1-2022

Saline vs heparin to lock central lines and effect on line-associated complications: Summary

Children's Mercy Kansas City

Critically Appraised Topic (CAT): Saline vs. Heparin to Lock Central Lines and Effect on Line-Associated Complications

Specific Care Question

In pediatric patients, does using saline to lock central venous catheters (CVCs) vs. using heparin to lock CVCs affect the incidence of line-associated complications, such as occlusion, loss of patency, infection, or venous thromboembolism (VTE)?

Recommendations Based on Current Literature (Best Evidence) Only

No recommendation can be made for or against normal saline (0.9% sodium chloride) or heparin to lock central lines, based on expert opinion and review of current literature by the subject matter expert and the Department of EBP. The overall certainty in the evidence is low to very low[a]. There was limited pediatric literature with only one systematic review (Bradford et al., 2020), which included two single studies for the meta-analysis. Bradford et al. (2020), stated there was not enough evidence to determine whether saline or heparin was more effective in reducing line-associated complications. One other systematic review was included within this summary. However, this systematic review (Zhong et al., 2017) only included adult single studies. The adult systematic review results were confounded with variations in single study protocols, catheter types, lumen types, line access sites, and patient diagnoses prompting the reviewers to conclude heparin is not superior to normal saline in reducing CVC occlusions (Zhong et al.). When there is a lack of scientific evidence, standard work should be developed, implemented, and monitored.

Literature Summary

Background

Central venous catheters (CVCs), described as a long, thin, hollow tube placed in a large central vein, are widely used in pediatric patients requiring prolonged administration of intravenous fluids, blood products, medications, parenteral nutrition, and for dialysis or central venous pressure monitoring (Ares & Hunter, 2017; Bradfort et al., 2016; Schallom et al., 2012). Of note there are three types of long-term CVCs used in medical practice today known as peripherally inserted central catheters (PICC), totally implantable venous access devices/ports (TIVAD/Ps), and tunnelled catheters (Bradford et al., 2020; Smith & Nolan, 2013). While there are considerable benefits for CVCs, including avoidance of multiple venipunctures, their use comes with risks that must be balanced when making the decision to use a CVC in the care of a patient. Risks, or complications, associated with CVCs include line occlusion, loss of patency, infection, and VTE (Goossens, 2015; Zhong et al., 2017). Line occlusion and loss of patency are associated with a build-up of fibrin deposits and can occur with infusion fluids or a mix of incompatible medications (Goossens, 2015; Jonker et al., 2010). This deposit of material can provide a nesting area for microorganisms, progressing to infection (Ferroni et al., 2014; Wu et al., 2021). VTEs can be attributed to CVC insertion or dysregulation of blood flow through the catheter (Jaffray et al., 2017).

Locking and flushing of CVCs is standard practice to maintain patency of the line and reduce occlusion, infection, and VTEs (Bradford et al., 2020; Lopez-Briz et al., 2014; Zhong et al., 2017). Heparin is used for flushing and locking CVCs because of its anticoagulant properties and is believed to resolve potential clotting or occlusions; however, there is controversy over heparin's effectiveness (Bertoglio et al., 2012). In pediatrics, the use of heparin has been linked to increased risk for bleeding secondary to the overdose of heparin due to frequent flushing or incorrect concentration of solution (Bradford et al., 2020). Normal saline (0.9% sodium chloride) being injected into CVCs to clear the catheter of blood or fibrin-deposited-material, is referred to as a flush. Some reports indicate that normal saline is just as effective as heparin (Bradford et al., 2020). Because of the potential risks of using heparin, it is important to review the literature to determine best practices and that those practices are based on scientific evidence. This review will summarize identified literature to answer the specific care question.

Study characteristics. The search for suitable studies was completed on December 13, 2021. Brittney Hunter, RN, BSN, CPN, and Shannon Carpenter, MD, MS, reviewed the 44 titles and/or abstracts found in the search and identified[b] seven single studies believed to answer the question. After an in-depth review of the single studies[b], none of the single studies answered the question. An additional search, using the same search strategy but with limitations for systematic reviews only, found two systematic reviews (Bradford et al., 2020; Zhong et al., 2017) to answer the question. This current review was unable to create a meta-analysis due to the heterogeneity of the studies.

Does the use of normal saline (0.9% sodium chloride) to lock central lines affect line associated complications?

Two systematic reviews (Bradford et al., 2020; Zhong et al., 2017) analyzed both pediatric and adult single studies to answer the question.

