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Comparison of Heparin and Saline for Prevention of Central Venous Catheter Occlusion in Pediatric Oncology: A Systematic Review and Meta-Analysis

Remziye Semerci[a,*], Hülya Bingöl[b], Sema Bay Büyükkapu[c], Aslı Akdeniz Kudubes[d], Murat Bektaş[e], Rejin Kebudi[f]

[a] *School of Nursing, Koç University, İstanbul, Turkey*
[b] *Pediatric Hematology-Oncology, Oncology Institute, Istanbul University, İstanbul, Turkey*
[c] *Pediatric Hematology-Oncology, Kanuni Sultan Süleyman Education and Research Hospital, İstanbul, Turkey*
[d] *Pediatric Nursing, Faculty of Health Sciences, Bilecik Şeyh Edebali University, Bilecik, Turkey*
[e] *Pediatric Nursing, Faculty of Nursing, Dokuz Eylül University, Izmir, Turkey*
[f] *Pediatric Hematology-Oncology, Oncology Institute, Istanbul University, İstanbul, Turkey*

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ABSTRACT

Objective: The management of central venous catheter (CVC) occlusion remains an area without clear evidence-based guidelines. Studies have been conducted that compare the use of heparin and normal saline for reducing thrombosis, but the evidence is not strong enough to suggest a significant advantage of one over the other. Therefore, the study aimed to assess the effectiveness of heparin and normal saline flushing in preventing CVC occlusion in pediatric patients with cancer.
Data Sources: A comprehensive search was conducted in PubMed, Web of Science, Cochrane, MEDLINE, CINAHL, Embase, World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov platform using specific keywords. The search was conducted until March 2022. Five randomized controlled trials are included in this study.
Conclusion: Five studies with a total of 316 pediatric cancer patients met the inclusion criteria. The studies were found to be heterogeneous due to variations in the types of cancer, heparin concentration, flushing frequency of CVCs, and methods used to measure occlusion. Despite these differences, there was no significant difference in the effect of flushing with heparin and normal saline in preventing CVC occlusion. The analysis revealed that normal saline is as effective as heparin in preventing CVC occlusion among pediatric cancer patients.
Implications for Nursing Practice: This systematic review and meta-analysis demonstrated that there is no significant difference between the use of heparin and normal saline flushing in preventing CVC occlusion among pediatric cancer patients. Considering the potential risks of heparin, the use of normal saline flushing may be recommended to prevent CVC obstruction.

Introduction

Central venous catheters (CVCs) are increasingly used in the medical management of chronic diseases and are essential in administering treatments.[1–3] CVCs offer convenient intravenous access for blood sampling, the administration of chemotherapy drugs, and supportive treatments such as antibiotics and blood products/components.[4–6] The widespread use of CVCs has facilitated the implementation of treatments, leading to shorter hospital stays, increased safety, and reduced hospital costs.[1,5] With the advantages of long-term use, CVCs have become standard tools in providing care for pediatric patients with cancer.[6–8]

There are many advantages to the use of CVCs, such as convenient access for medical treatments, but there are also many potential complications (eg, occlusion, infection, and dislocation) that can arise if proper care is not taken.[2,9,10] Obstruction of CVCs is a common problem, occurring in approximately 36% of children with cancer.[6,8] Although CVCs offer many benefits, studies have reported a 14% to 36% incidence of mechanical, infectious, or thrombotic complications after 2 years of implantation in patients.[7,11,12] CVC occlusions can lead to treatment delays, hospital readmissions, an increased risk of inflammation, life-threatening events, and the need for CVC removal or replacement.[5,7]

* Address correspondence to: Remziye Semerci, Pediatric Hematology-Oncology, Oncology Institute, Istanbul University, İstanbul, Turkey.
E-mail address: remziyesemerci@gmail.com (R. Semerci).

