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ORIGINAL PAPER

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# The Efficacy of Normal Saline (N/S 0.9%) Versus Heparin Solution in Maintaining Patency of Peripheral Venous Catheter and Avoiding Complications: a Systematic Review

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## ABSTRACT

**Introduction:** Heparin is a sulfated polysaccharide belonging to the glycosaminoglycan family with strong anticoagulant activity. It has been widely used to maintain intravascular catheters in patients requiring intravenous medication. It is believed that heparin prevents thrombus formation in the intravascular catheter, but since the 1980s, the necessity of the heparin solution for peripheral intravenous catheter (PIVC) flushing has been questioned in several clinical trials. According to the Institute for Safe Medication Practices (ISMP), there are four special categories of High Alert Medications (HAMs), including heparin. Aim: The aim of this systematic review was to investigate the efficacy of normal saline versus heparin solution in maintaining the patency and functionality of the PIVC and avoiding complications. Methodology: A systematic review using PubMed and Cochrane Library databases was conducted. Original research studies of hospitalized patients with PIVC, regardless of age, published in English, over the last decade (2009-2019) were eligible for inclusion. Results: The review concluded in 10 studies that met the inclusion criteria. From these studies, it appears that it is not fully documented whether the normal saline (N/S 0,9%) is superior to heparin solution (H/S) in the flushing of the PIVC for maintaining its patency and prevent complications. Researchers tend to support the use of N/S 0,9% due to safety, error avoidance, efficiency, ease of use and cost-effectiveness. Concern about the possible complications of the heparin solution was

the cause of guidelines development for N/S 0,9% in countries such as Australia. Conclusions: The use of normal saline seems to outweigh the heparin solution in maintaining the patency of PIVC.

**Keywords:** heparin flush, normal saline, peripheral catheter.

## 1. INTRODUCTION

For most of the patients admitted to the hospital, a peripheral intravenous catheter is inserted either for continuous or intermittent administration of fluids and drugs (1, 2). Since the peripheral venous catheter is widely used for intravenous infusion, the importance of its flushing is a topic of great interest to many health professionals (3, 4). Maintaining the patency and the functionality of the venous catheter plays a key role in reducing the pain, the suffering and the cost associated with its replacement and also in avoiding complications such as blockage of venous catheterization, thrombophlebitis, visible scars and infection (4, 5).

Maintaining the patency of venous catheters has been of concern to many researchers since the mid-1970s. Today, both heparin and normal saline are used to flush venous catheters although there is no convincing evidence in favor of heparin (1, 6). The instructions of some clinicians recommend washing the PIVC with heparin solution as it is believed that the antithrombotic properties of heparin will more

effectively prevent the accumulation of red blood cells and thus the thrombus formation (2). However, the CDC 2011 guidelines for the prevention of vascular catheter-associated infections suggest that systemic anticoagulants should not be used to avoid complications in all types of venous catheters (2, 7).

Heparin is a sulfated polysaccharide belonging to the glycosaminoglycan family with strong anticoagulant activity. It has been widely used for the insertion and maintenance of intravascular catheters in patients requiring intravenous medication (3, 8, 11). Regarding the mechanism of action, heparin binds to the enzyme inhibitor antithrombin III by inducing a change in its molecule and accelerating the thrombin inactivation (3, 8).

It is believed that heparin prevents the formation of thrombus in the intravascular catheter, but since the 1980s, the necessity of the heparin solution for PIVC flushing has been questioned in several clinical trials (3, 4, 9, 10, 11). In addition, heparin may interact with many commonly used drugs, such as acetylsalicylic acid, antihistamines, digoxin and others, therefore its use requires good knowledge of incompatibility between drugs (12).

According to the Institute for Safe Medication Practices (ISMP), four special categories of High Alert Medications (HAMs), including heparin, are described (13, 14, 15).

Hospital protocols for the maintenance of venous catheters vary from lack of flushing, the use of normal saline 0.9% and the use of heparin solution (10-100 IU/ml). There are many differences in the maintenance of peripheral venous lines, even in the same hospital (12).

The Queensland Government's guidelines (2015) of Australia for the maintenance of the PIVC, recommend flushing the PIVC with saline, using only single-dose solutions (ampoule). A sufficient volume of the flushing solution should be at least 2ml. PIVC flushing should be performed immediately after insertion, before and after IV administration and at least every 24h if not used (strong indication for removal) (16).