Bradford et al. (2020) reviewed four single studies (Cesaro et al., 2009; da Silva et al., 2018; Goossens et al., 2013; Smith et al., 1991). Only two studies were included in the meta-analysis (Cesaro et al., 2009; Goossens et al., 2013). Cesaro et al. (2009) included only pediatric patients, whereas Goossens et al. (2013), included both pediatric and adult patients. Goossens et al. (2013) did not evaluate the pediatric and adult data separately. Measured outcomes evaluated the use of normal saline to flush CVCs compared to heparin. The studies in the meta-analysis directly compared normal saline to heparin for long-term CVCs; however, the protocols varied in both the intervention and control arms of the studies using different concentrations of heparin and different frequencies of flushes. The authors of this systematic review concluded there was insufficient evidence to provide a clinical recommendation for either the use of normal saline or heparin in the standard care of CVCs in children.

Zhong et al. (2017) reviewed 10 single studies (Beigi et al., 2014; Bowers et al., 2008; Dal Molin et al., 2015; Fuente i Pumarola et al., 2007; Goossens et al., 2013; Kaneko et al., 2004; Lyons & Phalen, 2014; Rabe at et., 2002; Schallom et al., 2012; Ziyaeifard et al., 2015). All studies were included in the primary outcome of CVC line occlusion. The overall analysis did not demonstrate a difference between normal saline and heparin in adult patients for maintenance care of CVCs. Adult patients participating in the single studies were from various countries (Belgium, Germany, Iran, Italy, Japan, Spain, and USA), and had various diseases (cancer, cardiac, multi-disease, or nephropathy). This systematic review and meta-analysis considered CVC care and maintenance using normal saline or heparin from four different perspectives (catheter type, line access site, lumen type or patient diagnosis), providing an overall conclusion that flushing with normal saline was as effective as heparin for maintenance of CVC patency in adult patients but cautions the evidence is lacking in proving the effectiveness normal saline versus heparin in decreasing occlusion rates. The authors recommended that additional large randomized controlled trials are needed to strengthen the scientific evidence.

Summary by Outcome

CVC Occlusion Rate

Two systematic reviews (Bradford et al., 2020; Zhong et al., 2017) measured CVC occlusion rates, comparing flushing of the line with normal saline (0.9% sodium chloride) to heparin (N = 8,104). Bradford et al. (2020) reviewed two studies, with one representing pediatric hematology or oncology patients (Cesaro et al., 2009) and one representing both pediatric and adult cancer patients (Goossens et al., 2013), (n = 229), with pooled data resulting in the RR = .75, 95% CI [0.10, 5.51], p = .78, I^2 = 92%, indicating the intervention of normal saline was not different to the comparator of heparin. Zhong et al. (2017) pooled results from 10 single, adult studies (Beigi et al., 2014; Bowers et al., 2008; Dal Molin et al., 2015; Fuente i Pumarola et al., 2007; Goossens et al., 2013; Kaneko at al., 2004; Lyons & Phalen, 2014; Rabe et al., 2002; Schallon et al., 2012; Ziyaeifard et al., 2015), (n = 7,875), RR = 1.21, 95% CI [0.91, 1.61], p = .186 indicated the intervention of normal saline was not different to the comparator of heparin.

Certainty Of The Evidence For CVC Occlusion Rate. The certainty of the body of evidence was low to very low. The body of evidence was assessed to have serious risk of bias as demonstrated by lack of blinding and failure to obtain the appropriate sample size (Bradford et al., 2020; Zhong et al., 2017), very serious inconsistency with heterogeneity of 92% (Bradford et al., 2020), serious indirectness as evidenced by comparison of adult and pediatric patients (Bradford et al., 2020) and serious imprecision by measuring the occlusions from a variety of pathways (Zhong et al., 2017)

CVC-Associated Blood Stream Infection Rate

Two systematic reviews (Bradford et al., 2020; Zhong et al., 2017) measured CVC occlusion rates, comparing flushing of the line with normal saline (0.9% sodium chloride) to heparin, (N = 8,104). Bradford et al. (2020), reviewed two studies with one representing pediatric hematology or oncology patients (Cesaro et al., 2009) and one representing pediatric and adult cancer patients (Goossens et al., 2013), (n = 231), with pooled data resulting in the RR = 1.48, 95% CI [0.24, 9.37], p = .67, I^2 = 45%, indicated the intervention of normal saline was not different to the comparator of heparin. Zhong et al. (2017), pooled results from four single, adult studies (Dal Molin et al., 2015; Goossens et al., 2013; Lyons & Phalen, 2014; Schallon et al., 2012), (n = 1,630), RR = 0.84, 95% CI [0.11, 6.71], p = .871, indicated the invention of normal saline was not different to the comparator of heparin.

