significant, RCT = randomized controlled trial, S = statistically significant, SR = systematic review, TIVAD = totally implantable venous device.
↑ indicates higher numerical value and ↓ indicates lower numerical value and ↔ indicates same numerical value with saline compared with heparin. Statistical significance or non-significance is inserted in parenthesis, where available.

Pediatric patients

One systematic review[9] showed that in neonates with peripherally placed percutaneous CVC, the risk of occlusion was statistically significantly higher with saline compared with heparin however the duration of patency with saline compared to heparin was not statistically significantly different. These results were from a single RCT which was relevant for this report and included in the systematic review.

One RCT[4] showed that in newborns with PICC, catheter occlusion rate with saline was numerically higher than that with heparin, though not statistically significant (36 per 1,000 catheter-days for saline and 31 per 1,000 catheter-days for heparin). One RCT[11] showed that in pediatric patients with tunneled CVC, catheter occlusion rate with saline was statistically significantly higher than that with heparin (82.2% for saline and 40.2% for heparin).

Overall findings are summarized in Table 3 and details are available in Appendix 4.

Table 3: Comparison of saline versus heparin in pediatric patients

Study	Study type	Device	Occlusion
Shah[9]	SR (1 relevant RCT)	Peripherally placed percutaneous CVC	↑(S)
Araujo[4]	RCT	PICC	↑(NS)
Cesaro[11]	RCT	CVC	↑(S)

CVC = central venous catheter, NS = not statistically significant, RCT = randomized controlled trial, S = statistically significant, SR = systematic review

↑ indicates higher numerical value with saline compared with heparin. Statistical significance or non-significance is inserted in parenthesis.

What is the safety of saline compared with heparin to maintain patency of non-valved catheters in adult and pediatric patients?

Adult patients

In one RCT[10] with mostly adult patients (3.5% being younger than 18 years) with CVC, blood stream infection was numerically lower with saline than that with heparin, though not statistically significant (0.5% for saline and 1.5% for heparin). In this RCT venous thromboembolism was numerically lower with saline compared to heparin, but statistical significance was not reported (10.7% with saline and 13.1% with heparin). One RCT[1] showed that in adult patients with CVC, blood stream infection with saline was numerically higher than that with heparin, though not statistically significant (3.1 per 1,000 catheter-days for saline and 0 per 1,000 catheter-days for heparin). One non randomized study[6] in adult cancer patients with CVAD, catheter related infection was numerically higher with saline than that with heparin, however the P-value to determine statistical significance was not reported (5.7% with saline and 5.4% with heparin).

Pediatric patients

One systematic review[9] showed that in neonates with peripherally placed percutaneous CVC the risk of catheter-related sepsis was lower with saline than that with heparin, though not statistically significant (for heparin versus saline, relative risk [RR] 2.53, 95% confidence

interval [CI) 0.50 to 12.71). The risk of thrombosis was similar in both the saline and heparin groups (RR 1.01, 95% CI 0.56 to 1.83). These results were from a single RCT which was relevant for this report and included in the systematic review.

One RCT[4] showed that in newborns with PICC, numbers of patients with intracranial hemorrhage grades 1 or 2 or with thrombocytopenia were numerically higher with saline than with heparin though not statistically significant and numbers of patients with intracranial hemorrhage grade 3 were the same in both groups. One RCT[11] showed that in pediatric patients with tunneled CVC, proportion of patients with bacteremia or fungemia were statistically significantly higher in the saline group compared with the heparin group (23.8% with saline and 8.8% with heparin) and thrombosis was similar in both groups (1% in each group).

Limitations

Comparison between studies was difficult as there were differences in the doses of heparin used, the type of CVAD used, and the patient population.

Details regarding catheter material were not available in all the studies hence it was unclear if the type of material affected patency. Definitions of patency and occlusion were not always provided and the definitions varied between studies.

Not all studies reported the same outcomes. Adverse effects were sparsely reported and not all studies reported on adverse effects. Infection was reported in a number of studies but the reporting of infection varied (e.g. catheter related infection, blood stream infection, and exit site infection). Also, the studies were not powered to detect adverse events, so differences in rare event rates may not be detectable

The studies were conducted at single centers, mainly tertiary hospitals so generalizability of the findings may be limited.