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The most effective approaches to managing CVC occlusions are implementing flushing and locking protocols, which are more cost-effective and efficient and less invasive than removing or replacing the CVCs.[5,7] Currently, nurses routinely flush CVCs to maintain open lumens. Flushing occluded catheters with appropriate agents has become the first treatment option to avoid the risks and costs associated with removing and reimplanting CVCs. The solutions commonly used for catheter flushing include normal saline and heparin.[5] Although heparin is commonly used as the standard method to flush the CVCs, it can be unsafe for patients and costly for health institutions. Heparin use increases the risk of thrombocytopenia in patients, and up to 30% of patients experience allergic reactions to it.[1] Because the focus of health care institutions is on providing good-quality care to patients, it is preferable to use normal saline instead of heparin to flush the CVCs. Normal saline is safer than heparin and has been shown to be just as effective in preventing CVC occlusion.[1]

The management of CVC occlusion presents a significant clinical problem that disrupts antineoplastic treatment. However, the methods used for prevention and the associated risks and costs of diagnosis and treatment vary. As a result, the management of CVC occlusion remains a gap in evidence-based guidelines. Although prospective randomized controlled trials indicate no significant advantage of heparinized solutions over normal saline in reducing catheter dysfunction due to thrombosis,[3] the strength of evidence from these studies is limited.[12,13] A previous study performed by Bradford et al[12] as a Cochrane review compared the efficacy of heparin and normal saline in preventing CVC occlusion by including general pediatric patients. Because one in three CVCs in pediatric oncology patients is thought to be infected, thrombosed, or occluded during treatment[13,14] and CVC care is important for this population, a meta-analysis study is needed to compare the efficacy of heparin and normal saline to prevent obstruction. Therefore, this systematic review and meta-analysis aimed to compare the effectiveness of heparin and normal saline flushing in preventing CVC occlusion in pediatric cancer patients.

Hypotheses

Hypothesis 1. Heparin flushing will be more effective than normal saline flushing in reducing CVC occlusion in pediatric cancer patients.

Hypothesis 2. Normal saline flushing will be more effective than heparin flushing in reducing CVC occlusion in pediatric cancer patients.

Hypothesis 3. Heparin flushing and normal saline flushing will have the same effect on reducing CVC occlusion in pediatric cancer patients.

Methods

Study Design

This study is a systematic review and meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-analyzes (PRISMA) recommendations were followed.[15] The research was recorded in the International Prospective Register of Systematic Reviews database (PROSPERO) (CRD42022336316).

Outcomes

The outcome of this study was to compare the complete and/or partial CVC occlusion frequency between heparin and normal saline flushing among pediatric cancer patients.

Inclusion Criteria

The review inclusion criteria were studies that included pediatric cancer patients (0–18 years old) who have long-term (minimum: 1 month) use of a CVC (tunneled catheter or implanted catheter) and that evaluated the effects of heparin and normal saline flushing in preventing CVC occlusion, had a randomized controlled trial (RCT) design, had quantitative analysis data, and had sufficient statistical data to calculate the effect size.

Exclusion Criteria

The study's exclusion criteria were the temporary placement of CVCs, the use of a peripherally inserted central catheter, and studies in children with vascular problems.

Search Method

The Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) strategy was used to determine the article's eligibility (Table 1). The researchers searched databases (PubMed, Web of Science, Cochrane, MEDLINE, CINAHL, Embase, World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov platform) using key words through October 2022. The key words were heparin, +sodium chloride OR saline, +central venous catheter, +pediatric cancer patient OR children with cancer, OR malignancy, OR childhood cancer, +CVC occlusion, +thrombosis, +flushing. Within and across groups, we used the Boolean operators "OR" and "AND" (Table 2). The search was limited to the English language.

TABLE 1
Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) Criteria for Inclusion and Exclusion of Studies.

	Inclusion criteria	Exclusion criteria
Participants	The study sample consisted of pediatric cancer patients	The study sample did not consist of pediatric cancer patients
Intervention	Studies included flushing of the CVCs with heparin or normal saline solutions	Studies without flushing of the CVCs with heparin and normal saline solutions
Comparison	Heparin and normal saline solutions were used	Heparin and normal saline solutions were not used
Outcomes	Studies examined incidences of occlusion of long-term CVC use	Studies did not examine incidences of occlusion of long-term CVC use
Study type	Randomized clinical trials	Not randomized clinical trials

CVC, central venous catheter.

