

Heparin Versus Normal Saline

Flushing effectiveness in managing central venous catheters in patients undergoing blood and marrow transplantation

John Klein, BSN, RN, BMCTN®, Amelia Jepsen, MSN, RN, A-GNP, BMCTN®, Amy Patterson, MSN, RN, AOCNS®, BMCTN®, Richard R. Reich, PhD, and Tina M. Mason, MSN, ARNP, AOCN®, AOCNS®

BACKGROUND: Patients undergoing blood and marrow transplantation (BMT) use a central venous catheter (CVC); heparin is often employed to maintain patency but may increase the risk of complications. Research has not provided conclusive differences in efficacy and safety regarding heparin flushing versus normal saline flushing in CVC maintenance. Minimal research is specific to this patient population.

OBJECTIVES: This study aimed to determine if differences exist in CVC patency, tissue plasminogen activator usage, and the incidence of central line-associated bloodstream infections when flushing with normal saline only versus heparin and normal saline among patients undergoing BMT.

METHODS: A convenience sample of 30 patients undergoing allogeneic or autologous transplantation with a new non-port/non-peripherally inserted CVC were evaluated.

FINDINGS: Elimination of routine heparin use could positively affect outcomes in this patient population.

KEYWORDS

blood and marrow transplantation; central venous catheter; saline flush; central line

DIGITAL OBJECT IDENTIFIER

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PATIENTS UNDERGOING BLOOD AND MARROW TRANSPLANTATION (BMT) have increased hematologic risks and a need for platelet transfusions because of thrombocytopenia (Keeler, 2014). Evidence-based guidelines suggest that routine flushing with normal saline can prevent fibrin buildup and that routine administration of anticoagulants for prophylaxis is not recommended for patients with cancer with central venous catheters (CVCs) (López-Briz et al., 2014; Schiffer et al., 2013). A paucity of research exists in the BMT literature regarding routine flushing of the CVC with normal saline only versus heparin and normal saline.

Background

Evidence-based guidelines published by the Centers for Disease Control and Prevention (O'Grady et al., 2011) and the Cochrane Database of Systematic Reviews (López-Briz et al., 2014) identify best practices for CVC maintenance and the prevention of central line-associated bloodstream infections (CLABSIs). The Centers for Disease Control and Prevention guidelines were developed by a working group consisting of members from multiple professional organizations (e.g., Oncology Nursing Society, Infusion Nurses Society); however, these guidelines did not specifically recommend best practices for flushing CVCs in patients undergoing BMT. The Cochrane systematic review (López-Briz et al., 2014) assessed the effectiveness of intermittent flushing with heparin versus normal saline in adults. Reviewed studies included randomized, controlled trials and meta-analyses. Results included the following:

- Adverse events may be reduced by using normal saline flushes.
- No conclusive evidence exists showing important differences in terms of efficacy and safety between heparin intermittent flushing and normal saline flushing in CVC maintenance.
- Heparin is more expensive than normal saline, challenging its continued use in CVC flushing outside of the context of clinical trials.

Similar results were found in other studies (Heidari Gorji, Rezaei, Jafari, & Yazdani Cherati, 2015; López-Briz et al., 2014; Mitchell, Anderson, Williams, & Umscheid, 2009). Research indicates that heparin flush does not decrease the potential for occlusions (Jonker, Osterby, Vermeulen, Kleppin, & Kudsk,

2010; Stephens et al., 1997). A controlled trial focusing on apheresis CVC patency showed that heparin flush was not any more effective than normal saline flush for catheter patency (Goossens et al., 2013). Risks of using heparin may include increased bleeding or heparin-induced thrombocytopenia. In addition, the potential for nursing errors may be higher when lines are flushed with heparin (Keeler, 2014). More rigorous studies that are powered to discern if heparin is necessary for flushing protocols are needed (Dal Molin et al., 2014; Mitchell et al., 2009). A cohort study that was focused on the efficacy of normal saline flush versus heparin flush for locking long-term central lines in patients with cancer did not show any significant difference between normal saline flush versus heparin flush for the maintenance of line patency, suggesting the possibility of a safe switch to normal saline locks (Bertoglio et al., 2012).

The previously discussed literature shows no difference in the addition of heparin to flushing protocols versus normal saline alone. The literature also suggests that the use of a normal saline flush may decrease costs and adverse events and improve safety. These comparisons have yet to be made in a population of patients undergoing BMT. Patients undergoing BMT are unique because they have an increased risk for contracting CLABSI, heparin-induced thrombocytopenia, or coagulopathy and for being refractory to platelet transfusions (Aimoto et al., 2013; Mayo, Cullinane, Merryman, & Horne, 1999). In addition to hematologic complications, an increased risk for nursing errors may occur because of multiple catheters each receiving a different dose of heparin flush (Keeler, 2014).

Clinical research is needed to provide information that may be useful in developing safe and effective evidence-based CVC flushing protocols specifically for patients undergoing BMT. The aim of this nursing research study was to determine if a difference in line patency exists when using normal saline only versus

“Normal saline-only flushing appears to be a safe and effective way to care for central venous catheters in this patient population.”

heparin and normal saline, as well as tissue plasminogen activator (tPA) usage and incidence of CLABSI when flushing central lines in patients undergoing BMT.