None of the studies were conducted in Canada, so applicability to the Canadian setting is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In adult patients, catheter non-patency or occlusion appeared to be numerically higher with saline compared to heparin in many of the studies however the differences were not statistically significant in most cases. It was unclear whether these differences were clinically meaningful. In the light of this, it remains unclear as to whether saline or heparin is better for maintaining patency. In pediatric patients, catheter occlusion appeared to be higher with saline than with heparin however the differences were statistically significant in two out of three studies and findings need to be interpreted with caution.

In general, adverse effects associated with saline and heparin use were sparsely reported. Moreover, there were some inconsistencies in the findings between studies and definitive conclusions were not possible. Whichever option is used appropriate monitoring of adverse effects is an important consideration.

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REFERENCES

1. Schallom ME, Prentice D, Sona C, Micek ST, Skrupky LP. Heparin or 0.9% sodium chloride to maintain central venous catheter patency: a randomized trial. Crit Care Med. 2012 Jun;40(6):1820-6.

2. Jonker MA, Osterby KR, Vermeulen LC, Kleppin SM, Kudsk KA. Does low-dose heparin maintain central venous access device patency?: a comparison of heparin versus saline during a period of heparin shortage. JPEN J Parenter Enteral Nutr. 2010 Jul;34(4):444-9.

3. National Center for Emerging and Zoonotic Infectious Diseases. Central venous catheters - flushing techniques [Internet]. In: Basic infection control and prevention plan for outpatient oncology settings. Atlanta (GA): Centers for Disease Control and Prevention; 2011 [cited 2013 Sep 26]. Available from: http://www.cdc.gov/hai/pdfs/guidelines/basic-infection-control-prevention-plan-2011.pdf.

4. Araujo OR, Araujo MC, Silva JS, Barros MM. Intermittent heparin is not effective at preventing the occlusion of peripherally inserted central venous catheters in preterm and term neonates. Rev Bras Ter Intensiva. 2011 Sep;23(3):335-40.

5. Mitchell MD, Anderson BJ, Williams K, Umscheid CA. Heparin flushing and other interventions to maintain patency of central venous catheters: a systematic review. J Adv Nurs. 2009 Oct;65(10):2007-21.

6. Bertoglio S, Solari N, Meszaros P, Vassallo F, Bonvento M, Pastorino S, et al. Efficacy of normal saline versus heparinized saline solution for locking catheters of totally implantable long-term central vascular access devices in adult cancer patients. Cancer Nurs. 2012 Jul;35(4):E35-E42.

7. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2013 Sep 6];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2013 Sep 6];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

9. Shah PS, Shah VS. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. Cochrane Database Syst Rev. 2008;(2):CD002772. Updated 2011 Jan 3.