The guidelines of the Western Australia Department of Health (2017) recommend washing the PIVC with normal saline, using a 5-10 ml of solution. Flushing of PIVC should be done after its insertion, before and after each use, between multiple drug injections to avoid interactions and incompatibilities and at least every 12h if the PIVC is not used (strong indication for removal if not access has been made for 12h) (17).

## 2. AIM

The aim of this systematic review was to investigate the efficacy of normal saline versus heparin solution in maintaining the patency and functionality of the PIVC and avoiding complications.

## 3. METHODOLOGY

Articles were searched for in the PubMed and Cochrane Library databases with the following keywords: heparin flush, normal saline, peripheral catheter. Only primary studies, Clinical Trial, Controlled Clinical Trial, Multicenter Study and Randomized Controlled Trial, published in the last 10 years (2009-2019) were included.

### Study Inclusion Criteria:

- Publication in the English language
- Published in the last 10 years (2009-2019)
- Studies of patients of all ages

### Exclusion criteria:

- To refer to animals
- Publication in a language other than English

The review included 36 studies from PubMed and 23 studies from the Cochrane Library. A total of 59 studies from both databases. 37 studies were rejected because they were published before 2009. They were 22 studies remained. Of the 22 studies, 5 were excluded because of the title (central venous and arterial lines). From the 17 remained studies, 5 duplications were excluded. A total of 12 studies remained for further investigation. By the reading of the summary and the full text of these studies another 2 were excluded due to lack of relevance to the subject. From the 10 studies remained, another 2 were excluded because of the failure to complete the study. A total of 8 studies remained for the review. Another 2 studies were added, after searching the references for the above studies. A final total of 10 studies remained for the review (flowchart).

## 4. RESULTS

In a double-blind randomized clinical study by Arnts et al. 2011, (6) an evaluation of the effect of heparin against normal saline as a flushing solution to maintain the patency of venous catheter of neonates hospitalized in the ICU, was performed. 88 neonates divided into a N/S 0.9% group (46 neonates) and a heparin group (42 neonates) for 21 months, were assessed. Catheters of 24G were used, which were flushed with 0,7ml N/S 0,9% or 0,7mL heparin solution (10 U/ml) every 8 hours or more frequently (no restriction in the flushing). Venous catheters were used only to administer blood derivatives, bicarbonates and antibiotics. The researchers compared the efficacy of these two solutions in maintaining the patency of venous catheter as well as the onset of complications. Non-statistically significant results were found regarding the duration of catheter's patency with  $p = 0.265$  and the flushing solution-related complications with  $p = 0.632$ . The limitations of this study indicated that the effect of most flushing per day on the maintenance of catheter's patency was not analyzed.

In a comparative, randomized, clinical study by Cook et al. 2011, (1) the results of changing an evidence-based practice on the use of heparin in peripheral venous catheters to improve patient safety, were assessed. 70 neonates hospitalized in the ICU with a 24G venous catheter and for 3 months, were studied. Venous catheters were used exclusively for infusion of antibiotics, Lasix, phenobarbital and blood derivatives. Neonates were divided into a 0.9% N/S group (36 newborns) and a heparin group (34 newborns) in which the venous catheter was flushed with 0.4ml N/S 0.9% or 0.4ml of heparin solution (10U/ml) every 4 hours. The results showed a statistically significant difference in favor of saline with  $p = 0.02$ . An important limitation was the small sample and the short duration of the study.

In another stratified randomized clinical study by White et al. 2011, (13) the efficacy of the two solutions, heparin and saline, was evaluated and compared, regarding the

flushing of peripheral venous catheters. 62 hospitalized children aged from 1 month to 17 years were studied with 20, 22, 24G vein catheters. The children were divided into a group of N/S 0.9% (30 children) and a group of heparin (32 children) where the venous catheter was flushed with 2ml N/S 0.9% or 2ml of heparin solution (20 IU/ml) every 8 hours. The duration of the study is not mentioned. The results were non-statistically significant. The minimal complications (infiltration, phlebitis) in both groups were not correlated with the type of venous catheter flushing solution. The limitations of the study referred to the small sample due to refusal of parental consent, as the negative publicity about heparin raised concerns among them. In addition, several patients were not English speaking, so they could not be included in the study. Also, during the same period, the hospital installed EMR (Endoscopic Mucosal Resection), leading the hospital administration to discontinue the heparin - N/S 0.9% study for 6 months to minimize the concerns of nurses due to 2 major practice changes at the same time.