Certainty Of The Evidence For CVC-Associated Blood Stream Infection Rate. The certainty of the body of evidence was very low. The body of the evidence was assessed to have serious risk of bias as demonstrated by lack of blinding and failure to obtain the appropriate sample size

(Bradford et al., 2020; Zhong et al., 2017), serious inconsistency with heterogeneity of 45% and 52% respectively (Bradford et al., 2020; Zhong et al., 2017), serious indirectness as evidenced by comparison of adult and pediatric data (Bradford et al., 2020), and serious imprecision as demonstrated by low sample size and low number of events (Zhong et al., 2017).

Central Venous Thrombosis

One systematic review, (Zhong et al., 2017) measured the incidence of central venous thrombosis, comparing flushing of the line with normal saline (0.9% sodium chloride) to heparin, (N = 1,512). Zhong et al. (2017), pooled results from three single, adult studies (Dal Molin et al., 2015; Goossens et al., 2013; Schallom et al., 2012), (n = 1,512) with the RR = .81, 95% CI [0.50, 1.31], p = .381, indicated the intervention of normal saline was not different to the comparator of heparin.

Certainty Of The Evidence For CVC-Associated Blood Stream Infection Rate. The certainty of the body of evidence was very low. The body of the evidence was assessed to have serious risk of bias as demonstrated by lack of blinding and serious imprecision due to low number of subjects and low number of events (Zhong et al., 2017).

Identification of Studies

Search Strategy and Results (see Figure 1)

CINAHL: MH "Central Venous Catheters+/AE" OR MH "Catheterization, Central Venous+/AE"<MH "Adverse Health Care Event+" OR "adverse effects" OR "complication" < MH "Central Venous Catheters+" OR MH "Catheterization, Central Venous+" OR "central line" OR "cvc"< MH "Catheter-Related Infections+") OR (MH "Catheter-Related Bloodstream Infections") OR (MH "Catheter-Related Thrombosis") OR (MH "Vascular Patency" OR MH "Catheter Occlusion"< saline OR heparin < lock therapy OR locking OR lockEMBASE: 'catheter thrombosis'/exp OR 'catheter infection'/exp OR 'catheter occlusion'/exp OR 'vascular patency'/exp OR 'central line infection'/expOR 'central line associated blood stream infection'/exp < 'central venous catheter'/exp OR 'central venous catheter' OR 'central venous catheterization'/exp < OR 'central venous catheterization' OR 'central line'/exp OR 'central line' OR 'cvc' 'adverse event'/exp OR 'adverse event' OR 'complication'/exp OR complication OR 'adverse device effect'/lnk OR 'complication'/lnk < 'central venous catheter'/exp/dv_am < 'saline'/exp OR saline OR 'heparin'/exp OR heparin < 'lock therapy' OR lock OR locking

Records identified through database searching n = 0

Additional records identified through other sources n = 2

Studies Included in this Review

Citation	Study Type
Bradford et al. (2020)	SR
Zhong et al. (2017)	SR

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Barbour et al. (2015)	Wrong comparison
Boersma et al. (2015)	Wrong comparison
Levett-Jones (2019)	Review
Morgan et al. (2017)	Wrong comparison
Tusin et al. (2018)	Wrong comparison
Willsmore et al. (2020)	Wrong comparison
Wu et al. (2021)	Wrong outcome

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings (SOF) table(s) for this analysis. Using the GDT, the author of this CAT rates the certainty of the evidence based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. Each factor is subjectively judged against the author's confidence of the estimated treatment effect. Confidence is assessed as not serious, serious or very serious. If the attribute of serious or very serious is assessed, the author will provide an explanation.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

References to Appraisal and Synthesis Methods

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[c]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal. pmed1000097 **For more information, visit www.prisma-statement.org.**

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Acronyms Used in this Document

Acronym	Explanation
AGREE II	Appraisal of Guidelines Research and Evaluation II
CAT	Critically Appraised Topic
CVC	Central Venous Catheter
EBP	Evidence Based Practice
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
VTE	Venous Thromboembolism