TABLE 2
Database Search Method

Concept 1	Concept 2	Concept 3	Concept 4
Sodium heparin or "heparin" [MeSH] OR heparin sodium or "saline solution" [MeSH] OR saline OR "sodium chloride" [MeSH] OR sodium chloride	Central venous catheters" [MeSH] OR central venous catheter	"Pediatric oncology patient" OR children with cancer OR malignancy OR childhood cancer	Occlusion OR thrombosis OR flushing OR "thrombosis" [MeSH] OR thrombus OR thromboses OR "flushing" [MeSH] OR flushings OR flushing

Each concept was combined with "AND."

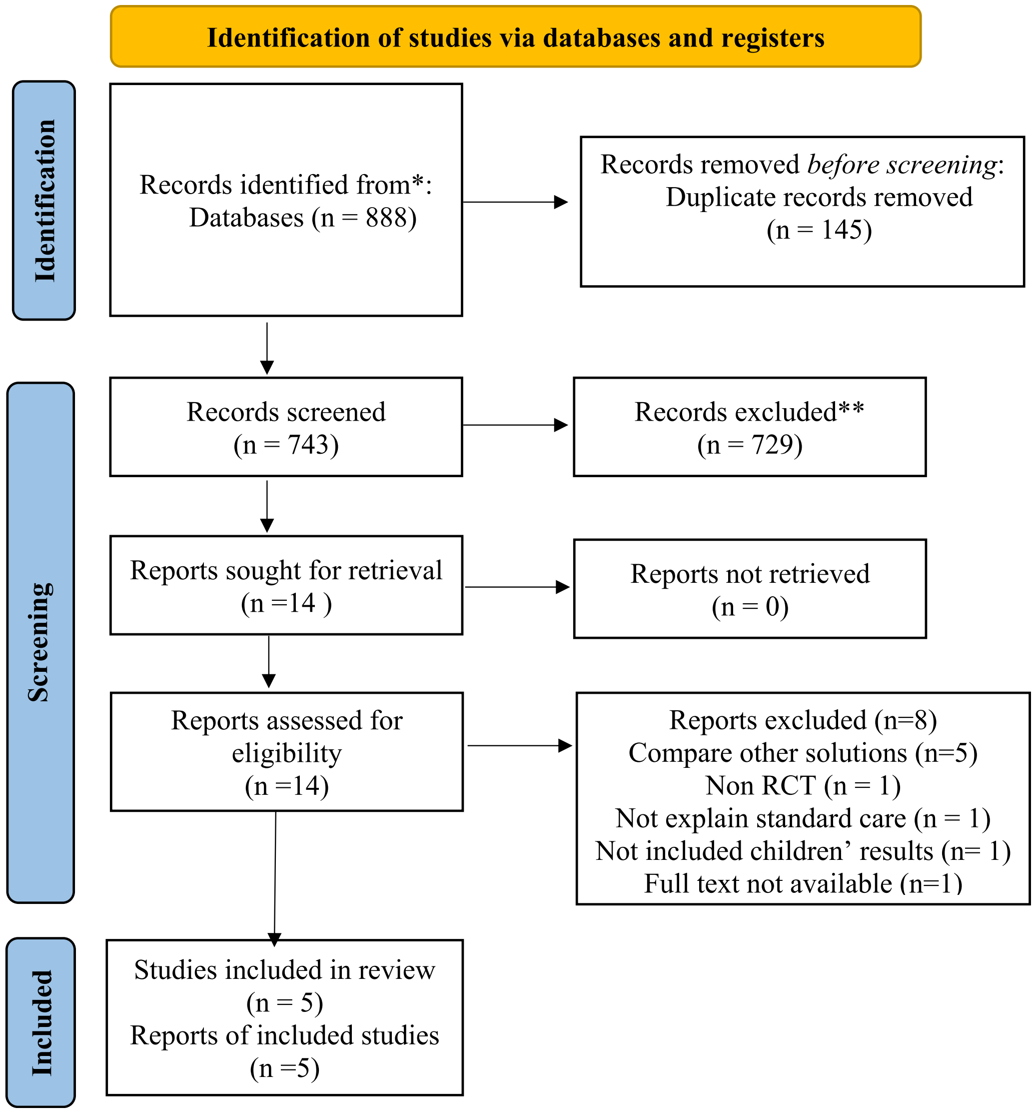

FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-analyzes (PRISMA) flowchart of the research.