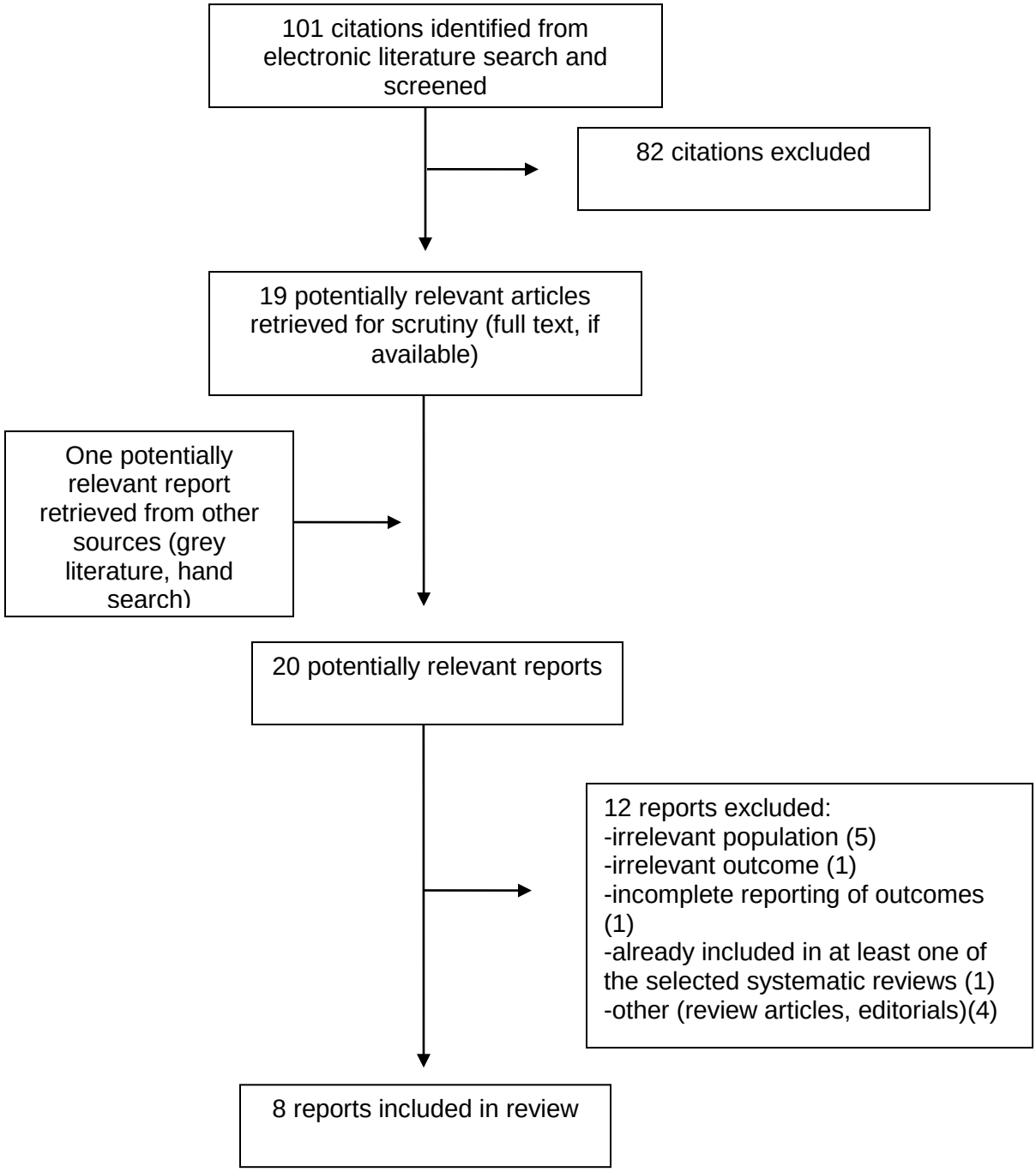
10. Goossens GA, Jerome M, Janssens C, Peetermans WE, Fieuws S, Moons P, et al. Comparing normal saline versus diluted heparin to lock non-valved totally implantable venous access devices in cancer patients: a randomised, non-inferiority, open trial. Ann Oncol. 2013 Jul;24(7):1892-9.

11. Cesaro S, Tridello G, Cavaliere M, Magagna L, Gavin P, Cusinato R, et al. Prospective, randomized trial of two different modalities of flushing central venous catheters in pediatric patients with cancer. J Clin Oncol [Internet]. 2009 Apr 20 [cited 2013 Sep 9];27(12):2059-65. Available from: http://jco.ascopubs.org/content/27/12/2059.full.pdf+html

ABBREVIATIONS

AE	adverse effect
CI	confidence interval
CR-BSI	catheter related blood stream infection
CVAD	central venous access device
CVC	central venous catheter
H	heparin
Hr	hour
ICU	intensive care unit
MD	mean difference
mL	millilitre
NR	not reported
nRCT	non-randomized study
NS	not significant
PCVC	percutaneous central venous catheter
PICC	peripherally inserted central catheter
RCT	randomized study
RR	relative risk
S	saline
SD	standard deviation
SR	systematic review
TIVAD	totally implantable venous access device