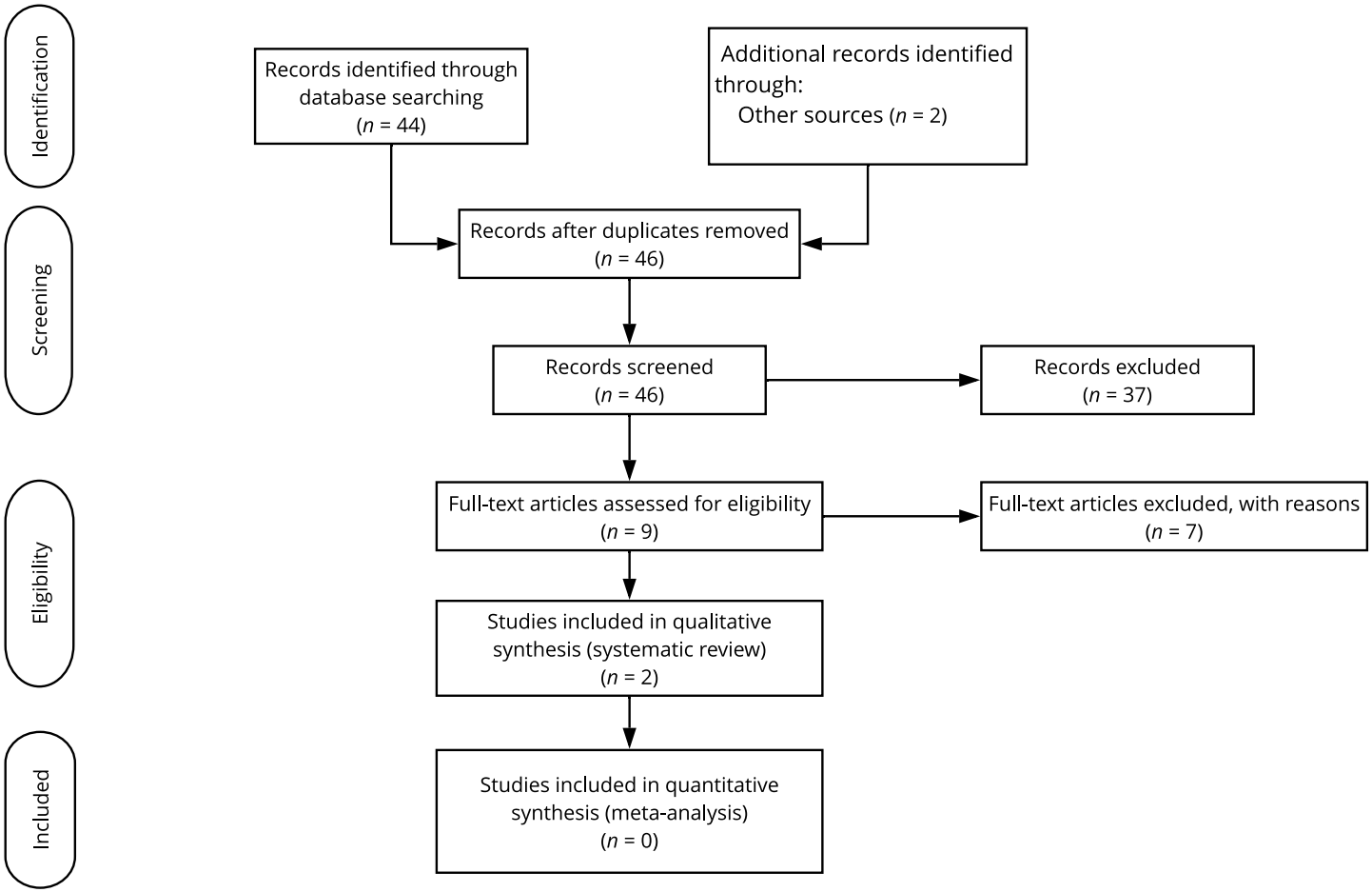
Statistical Acronyms Used in this Document

Statistical Acronym	Explanation

CI	Confidence Interval
I^2	Heterogeneity test
M or $\bar{X}$	Mean
n	Number of cases in a subsample
N	Total number in sample
OR	Odds Ratio
P or p	Probability of success in a binary trial
RCT	Randomized controlled trial
RR	Relative risk
SR	Systematic Review

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[c]