Data Selection Procedure

The data management tool Endnote version 20 was used for reference management. The selection of articles for quantitative synthesis was carried out independently by two researchers in three stages. In the first stage, after deleting duplicate studies, two authors (RS and AAK) evaluated all study titles and abstracts based on the inclusion and exclusion criteria. Two authors (RS and AAK) searched for data, checked it for accuracy and discrepancies, and resolved any disagreements or sent it to a third author (MB) for adjudication. Any differences were resolved through agreement. In the second stage, the two authors (RS and AAK) conducted a prescreening of the full texts. If necessary information could not be obtained from the literature, the authors of the articles were contacted via email to obtain the relevant information. Because the two publications included in this analysis provided data on both children and adults, the authors were contacted, and only data on children were requested. In the third stage, two researchers assessed the full texts based on the inclusion and exclusion criteria.

Data Extraction

Data extraction was performed using a predesigned form after the screening, selection, and evaluation of the quality of the selected studies. The studies were recorded with author/year/country, study design, population (sample size), intervention procedure, standard care, measurement, results/outcomes, and conclusions (see Supplementary File 1). Two authors (RS and AAK) extracted the data, and a third author (MB) confirmed the extracted data. In case of any disagreement, the researchers discussed until reaching a consensus.

A total of 888 articles were retrieved from databases; 145 duplicates were removed, leaving 743 articles for title and abstract screening. After excluding 729 irrelevant articles, 14 papers were evaluated for relevance, and their quality was assessed. After all stages, five articles were selected and included in the systematic review. Data were presented in a PRISMA flowchart to document and report the screening results (Fig 1).

Risk of Bias

The Cochrane tool was used to assess the risk of bias.[16] Two reviewers (RS and AAK) separately assessed the bias risk, and consensus was used to solve disagreements. Scale items 1 indicated random sequence generation (selection bias); 2, allocation concealment (selection bias); 3, blinding of patients and personnel (performance bias); 4, blinding of outcome assessment (detection bias); 5, incomplete outcome data (attrition bias); 6, selective reporting (reporting bias); and 7, other bias (other potential bias, not included in the domains described above). Bias is measured as a score (high, low, or unclear) for specific items from five domains (selection, performance, attrition, reporting, and others).[17]

Synthesis of Results

The Comprehensive Meta-Analysis software statistical package program was used to perform meta-analyses by combining data from the same outcomes using the random-effects model.[18] Hedges' *g* was used to estimate the pooled mean effect sizes of continuous outcome scores because it accurately estimated the overall effect size when the included trials had small sample sizes.[19] The effect size was categorized as small (0.2), medium (0.5), large (0.8), or very large (1.2).[20]

Random-effects models are used in meta-analysis research based on heterogeneity.[21] The Cochran *Q* test was used to assess statistical heterogeneity, with $P = .10$ indicating the presence of significant statistical heterogeneity.[18] The I^2 statistic was used to estimate the level of heterogeneity.[21] In the heterogeneity assessment, I^2 was interpreted as 0% to 40% (might not be important), 30% to 60% (moderately important), 50% to 90% (substantially essential), and 75% to 100% (considerably important).[22] Funnel plot graph, Egger's regression intercept, and Begg and Mazumder rank correlations were used to evaluate publication bias.[23] The significance level of statistical analysis was determined as .05.

Results

Study Characteristics

Supplementary File 1 summarizes RCT characteristics. Five RCTs were included in this study; five studies had full text.[13,24–27] Studies were conducted between 1991 and 2022 in Italy,[24] Belgium,[25] Australia,[13] Brazil,[26] and Canada.[27]

Most of the studies were conducted with hematology or oncology patients. Cesaro et al,[24] Ullman et al,[13] and Goossens et al[25] conducted their studies with pediatric hematology or oncology patients. da Silva et al[26] conducted their study with pediatric patients undergoing hematopoietic stem cell transplantation, and Smith et al[27] conducted their study with pediatric oncology patients.