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (N)	Intervention	Comparators	Outcomes Measured
Systematic reviews and meta-analyses					
Shah,[9] 2011, Canada	SR (3 rcts [1 rct: H vs S and 2 rcts: H vs no H)	Neonates with peripherally placed percutaneous CVC N= 201 for H vs S (1 rct) & N= 477 for all 3 rcts	Saline (S) or no heparin (for RCT comparing H vs S, normal saline used)	Heparin (H) (for RCT comparing H vs S, 0.5 mL /hr or 1 mL/hr H [0.5 IU/kg/hr]	Occlusion, thrombosis, patency duration, adverse effects
Mitchell,[5] 2009, USA	SR (2 rcts, 1 nrct relevant for this report)	In-patients and patients in ICU with CVAD (CVC or PICC) N= 197 (in 2 rcts) and 59 (in 1 nrct)	Saline (5 mL or 10 mL saline)	Heparin (2.5 mL or 3 mL heparin [100 U/mL] or 5 mL heparin [20 U/mL])	Patency
Randomized controlled trial					
Goossens,[10] 2013, Belgium	Open-label RCT , non-inferiority trial (single centre: teaching hospital) Duration: January 23 2009 to June 5, 2011	Cancer patients with TIVADs Age(years) (mean ± SD): 54.9 ± 6.6 and 56.7 ± 4.8 in H and S groups respectively (included some ≤ 18 years as well) N = 802 (398 in H group and 404 in S group)	Saline (locked with normal saline)	Heparin (locked with 3 mLheparin 100 U/mL)	Injection/ aspiration problems, adverse effects
Schallom,[1] 2012, USA	RCT (single centre: ICUs at academic medical center) Duration: April 2009 to May 2010	Adult patients with multilumen CVC Age (years): 59.1 ± 15.2 for H group and 58.3 ± 17.5 in S group Male (%):46.9 in H group and 55.3 in S group N = 341	Saline (flushing with 10 mL saline every 8 hours)	Heparin (flushing with 3 ml heparin 10 U/mL every 8 hours)	Non patency rate, adverse effects
Araujo,[4] 2011, Brazil	Open-label RCT (single centre:	Newborns with PICC Age (weeks): 33.3 for H group and 32.3	Saline (flushing with 0.5 mL saline every 4 hours)	Heparin (flushing with 0.5 mL heparin 10 U/mL every	Occlusion

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (N)	Intervention	Comparators	Outcomes Measured
	Neonatal ICU of tertiary hospital) Duration: June 2006 to August 2007	for S group Male(%): 50 in H group and 52.2 in S group N = 133 (64 in H group and 69 in S group)		4 hours)	
Cesaro,[11] 2009, Italy	Open-label RCT (single centre: tertiary centre) Duration: January 1, 2003 to January 31, 2005.	Pediatric patients with hematologic or oncologic disease with tunneled CVCs Age(years): <5 for 40% and ≥5 for 60% of patients Male (%): 59 N= 203 (102 in H in group and 101 in S group)	Saline (flushing with normal saline at least weekly)	Heparin (flushing with 3 mL of normal saline with heparin 200 IU/mL twice a week)	Occlusion, adverse effects
Non-randomized studies					
Bertoglio,[6] 2012, Italy	Retrospective (single center: National Cancer Institute, Italy) Duration: January 1, 2007 to July 31, 2008 for H group and August 1, 2008 to December 31, 2009 for S group	Consecutive adult cancer patients (out-patients) with CVAD, who had a port implanted. Age: 45% patients <60 years; 55% patients ≥60 years N = 610 (297 in H group and 313 in s group)	Saline (locking monthly with 10 mL normal saline)	Heparin (locking monthly with 10 mL saline/ 500 U heparin)	Occlusion, adverse effects
Jonker,[2] 2010, USA	Retrospective (single centre: tertiary academic medical centre)	Adult in-patients with CVAD N = NR (Total patient days per month = 11,575.1 ± 355.4 for H group and	Saline (flushing with 10 mL normal saline every 8 hours or after each use)	Heparin (flushing with 5 mL heparin (10 units/ mL)	Alteplase use for catheter clot clearance,

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (N)	Intervention	Comparators	Outcomes Measured
	Duration April 23, 2007 to December 31, 2008 (before and after H shortage and during H shortage)	11,157.5 ± 382.5 for S group			

CR-BSI = catheter related blood stream infection, CVAD = central venous access device, CVC = central venous catheter, H = heparin, hr = hour, ICU = intensive care unit, mL = milliliter, PICC = peripherally inserted central catheter, S = saline, SR = systematic review, TIVAD = totally implantable venous access device

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Systematic review and meta-analysis		
Shah,[9] 2011, Canada	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, as well cross references from relevant articles, meeting abstracts and trial registries. • List of included and excluded studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Conflict of interest was stated and there appeared to be none	• Study selection was not described in detail • Publication bias was not explored
Mitchell,[5] 2009, USA	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, as well cross references from relevant articles. • Study selection described • List of included studies provided Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Conflict of interest was stated and there appeared to be none	• List of excluded studies not provided. • Unclear if article selection and data extraction were done in duplicate • Publication bias was not explored
Randomized controlled trial		
Goossens,[10] 2013, Belgium	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized but, open label study. Computerized random numbers were used for the randomization procedure. Allocation sequence was	• Generalizability limited; uncertain as to whether study patients were representative of all patients.