Characteristics of Intervention Studies

Bradford 2020

Design	Quantitative Synthesis (meta-analysis)
Objective	Objective of Intervention review: "To assess the clinical effects (benefits and harms) of intermittent flushing of normal saline versus heparin to prevent occlusion in long term CVCs in infants and children. "
Methods	**Criteria for considering studies for this review** • **Types of studies:** RCT • **Participants:** Pediatric patients (up to age 18 years) with a Central Venous Catheter (CVC) • **Target Condition(s):** Heparin (standard of care) vs normal saline flush as it relates to CVC patency and complications **Search methods for identification of studies** • **Electronic databases searched:** ○ Cochrane Vascular Specialized Register ○ CENTRAL ○ MEDLINE ○ Embase ○ CINAHL ○ World Health Organization International Clinical Trials Registry Platform ○ ClinicalTrials.gov trials register • **Search strategy employed:** ○ Dates of studies up to and including 09 April 2019 ○ RCTs ○ MeSH check words: Child; Child, Preschool; Humans; Infant ○ Medical subject headings: Catheter Obstruction; *Central Venous Catheters; Fibrinolytic Agents [*administration & dosage]; Heparin [*administration & dosage]; Randomized Controlled Trials as Topic; Sodium Chloride [*administration & dosage] • **Searching other resources (such as reference list):** Used, included reference checking, citation searching and contact with study authors to identify additional studies **Data collection and analysis** • **Inclusion criteria:** RCTs that compared the efficacy of intermittent flushing with normal saline versus heparin to prevent occlusion of long-term CVCs in infants and children aged up to 18 • **Exclusion criteria:** ○ Temporary CVCs ○ Peripherally inserted central catheters (PICC) ○ Quasi-randomized studies • **Population:** Pediatric patients with a CVC • **Setting:** All studies took place at large teaching (tertiary) hospitals • **Study Design:** All included studies were RCTs • **Data collection process:** ○ Two authors independently reviewed the studies

	○ When there was a disagreement between the two authors, a third author acted as an arbitrator • **Assessment of the certainty of the evidence:** The overall certainty of the evidence ranged from moderate to very low. • **Data Synthesis:** ○ **Overall Effect Size:** measured as Rate Ratio ○ **CI:** Considered ○ **Heterogeneity:** Considered
Results	**Study Selection (actual results/data)** **Number of articles identified:** *N* = 464 **Full-text articles assessed for eligibility:** *n* = 23 ○ **Studies included in qualitative synthesis:** *n* = 4 studies (5 reports) with two studies included for quantitative analysis **Synthesis of quality of evidence** (strength of evidence): The overall certainty of the evidence was moderate to very low. **Synthesis of quantitative evidence:** ○ **Overall Effect Size** ▪ Outcome measures were not reported consistently, authors calculated rate ratios ▪ Confidence intervals considered wide by authors, heterogeneity and inconsistency between studies was high ○ **Heterogeneity:** Considered high by authors ▪ Not all studies reported duration of catheter placement ▪ Many studies were inadequately blinded ▪ Studies had different interventions and methods ▪ Studies reported different outcomes of interest ▪ Heparin concentration and/or frequency of flushes varied between studies ▪ Sample sizes were very small in two studies
Discussion	**Summary of evidence:** Not enough evidence to determine the effects of intermittent flushing with normal saline versus heparin **Author reported results:** For CVC occlusion per 1000 catheter days between the normal saline and heparin groups, (*n* = 229), the *RR* = 0.75, 95% CI [0.10,5.51]. The certainty of the evidence was very low. For CVC-associated blood stream infections, (*n* = 231), the *RR* = 1.48, 95% CI [0.24,9.37]. The certainty of the evidence was low. **Limitations:** Heterogeneity considered very high with an I^2 = 92% and 45%
Funding	• Children's Health Queensland Hospital and Health Service, Australia • Royal Children's Hospital provided salary and facilities for RE to conduct this systematic review • Queensland University of Technology, Australia • Queensland University of Technology provided salary and facilities to support NB and RC

Zhong 2017

Design	Quantitative Synthesis (meta-analysis)
Objective(s)	Objective of intervention review: to assess the efficacy of normal saline (NS) versus heparin in the maintenance of the patency of CVCs in adult patients.