The five RCTs included a total of 338 pediatric patients, with 203 pediatric hematology or oncology patients from Cesaro et al,[24] 61 pediatric patients with oncological or malignant hematological diseases from Ullman et al,[13] 28 pediatric patients with oncological or malignant hematological diseases from Goossens et al,[25] 10 pediatric patients undergoing hematopoietic stem cell transplantation from da Silva et al,[26] and 14 pediatric oncology patients from Smith et al.[27]

Smith et al[27] and Cesaro et al[24] used Broviac-Hickman catheters, da Silva et al[26] used Hickman catheters, Ullman et al[13]. (2022) used PICCs and tunneled and implanted catheter, Goossens et al[25] used implantable venous access devices.

Intervention Procedure

In all five studies, pediatric patients received standard care or experimental care. Most children in the experimental groups received a heparin solution to flush the CVCs. Children in the control or usual-care groups received normal saline to flush the CVCs.

Cesaro et al[24] used a positive-pressure CVC valve cap device to flush CVCs with normal saline at least weekly. Goossens et al[25] flushed CVCs with 10 mL of normal saline, 3 mL of heparin (100 U/mL), and positive-pressure locking. Ullman et al[13] used sodium heparin solution with 50 U/5 mL (1 to 2 mL per catheter lumen flushing) and sodium heparin solution with 100 U/mL (2 mL per totally implanted central venous access device). da Silva et al[26] used 50 IU/mL heparin solution to flush the catheters. Smith et al[27] used 5 mL of a solution of 10 U of heparin/mL of isotonic saline to flush the catheter twice a day.

Standard Care/Control Procedure

In five studies, normal saline solution was used to flush the CVCs of pediatric patients as standard care. Cesaro et al[24] used 3 mL of normal solution and heparin 200 IU/mL twice a week to flush the CVCs. Goossens et al[25] used a pulsatile technique; CVCs were flushed with 10 mL of normal saline and then locked with use of the positive-pressure method. Ullman et al[13] flushed with 10 mL of normal saline. da Silva et al[26] used normal saline to prevent occlusion in catheters,[27] and Smith et al[27] used 9 mL of isotonic saline to flush the catheter once a week.

Risk of Bias Within Studies

Figure 2 shows a summary of the risk of bias: 60% have high risk[24,25,28] and 40% have low risk.[13,26] Bias risks were found to be most prevalent in the following domains: blinding of participants and personnel (66.67%), blinding of outcome assessment (66.67%), and other sources of bias (50%) (Fig 3).

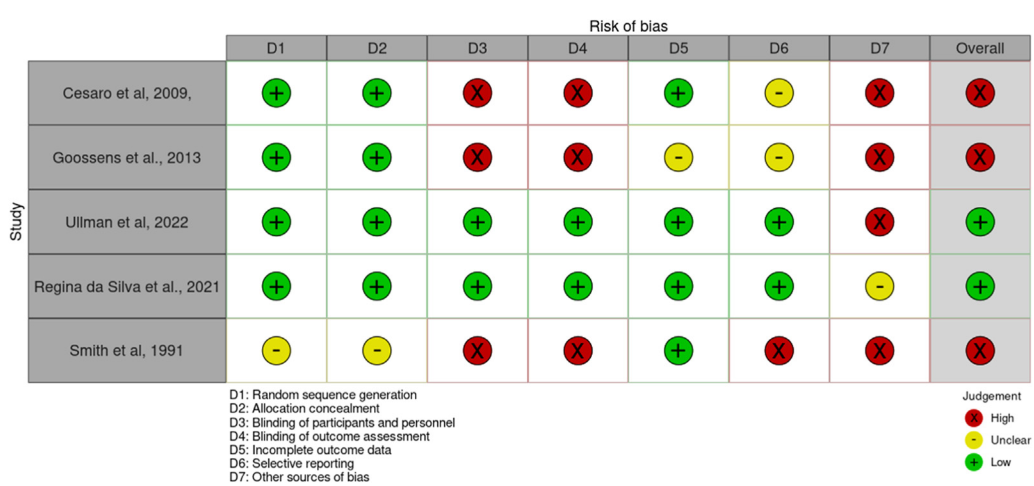

FIG 2. Risk of bias within studies.