In an open-label, randomized clinical trial by Bertolino et al. 2012, (18) the efficacy of the heparin solution (100 IU/mL) was investigated compared to normal saline in maintaining the peripheral venous catheter patency. 214 patients were included, divided into a N/S 0.9% group (107 patients) and a heparin group (107 patients). 18, 20, 22G size catheters were flushed with 3 ml of N/S 0.9% or 3 ml of heparin solution (100 IU/ml) after each IV drug administration. The duration of the study was 2 years and 2 months. The results showed a statistically significant difference in the patency of catheters of the heparin group compared to the 0.9% N/S group with  $p = 0.002$ . The authors reported the lack of blind method in patient selection as a limitation of the study.

In a prospective clinical study by Wang et al., 2012, (10) the efficacy of the two solutions, heparin and normal saline, was compared and evaluated in the flushing of peripheral venous catheters of size 22, 24G. 359 patients with gastroenterological or hepatic diseases were studied, divided into a N/S 0.9% group (181 patients) and a heparin group (178 patients) for 3 months. The flush volume (ml) is not mentioned. The heparin solution was at a low concentration (10 IU/ml). The results were non-statistically significant with  $p = 0.502$ . There were non-statistically significant complications between the two groups, which were not correlated with the type of solution. Study limitation is not mentioned.

In another randomized clinical study by Patidar et al. 2014, (12) 75 hospitalized adult surgical department's patients with a 22G venous catheter were studied over a 3 day (72 hour) period. The patients were divided into 3 groups: control group (25 patients), N/S 0.9% group (25 patients) and heparin group (25 patients). In N/S 0.9% and heparin groups, the venous catheters were flushed with 1 ml of N/S 0.9% or 1 ml of heparin solution (10 IU/ml) after each IV drug administration. There was no intervention in the control group. There was a statistically significant difference between the control group and the 0.9% N/S group, as well as between the control group and the heparin group with  $p < 0.05$ . However, there was no statistically significant difference in the duration of venous catheter's patency be-