Methods	**Criteria for considering studies for this review**
	• **Types of studies:** Randomized Controlled Trials
	• **Participants:** Adult patients with CVCs
	• **Target Condition(s):**
	  ○ Patients (six studies),
	  ○ catheters (two studies),
	  ○ lumens (one study; multilumen CVCs) and
	  ○ line access (one study; flushing central lines before and after each use)
	
	Search methods for identification of studies
	• **Electronic databases searched:**
	  ○ Pubmed,
	  ○ Embase,
	  ○ Cochrane library
	• **Search strategy employed:**
	  ○ "Sodium Chloride",
	  ○ "Saline Solution, Hypertonic",
	  ○ "NaCl", "Heparin",
	  ○ "Catheterization, Central Venous",
	  ○ "Randomized Controlled Trial"
	• **Searching other resources (such as reference list):**
	  ○ Bibliographies in the retrieved articles
	
	Data collection and analysis
	• **Inclusion criteria:** Clinical randomized controlled trials (RCTs) of NS flushing vs flushing with HS solution in adults
	• **Exclusion criteria:**
	  ○ Age <18 years, and
	  ○ Case reports,
	  ○ letters,
	  ○ reviews,
	  ○ case-control studies and
	  ○ cohort studies, or non-human studies
	• **Population:** Adults with CVCs
	• **Setting:** Single center hospital studies, multi-site hospital studies, or home care studies.
	• **Study Design:** All studies were RCTs
	• **Data collection process:**
	  ○ Data were independently extracted by three reviewers
	• **Assessment of the certainty of the evidence**

	○ Certainty of evidence not reported; state the reviewers assessed the quality of the studies based on the Cochrane handbook for systematic reviews of interventions. ○ Subgroup analysis examining effect of duration of catheter placement on the outcome • **Data Synthesis:** ○ **Overall Effect Size:** ▪ Mantel-Haenszel random-effects model for pooled data ▪ Pooled effects using relative risk (RR) with 95% CI for dichotomous outcomes ○ **Heterogeneity:** ▪ Measured with X^2 test, *p* values and the I^2 statistics
Results	**Study Selection** **Number of articles identified:** *N* = 542 **Full-text articles assessed for eligibility:** *n* = 86 ○ **Studies included in qualitative synthesis:** *n* = 10 **Synthesis of quality of evidence** (strength of evidence): • Two papers had high risk of bias as they failed to obtain the expected sample size • One study was subject to detection bias, as the outcome measurement could have been influenced by lack of blinding • Goossens et al. (2013) study complied completely with the inclusion standards, but examination of the funnel plot suggests that there was also publication bias **Synthesis of quantitative evidence:** ○ **Overall Effect Size:** NS vs Heparin and the incidence of catheter occlusion overall ▪ Data pooled into category NS vs HS: *n* = 7875 ▪ **Risk ratio (RR):** 1.21 ▪ **CI:** 95% CI 0.91 to 1.61, *p* = .186 ▪ **Heterogeneity Pooled Analysis** • X^2 = 8.39 • *p* = .299 • I^2 = 16.6% ○ **Overall Effect Size:** NS vs Heparin and incidence of catheter-related bloodstream infection ▪ Data: *n* = 1630 ▪ **Risk ratio (RR):** 0.84 ▪ **CI:** 95% CI 0.11 to 6.71, *p* = .871) ▪ **Heterogeneity Pooled Analysis** • *p* = .126 • I^2 = 51.7% ○ **Overall Effect Size:** NS vs Heparin and incidence of central venous thrombosis ▪ Data: *n* = 1512 ▪ **Risk ratio (RR):** 0.81 ▪ **CI:** 95% CI 0.50 to 1.31, *p* = .381) ▪ **Heterogeneity Pooled Analysis** • *p* = .872 • I^2 = 0.0%

Discussion	**Summary of evidence:** • This meta-analysis did not demonstrate any superiority of heparin locked saline solutions over NS for the maintenance of CVC lumen patency in adult patients. • Additional large prospective RCTs might be needed in this field due to the inconclusive evidence available. **Limitations:** • Although the statistical heterogeneity was low, the clinical and methodological heterogeneity cannot be ignored. • The potential hazards might occur after long-term follow up, thus, some of these complications could be discarded due to the short duration of some included studies • This meta-analysis was limited to studies conducted in Asia, Europe and North America, and thus, might not be generalizable to other parts of the world • There was a publication bias in our study as small studies with null results tend not to be published. Hence, uniform study design and multi-center studies should be launched in different countries and regions to establish the best approach to long-term maintenance of CVCs
Funding	**Funding** • This research received no specific grant from any funding agency.

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Studies marked with an asterisk* are found in the systematic reviews and meta-analyses.

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