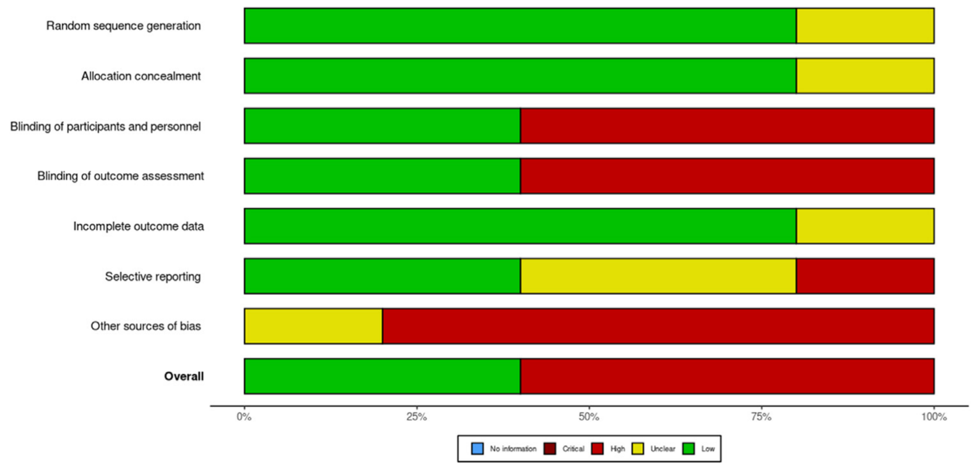

FIG 3. Risk of bias summary.

Outcomes of Meta-Analysis

Five studies[13,24–27] included 316 pediatric cancer patients to evaluate the effect of heparin and normal saline flushing in preventing CVC occlusion in pediatric cancer patients. All studies presented their results with the frequency of occlusion rate. There is no statistically significant difference in the frequency of occlusion rate between the heparin group and the normal saline group (P = .279). The heterogeneity test results of five studies included in the meta-analysis for frequency of occlusion rate were found to be moderately important: Q = 10.665, df = 4, I^2 = 62.495, and z = 1.083 (P = .279) (Table 3).

Funnel plot asymmetry, which is one of the important methods of showing publication bias, shows that the studies in this data set have a symmetrical distribution at the top of the funnel. This indicates that there is no publication bias (Fig 4). Publication bias between studies was determined by Egger's method. According to Egger's method, publication bias was not statistically significant (intercept = 1.19210, SE = 0.73, 95% confidence interval [CI] [−4.52 to 0.14], t = 2.98973, df = 3, and a two-way P value of .05). Additionally, there is no publication bias according to the Begg and Mazumdar correlation ($P > .05$).

Effect of Heparin and Normal Saline on CVC Occlusion

Figure 5 presents the pooled meta-analysis results from five RCTs that evaluated the effect of heparin and normal saline on CVC occlusion among pediatric cancer patients. A total of 338 children were included. There is no significant difference in occlusion frequency rate between heparin and normal saline (odds ratio = 2.058, 95% CI = 0.55−7.59, z = 1.063, P = .279).

Discussion

The present study is a systematic review and meta-analysis that aims to evaluate the effectiveness of heparin and normal saline

TABLE 3
Heterogeneity of the Study.

		Effect size and 95% interval			Test of null			Heterogeneity			tau-squared	
Model	Number of studies	Point estimate	Lower	Upper	Z	P	Q	$df(Q)$	P	I^2	tau	SE
Fixed	5	4.549	2.616	7.910	5.367	.000	10.665	4	.031	62.495	1.085	1.177
Random	5	2.058	0.557	7.596	1.083	.279						

SE, standard error.