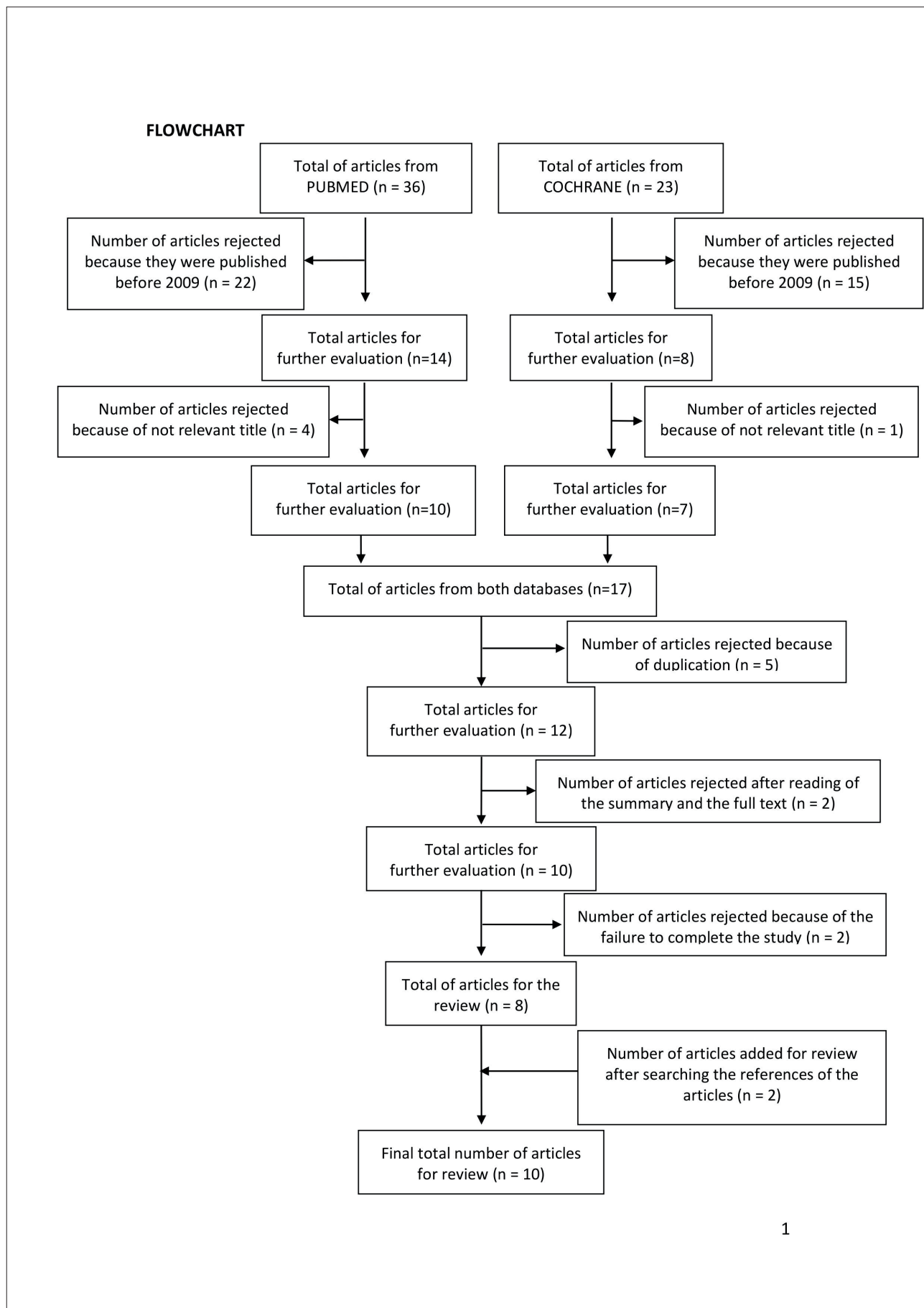
tween heparin and saline groups with  $p = 0.50$ , leading to the conclusion that flushing with 1 ml of N/S 0.9% is more effective than if it does not happen at all. Regarding the complications, double occurrence of phlebitis was in the control group compared to the other two groups. Study limitations are not mentioned.

In a double-blind, randomized clinical study by Upadhyay et al. 2015, (19) an evaluation of the efficacy of the heparin solution in maintaining the functionality of the 24G peripheral venous catheter in neonates treated in the ICU was evaluated. 120 neonates were included, divided into a N/S 0.9% group (60 newborns) and a heparin group (60 newborns) for 11 months. The catheters included in the study were used only for the administration of antibiotics. The venous catheters were flushed with 1 ml of N/S 0.9% or 1 ml of heparin solution (10 IU/ml) before and after each IV administration of antibiotics. Statistically significant results were found in favor of heparin with  $p < 0.005$  and minimal complications in both groups. Study limitations are not mentioned.

In a single-blind, randomized clinical study by Wang et al., 2015, (3) the efficacy of heparin and saline solutions was evaluated in flushing catheters in patients with decompensated liver cirrhosis. 68 patients with moderate to severe liver cirrhosis were studied, with 22, 24G catheters for 11 months. Patients were divided into a 0.9% N/S group (32 patients) and a heparin group (36 patients), in which the venous catheter was flushed with 5ml N/S 0.9% or 5ml of heparin solution (50 IU/ml) twice a day. The results showed a non-statistically significant difference between the flush solutions with  $p = 0.397$ . The small sample and the high withdrawal rate of participants (19%, 16/84) due to a refusal to participate after the allocation are mentioned as a limitation of the study.

In another open-label, randomized clinical study by Xu et al. 2017, (4) the effect of the heparin solution against normal saline was evaluated as a flushing solution to maintain the patency of peripheral venous catheters. The study lasted 2 months and involved 286 hepatobiliary operated patients. Patients with an 18-24G venous catheter were divided into a N/S 0.9% group (146 patients) and a heparin group (140 patients). The catheter was flushed with 3 ml of N/S 0.9% or 3 ml of heparin solution (50 IU/ml) after each IV use. The results showed that there was no statistically significant difference between the two groups with regard to complications and venous catheter obstruction. The authors stated that one of the study limitations is that they did not measure the prothrombin time as well as the presence of confounding factors in selecting patients (open-label design).