First Author, Publication Year, Country	Strengths	Limitations
	concealed from the researcher enrolling patients. • Sample size calculation was described • Number discontinued or lost to follow up were reported • Intent-to-treat analysis • P-values provided occasionally	
Schallom,[1] 2012, USA	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized and likely open label as there was no mention about blinding. Computerized random numbers were used for the randomization procedure. Allocation sequence was concealed • Sample size calculations described • Number discontinued or lost to follow up were reported • Intent-to-treat analysis • P-values provided	• Generalizability limited; uncertain as to whether study patients were representative of all patients.
Araujo,[4] 2011, Brazil	• Objectives were stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Randomized but, open label study. For the randomization procedure, software was used. Nothing was mentioned with respect to allocation concealment. • P-values provided	• Sample size calculation was not described • Number discontinued or lost to follow up were not reported • It was not mentioned if the analysis was intent-to-treat analysis • Generalizability limited; uncertain as to whether study patients were representative of all patients.
Cesaro,[11] 2009, Italy	• Objectives were stated. • Inclusion criteria were stated; exclusion criteria were not explicitly stated. • Patient characteristics, interventions, and outcomes were described.	• Generalizability limited; uncertain as to whether study patients were representative of all patients.

First Author, Publication Year, Country	Strengths	Limitations
	• Randomized but, open label study. Computerized random numbers were used for the randomization procedure. Allocation sequence was concealed • Sample size calculations described • Number discontinued or lost to follow up were reported • Appeared to be intent-to-treat analysis, though not explicitly mentioned • P-values provided	
Non-randomized studies		
Bertoglio,[6] 2012, Italy	• Objectives were stated. • Inclusion criteria were stated; exclusion criteria were not explicitly stated. • Patient characteristics, interventions, and outcomes were described. • P-values provided	• Not randomized; retrospective study • Sample size calculation was not described • Generalizability limited; uncertain as to whether study patients were representative of all patients.
Jonker,[2] 2010, USA	• Objectives were stated. • Interventions and outcomes were described • P-values provided	• Inclusion and exclusion criteria were not explicitly stated. • Patient characteristics were not described. • Not randomized; retrospective study • Sample size calculation was not described • Generalizability limited; uncertain as to whether study patients were representative of all patients.

APPENDIX 4: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Systematic reviews and meta-analuses</td></tr>
<tr><td>Shah,[9] 2011, Canada</td><td>
Main Findings:
Comparison of heparin versus saline (from one study with 201 parients) in neonates with with peripherally placed percutaneous CVC
<table>
<tr><th>Outcome</th><th>Effect measure</th><th>Effect size</th></tr>
<tr><td>Catheter occlusion</td><td>RR (95% CI)</td><td>0.20 (0.09, 0.45)</td></tr>
<tr><td>Catheter patency duration</td><td>MD (95% CI)</td><td>1.40 (-0.85, 3.65)</td></tr>
<tr><td>Thrombosis</td><td>RR (95% CI)</td><td>1.01 (0.56, 1.83)</td></tr>
<tr><td>Catheter related sepsis</td><td>RR (95% CI)</td><td>2.53 (0.50, 12.71)</td></tr>
<tr><td>Mortality</td><td>RR (95% CI)</td><td>3.03 (0.32, 28.64)</td></tr>
</table>
Comparison of heparin versus saline (from 1 study) or no heparin (from 2 studies)
<table>
<tr><th>Outcome</th><th>No. of patients</th><th>Effect measure</th><th>Effect size</th></tr>
<tr><td>Catheter occlusion</td><td>477</td><td>RR (95% CI)</td><td>0.39 (0.22, 0.67)</td></tr>
<tr><td>Catheter patency duration</td><td>477</td><td>MD (95% CI)</td><td>0.87 (-0.66, 2.39)</td></tr>
<tr><td>Thrombosis</td><td>267</td><td>RR (95% CI)</td><td>0.93 (0.58, 1.51)</td></tr>
<tr><td>Catheter related sepsis</td><td>477</td><td>RR (95% CI)</td><td>0.82 (0.43, 1.57)</td></tr>
<tr><td>Mortality</td><td>477</td><td>RR (95% CI)</td><td>0.83 (0.33, 2.09)</td></tr>
</table>
Authors' Conclusion:
"Prophylactic use of heparin for peripherally placed PCVC allows a greater number of infants to complete their intended use (complete therapy) by reducing occlusion. Evidence from this systematic review support the prophylactic use of heparin for PCVC in neonates. None of these studies was powered to evaluate a lower incidence rate of adverse events. If this therapy is adopted in routine practice, monitoring of side effects is indicated." P. 2