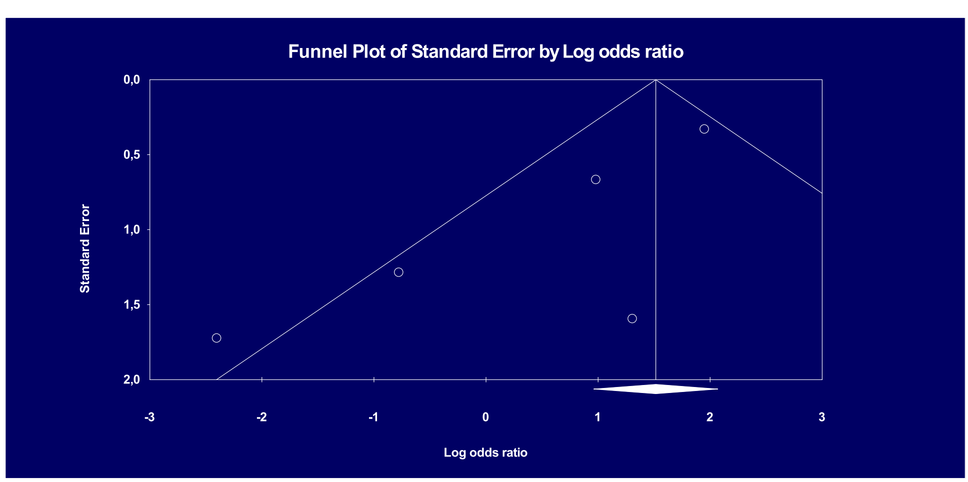

FIG 4. Funnel plot asymmetry.

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	z-value	p-value
Cesaro et al., 2009	7.059	3.672	13.570	5.860	0.000
Goossens et al., 2013	3.710	0.162	84.916	0.821	0.412
Ullman et al., 2022	2.679	0.721	9.956	1.471	0.141
Regina da Silva et al., 2021	0.091	0.003	2.682	-1.389	0.165
Smith et al., 1991	0.462	0.037	5.768	-0.600	0.548
	2.058	0.557	7.596	1.063	0.279

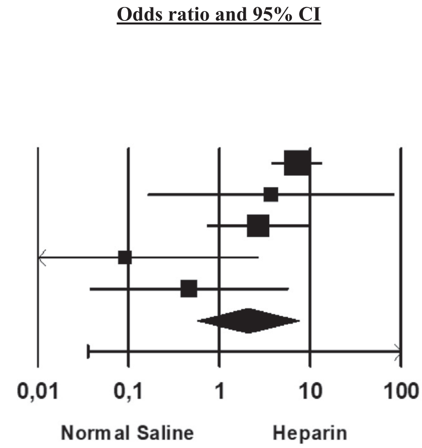

FIG 5. Forest plot diagrams.

flushing in preventing CVC occlusion in pediatric cancer patients. There is a significant variation in the literature on preventing complications associated with CVCs in this patient population. Although there is debate and disagreement about the use of heparin,[29] some studies suggest that normal saline may be just as effective as heparin. For instance, Bradford et al reported in a Cochrane review that there is no significant difference between normal saline and heparin flushing in preventing CVC occlusion among pediatric patients.[12,28] Bradford et al conducted their Cochrane review with all children; our systematic review included just pediatric cancer patients, and the results are similar.[12,28]

It has been determined that the studies included in this systematic review are heterogeneous due to different types of cancer, different heparin concentrations, flushing frequency of CVCs, and different measurement methods for occlusion. Despite all heterogeneous conditions, it can be said that flushing with heparin and flushing with normal saline are equal to each other in preventing CVC occlusion. Similarly, in previous systematic reviews in children[12,28,30] and Guidelines of the Italian Association of Pediatric Hematology and Oncology,[3] it was reported that normal saline and heparin solutions have the same effect of preventing occlusion in CVCs; it is said that normal saline should be preferred to heparin because it is easy to administer and has a lower risk of side effects, especially in newborns. Despite the discussions in many centers around the world of whether heparin or normal saline should be used in preventing occlusions associated with CVCs in children, the findings of our systematic review and meta-analysis provide crucial evidence that normal saline is as effective as heparin in preventing occlusion in CVCs.