In a double-blind, randomized clinical study by Mathews et al. 2017, (20) the efficacy and safety of the use of the heparin solution as a flushing solution of the venous catheters in neonates in comparison to normal saline were investigated and evaluated. 100 neonates hospitalized in ICU, were studied, which were divided into a 0.9% N/S group (41 neonates) and a heparin group (59 neonates). The duration of the study was 12 months. The size of the venous catheters included in the study was 24G, which were used exclusively for infusion of antibiotics, antiepileptic and antifungal medicines. The flushing was done with 1 ml of N/S 0.9% or 1 ml of heparin



Flowchart 1. Review of 10 studies from total amount of 59 studies included for analysis in our investigation



solution (1 IU/ml: 0.1 ml of heparin diluted in 100 ml of N/S 0.9%) before and after each IV drug administration. Non-statistically significant results were found with  $p = 0.584$ . In the study's limitations, the authors reported that all the related complications with the venous catheter have not been studied in detail. In addition, the patency associated with the frequency of flushing could not be estimated due to the non-uniform frequency of the flushings.

## 5. DISCUSSION

From the results of the studies of this systematic review, the use of normal saline (N/S 0.9%) is proposed in the absence of a clear advantage of the heparin solution (1, 3, 4, 6, 10, 12, 13, 20). However, it is not fully documented whether the flushing of PIVC with saline (N/S 0.9%) compared to heparin solution, achieves its maintenance of patency and avoidance of complications (18, 19, 20).

Researchers tend to favor 0.9% N/S use due to safety and avoidance of errors, efficiency, ease of use and cost savings (4, 13). The ability of a child or newborn to metabolize heparin is different from an adult. Reactions to heparin may be serious and life-threatening as heparin is referred to as a high-risk medicine. There is an increased probability of error in peripheral heparin flushing associated with incorrect heparin dosing or error in heparin concentration in the solution used to flush venous catheters (13, 14, 15). The concern about the possible complications (hemorrhage, thrombocytopenia) of the heparin solution probably gave rise to the development of guidelines for N/S 0.9% in hospitals in some countries such as Australia (3, 6, 13, 16, 17).

However, the studies present a number of methodological problems that require the results to be treated with caution and skepticism. The short duration of the studies consists of an important limitation of the studies (1, 12) as well as the small sample of patients used in some of these studies (1, 3, 12, 13). In addition, the absence of a common methodology and the heterogeneity of heparin solutions in relation to the concentration of heparin units in the flushing of venous catheters was another important limitation (1, 3, 4, 6, 10, 12, 13, 18, 19, 20).

In the studies by Arnts et al. 2011 (6), Cook et al. 2011 (1), Upadhyay et al. 2015 (19) and Mathews et al. 2017 (20), neonatal population with small lumen venous catheters was studied and therefore there was a possibility of increased degree of obstruction in relation to larger size catheters in adults (3, 4, 10, 12, 18).

Due to different methodology, different sample size, heterogeneity in the sample (different populations), use of different size and brand/quality of venous catheters, inconsistency in dosage and concentration of heparin, different frequency of flushing as well as different medications, it is difficult to reach in safe and sure conclusions for or against the use of the heparin solution in flushing peripheral venous catheters.

The limitations of this systematic review are the small number of studies, the search of relevant bibliography in only two electronic databases and the fact that only studies published in English were used. However, it is not surprising that the use of normal saline seems to outweigh the heparin solution, in maintaining the patency of peripheral venous

catheter (1, 3, 4, 6, 10, 12, 13, 20).

## 6. CONCLUSION

The use of normal saline seems to outweigh the heparin solution in maintaining the patency of peripheral venous catheters. Eight out of the 10 review studies concluded that, in the absence of a clear advantage of the heparin solution, the use of N/S 0.9% is recommended due to possible serious complications from heparin. However, because of the small number of studies, these findings cannot be generalized. More primary and multicenter studies are needed on the use of normal saline in combination with heparin solution, which may provide safer conclusions. Searching for more electronic databases as well as studies written in a language other than English would potentially give a larger volume of studies on this subject.

Taking into account the results of the relevant studies, the flushing of peripheral venous catheters with normal saline solution only has many advantages. The use of N/S 0.9% seems to be an effective, cheap, safe and reliable alternative to heparin solution.

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- **Conflict of interest:** There are no conflict of interest.
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