(PCVC = percutaneous central venous catheter)
</td></tr>
<tr><td>Mitchell,[5] 2009, USA</td><td>
Main Findings:
Results of individual studies were presented separately. There was no pooling.
Comparison of saline versus heparin (from 3 studies) for adult in-patients
<table>
<tr><th rowspan="2">Study</th><th rowspan="2">No. of patients</th><th colspan="2">Patency</th><th rowspan="2">P value</th></tr>
<tr><th>Saline</th><th>Heparin</th></tr>
<tr><td>RCT</td><td>102</td><td>47/50</td><td>52/52</td><td>NS</td></tr>
<tr><td>RCT</td><td>95</td><td>25/25</td><td>18/18</td><td>NS</td></tr>
<tr><td>nRCT</td><td>59</td><td>20/28</td><td>12/12</td><td>0.04</td></tr>
</table>
Authors' Conclusion:
"The evidence base on heparin flushing and other interventions to prevent catheter occlusion is small, and published studies are of low quality. There is insufficient evidence on which to conclude that flushing catheters with heparin is more effective than flushing with saline solution." P. 2007
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Randomized controlled trials</td></tr>
<tr><td>Goossens,[10] 2013, Belgium</td><td>
Main Findings:
Comparison of saline versus heparin in cancer patients (3.5% being younger than 18 years) with TIVAD
<table>
<tr><th>Outcome</th><th>Saline</th><th>Heparin</th><th>P-value</th></tr>
<tr><td>Easy injection, impossible aspiration (%)*</td><td>3.5</td><td>3.8</td><td>NR</td></tr>
<tr><td>Injection problems (%)*</td><td>0.4</td><td>0.8</td><td>NR</td></tr>
<tr><td>Aspiration problems (%)*</td><td>5.4</td><td>5.8</td><td>NR</td></tr>
<tr><td>Lab-confirmed blood stream infection (%)</td><td>0.5</td><td>1.5</td><td>0.18</td></tr>
<tr><td colspan="4">*Observed rates with respect to number of accesses</td></tr>
</table>
Authors' Conclusion:
"NS is safe and effective locking solution in implantable ports if combined with a strict protocol for device insertion and maintenance." P. 1893

(NS = normal saline)
</td></tr>
<tr><td>Schallom,[1] 2012, USA</td><td>
Main Findings:
Comparison of saline versus heparin in adult patients with CVC
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Effect</th><th rowspan="2">RR (95% CI) for S vs H</th><th rowspan="2">P value</th></tr>
<tr><th>Saline (S)</th><th>Heparin (H)</th></tr>
<tr><td>Non patency rate</td><td>6.3%</td><td>3.8%</td><td>1.66 (0.86, 3.22)</td><td>0.136</td></tr>
<tr><td>Loss of blood</td><td>27.8%</td><td>22.3%</td><td>1.25 (0.97, 1.62)</td><td>0.091</td></tr>
<tr><td>Alteplase use</td><td>6.3%</td><td>2.8%</td><td>2.19 (1.00, 5.01)</td><td>0.049</td></tr>
<tr><td>CR-BSI per 1000 catheter days</td><td>3.1 (0.8, 7.9)</td><td>0(0.0, 2.9)</td><td>NR</td><td>0.125</td></tr>
<tr><td>Venous thromboembolism</td><td>10.7%</td><td>13.1%</td><td>NR</td><td>NR</td></tr>
</table>
Authors' Conclusion:
"0.9% sodium chloride and heparin flushing solutions have similar rates of lumen nonpatency. Given potential safety concerns with use of heparin, 0.9% sodium chloride may be the preferred flushing solution for short-term use central venous catheter maintenance." P. 1820
</td></tr>
<tr><td>Araujo,[4] 2011, Brazil</td><td>
Main Findings:
Comparison of saline versus heparin in newborns
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Effect</th><th rowspan="2">P value</th></tr>
<tr><th>Saline</th><th>Heparin</th></tr>
<tr><td>No. of de novo occlusion</td><td>36 (or 36/1,000 catheter-days)</td><td>26 (or 31/1,000 catheter-days)</td><td>0.2</td></tr>
<tr><td>No. of relapsed obstructions</td><td>40 in 19 catheters</td><td>9 in 5 catheters</td><td><0.0001</td></tr>
<tr><td>No. of patients with Grade I or II intracranial hemorrhage</td><td>10</td><td>5</td><td>0.12</td></tr>
<tr><td>No. of patients with Grade III hemorrhage</td><td>1</td><td>1</td><td>0.97</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
<table>
<tr><td>No. of patients with thrombocytopenia</td><td>18</td><td>12</td><td>0.16</td></tr>
</table>