Methods

A randomized, controlled pilot study was conducted to determine whether normal saline flushing of CVC lines was safe and effective, paying particular attention to patency, tPA usage, and occurrence of CLABSI when compared to the standard of care (heparin and normal saline). See Table 1 for flushing protocols (all lines required weekly cap changes). Patients were assigned to groups using block randomization of six blocks to receive either standard of care or normal saline-only flushing. The study was conducted on a 36-bed BMT unit and in an outpatient BMT treatment center at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida.

Sample

A convenience sample of 30 patients undergoing BMT, each with a new CVC, was randomized to receive either heparin and normal saline or normal saline alone for flushing. This pilot study had 15 patients per group (Julious, 2005). Although the number of patients was small, 698 observations were able to be made. Patients remained in the study for 90 days post-transplantation or until the CVC line was removed. Patients selected for inclusion were those who were undergoing BMT and had newly placed central lines, including tunneled double-lumen apheresis catheters, tunneled triple-lumen catheters, and non-tunneled double-lumen catheters, that had been placed at the Moffitt Cancer Center. Exclusion criteria included peripherally inserted central lines, implanted ports, and lines placed at an outside facility. If a patient was readmitted to a unit other than the BMT unit, or if a patient was transferred from the BMT unit to another unit, such as the intensive care unit, the patient no longer qualified to participate in the research study.

TABLE 1.
GUIDELINES FOR FLUSHING CENTRAL VENOUS CATHETERS

CATHETER TYPE	WHEN	STANDARD FLUSH	SALINE-ONLY FLUSH
Tunneled/non-valved	Daily and as needed	10 ml normal saline, then 3 ml heparin 10 u/ml	10 ml normal saline turbulent flush
Non-tunneled	Daily and after use	10 ml normal saline, then 1 ml heparin 10 u/ml	10 ml normal saline turbulent flush
Apheresis tunneled	Monday, Wednesday, and Friday and as needed	10 ml normal saline, then 2 ml heparin 1,000 u/ml	10 ml normal saline turbulent flush

Note. Guidelines are based on protocols used at the Moffitt Cancer Center.

Instruments

An investigator-developed demographic form was used to collect the following information: age, gender, ethnicity, disease, type of transplantation, and type of central line. In addition, an investigator-developed central line patency audit form was used to collect data regarding line problems, specifically patency, tPA usage, and occurrence of CLABSI.

Recruitment and Data Collection

Patients were given a study recruitment flyer by the transplantation nurse coordinator during the nurse visit appointment in the BMT clinic prior to CVC placement. Patients who wanted more information about the study or who were interested in participating in the study contacted one of the study co-investigators via email or telephone or during a visit at the BMT treatment center. A co-investigator explained the study and gave the consent form to the patient to read. If the patient chose to participate, he or she signed the consent form, and the patient was systematically randomized. Once the group assignment was made, the co-investigator placed a corresponding heparin or saline label on the CVC dressing.

Patency data were collected on each patient with the central line patency audit tool. Inpatient nursing staff work in 12-hour shifts, and line patency was documented once per shift (twice daily). Outpatient nursing staff documented patency after each line access. Education was provided to the inpatient and outpatient nursing staff through huddles (informal meetings) and one-on-one education. Data collection sheets were explained in detail, and identifying stickers (colored stickers that were used to identify the arm of the study and that were placed on each patient's dressing after randomization) were shown to the staff. The BMT physician group, the BMT nurse practitioner group, and the BMT physician assistant group were educated on the details of the study and coached on the appropriate orders for CVC maintenance for the normal saline group versus the heparin and normal saline group. Regulatory approval was obtained from the center's scientific review committee and institutional review board. Informed consent was also obtained. No increased risk or burden was placed on the participants. Participation was voluntary.

Analysis

Descriptive statistical analyses were conducted using SAS. Inferential analyses of difference between the two flushing protocols were conducted using R. Three participants were excluded from analysis (one from the normal saline group and two from the heparin and normal saline group) because of incomplete flushing records. One patient was excluded because of excessive CVC line problems; this patient was from the normal saline group, and the line was positional and sluggish for 31 of 53 flushes and required tPA for patency four times. Because the 698 patency observations

involved 26 patients, the authors ran a hierarchical model using logistic regression to predict line problems. In this hierarchical model, observations were nested within patients. This hierarchical model allowed the authors to assess the influence of individual patients on results. The generalized linear mixed-effects function in R was used for this latter analysis with a nominal alpha of 0.05.