This systematic review included five RCTs with 316 pediatric cancer patients. Although all studies were conducted with an RCT design, three studies have high risk.[24,25,27] The most common sources of bias are in blinding participants and personnel, in blinding of outcome assessment, and other sources. According to the funnel plot asymmetry, Egger's method, and Begg and Mazumdar correlation, publication bias is not statistically significant. Previous systematic reviews by Bradford et al reported that there is a high risk of bias for blinding and that the methods and interventions of the studies differ, so they did not find sufficient evidence to determine which heparin or saline solution was more effective in reducing complications.[12,28,30] In addition to previous systematic reviews, this study found enough evidence to evaluate heparin and normal saline in the prevention of CVC occlusion despite heterogeneity and some bias risks. As a result of this study, it was determined that flushing with heparin and normal saline had the same effect on preventing CVC occlusion in pediatric cancer patients.

The study results from five RCT meta-analyses showed no significant difference in occlusion frequency rate between heparin and normal saline. In line with these findings, hypotheses 1 and 2 were rejected, and hypothesis 3 was accepted. It was revealed that normal saline is as effective as heparin in preventing the occlusion of CVCs among pediatric cancer patients. Considering the potential risks associated with heparin, it is recommended that normal saline be preferred in CVC care to prevent obstruction.

Limitations

Due to several limitations, the current findings of the study should be interpreted with caution. First, considering that five RCTs were included in this study, different cancer types (where different chemotherapeutics and medications that may induce thrombosis, such as L-asparaginase, are used), different types of catheters, the fact that some studies were conducted with both adults and children, and the small number of children included may have caused the study results to be heterogeneous. Second, the studies used different heparin solution concentration to flush the CVCs, and the frequency of the flushing rate varied. Finally, the measurement methods used to evaluate occlusion differ in these five studies. Despite all these differences, the heterogeneity of the studies was moderate. Future studies can be created using improved data-gathering methods to address the identified gaps in the literature.

Study Strengths

The study is a meta-analysis, which is a powerful research method that combines and analyzes data from multiple studies. This strengthens the study's findings as it can increase the statistical power and generalizability of the results. The study includes randomized controlled studies, which are considered the gold standard in clinical research because they minimize bias and confounding factors. The inclusion of these studies further strengthens the study's findings. The study includes pediatric oncology patients, which is important as it allows for generalization of the findings to this specific population. The study is the first to evaluate the effectiveness of heparin and normal saline flushing in preventing CVC congestion in pediatric cancer patients. This is important because it fills a gap in the literature and provides new information that can inform clinical practice. Overall, these strengths contribute to the study's overall robustness and the importance of its finding.

Implications for Nursing Practice

Prevention of occlusions related to CVCs differs widely across the world. Most institutions suggest heparin to prevent obstruction, although there is evidence that 0.9% sodium chloride (normal saline) can be just as effective. Our study findings revealed significant evidence that normal saline is just as effective as heparin in preventing obstruction. Therefore, it is recommended that institutions may use normal saline to prevent occlusion of CVCs among pediatric cancer patients. Finally, RCTs are recommended to create a protocol for normal saline administration in pediatric cancer patients and to develop evidence-based clinical practice guidelines to facilitate consistency.

Conclusion

The current systematic review and meta-analyses revealed that there is no significant difference between the flushing of heparin and normal saline to prevent the occlusion of CVCs among pediatric cancer patients. RCTs with consistent measurement methods, the same concentration of heparin and flushing frequency, and larger sample sizes are required to compare heparin and normal saline to prevent the occlusion of CVCs among pediatric cancer patients. Also, the frequency of flushing with saline and, the amount of saline to be used, the pressure to be applied must be studied.

In line with the findings of this meta-analysis and previous systematic reviews, it is recommended to use normal saline in pediatric cancer patients to ensure the patency of CVCs, considering the risk factors and high cost of heparin.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.soncn.2023.151426.

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