Authors' Conclusion:
"Intermittent heparin is not effective for preventing the occlusion of peripherally inserted central catheters in neonates but reduces relapses when clearance maneuvers were successful." P. 335
</td></tr>
<tr><td>Cesaro,[11] 2009, Italy</td><td>
Main Findings:
Comparison of saline versus heparin in pediatric patients
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Effect</th><th rowspan="2">P value</th></tr>
<tr><th>Saline</th><th>Heparin</th></tr>
<tr><td>CVC occlusion (%)</td><td>82.2</td><td>40.2</td><td>0.0002</td></tr>
<tr><td>Bacteremia/fungemia (%)</td><td>23.8</td><td>8.8</td><td>0.01</td></tr>
<tr><td>Exit site infection (%)</td><td>9.9</td><td>13.7</td><td>0.4</td></tr>
<tr><td>Thrombosis (%)</td><td>1.0</td><td>1.0</td><td>1</td></tr>
</table>

Authors' Conclusion:
"An increased complication rate was found with normal saline flushing, but additional investigation is warranted to clarify whether it is related to saline use or to once-a-week flushing." P. 2059
</td></tr>
<tr><td colspan="2">Non-randomized studies</td></tr>
<tr><td>Bertoglio,[6] 2012, Italy</td><td>
Main Findings:
Comparison of saline versus heparin in adult cancer patients
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Percentage of patients</th><th>P value</th></tr>
<tr><th>Saline</th><th>Heparin</th><th></th></tr>
<tr><td>Irreversible occlusion*</td><td>5.7</td><td>6.7</td><td>0.907</td></tr>
<tr><td>Other complications*</td><td>8.6</td><td>7.4</td><td>0.58</td></tr>
<tr><td>Catheter-related infection*</td><td>5.7</td><td>5.4</td><td>NR</td></tr>
<tr><td>Local infection*</td><td>1.3</td><td>1</td><td>NR</td></tr>
<tr><td colspan="4">*Reason for port removal</td></tr>
</table>

Authors' Conclusion:
"Normal saline solution seems to be as effective as heparinized solution for keeping patent implanted ports in adult cancer patients." P.E36
</td></tr>
<tr><td>Jonker,[2] 2010, USA</td><td>
Main Findings:
Comparison of saline versus heparin in adult patients
<table>
<tr><th>Outcome</th><th>Saline</th><th>Heparin</th><th>P value</th></tr>
<tr><td>Patients receiving alteplase per month for CVAD occlusion</td><td>92.0 ± 17.0*</td><td>57.7 ± 11.9*</td><td>0.04</td></tr>
<tr><td>Total alteplase per month (mg)</td><td>146.8 ± 11.7*</td><td>95.9 ± 29.4*</td><td>0.05</td></tr>
<tr><td>PICC line</td><td>24%</td><td>15%</td><td>< 0.03</td></tr>
</table>
</td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion
	replacements | | | | *mean ± SD **Authors' Conclusion:** "Heparin flush (10 units/mL) decreases thrombotic occlusion of CVADs, resulting in decreased alteplase use and fewer PICC line replacements." P. 444 (CVAD = central venous access device, PICC = percutaneous inserted central catheter)

CI = confidence interval, CR-BSI = catheter related blood stream infection , CVAD = central venous access device, MD = mean difference, NR = not reported, nRCT= non-randomized study, NS = not significant, PICC = percutaneously inserted central catheter , PVCV = percutaneous central venous catheter, RCT= randomized study, RR = relative risk, SD = standard deviation