Results

The sample consisted of 10 women and 16 men with a mean age of 54 years (see Table 2). Among the 698 events, the rates of line problems were similar between flushing with heparin and normal saline (8.8%) and with normal saline (8.5%) ($p = 0.88$). These rates did not change at the patient level ($p = 0.95$). For patients with line problems, tPA was given at similar rates for the heparin

TABLE 2.
SAMPLE CHARACTERISTICS (N = 26)

CHARACTERISTIC	n
Gender	
Male	16
Female	10
Ethnicity	
Caucasian	19
Hispanic	5
African American	1
Indian	1
Diagnosis	
Multiple myeloma	10
Lymphoma	8
Acute leukemia	7
Myelodysplastic syndrome	1
Type of transplantation	
Autologous	19
Allogeneic	7
Type of central line	
Tunneled double-lumen apheresis catheter	14
Tunneled triple-lumen catheter	10
Non-tunneled double-lumen catheter	2

flush (25%) and the normal saline flush (27%) (chi-square = 0.02; not significant) (see Table 3). One CLABSI occurred in the normal saline-only group. When this CLABSI was factored into the BMT CLABSI rate data, it was determined that it did not represent a deviation from historical CLABSI rates.

Discussion

Consistent with literature involving other populations, in this study, normal saline flushing appears to be a comparably safe and effective alternative to heparin and normal saline flushing in the population of patients undergoing BMT. In an effort to influence a practice change at the Moffitt Cancer Center, the results of this research have been presented to nursing, BMT, and hospital leadership, as well as the Nursing Practice Council. With their support, the center moved toward eliminating heparin from these flushing protocols; this elimination took effect in November 2017.

Although published evidence exists to support normal saline-only CVC flushing in the general population, studies had not addressed the population of patients undergoing BMT. This population is unique because of the length of time that the catheter remains in place and because of the higher doses of heparin used for line maintenance. The current authors feel that their results, which are consistent with published findings discussed previously in this article, can be generalized to the non-BMT patient population at their center. One limitation of this study is the small sample size; larger studies involving this population are warranted. In addition, tracking participants who required a readmission was challenging in terms of data collection.

Implications for Nursing and Conclusion

Because of the high number of potential hematologic complications that a patient undergoing BMT faces during treatment, the elimination of routine heparin use could positively affect outcomes by reducing or eliminating complications. This research may contribute to the foundations for practice change in a broader population of at-risk patients.

TABLE 3.
RATES OF PATENCY AND tPA USE (N = 26)

FLUSHING PROTOCOL	PATENCY				tPA USE			
	YES		NO		YES		NO	
	n	%	n	%	n	%	n	%
Normal saline/ heparin	313	91	30	9	6	25	18	75
Normal saline	325	92	30	8	7	27	19	73

tPA—tissue plasminogen activator

IMPLICATIONS FOR PRACTICE

- Anticipate that heparin is often used in flushing protocols for the care of central venous catheters.
- Raise awareness that heparin use can increase the risk of complications, such as bleeding and heparin-induced thrombocytopenia.
- Emphasize that studies have not shown conclusive differences in the efficacy and safety of heparin with normal saline flush versus normal saline-only flush for the care of central venous catheters.

Normal saline-only flushing appears to be a safe and effective way to care for CVCs in this patient population. The benefits of normal saline-only flushing protocols include decreased cost, amount of CVC accesses, and overall number of flushing protocols. Although cost was not evaluated in this study, the institution's cost of a 1 ml vial of heparin 1,000 u/ml is \$2.40 (\$4.80 per 2 ml flush/lumen), and heparin 10 u/ml is \$0.43 per 5 ml syringe/lumen, as of January 2018. Another advantage of removing heparin from flushing protocols is the elimination of potential drug incompatibilities. Flushing with normal saline prior to administering a medication is recommended, but this step could be omitted, leading to drug-drug interactions.

The evidence identified in the literature review and in the current authors' nursing research shows no benefit to the addition of heparin to central line flushing protocols. Using evidence-based practice, oncology nurses can minimize risks associated with heparin-based flushing.

John Klein, BSN, RN, BMCTN®, is an assistant manager in the blood and marrow transplantation inpatient unit at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, FL; **Amelia Jepsen, MSN, RN, A-GNP, BMCTN®**, is an RN at the Central Florida SurgiCenter in Lakeland; and **Amy Patterson, MSN, RN, AOCNS®, BMCTN®**, is a clinical specialist in the Department of Nursing Professional Development, **Richard R. Reich, PhD**, is a biostatistics core facility manager in the Department of Biostatistics and Bioinformatics, and **Tina M. Mason, MSN, ARNP, AOCN®, AOCNS®**, is a nurse researcher in the Department of Nursing Research, all at the H. Lee Moffitt Cancer Center and Research Institute. Klein can be reached at john.klein@moffitt.org, with copy to CJONEditor@ons.org. (Submitted May 2017. Accepted August 17, 2017.)

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REFERENCES

- Aimoto, M., Yamane, T., Shiimoto, K., Sakamoto, C., Nakashima, Y., Koh, H., . . . Miyata, S. (2013). Refractoriness to platelet transfusion in acute myeloid leukemia correlated with the optical density of anti-platelet factor 4/heparin antibodies. *International Journal of Hematology*, 98, 472–477. <https://doi.org/10.1007/s12185-013-1427-4>
- Bertoglio, S., Solari, N., Meszaros, P., Vassallo, F., Bonvento, M., Pastorino, S., & Bruzzi, P. (2012). 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 Nursing*, 35, E35–E42. <https://doi.org/10.1097/NCC.0b013e31823312b1>

Dal Molin, A., Allara, E., Montani, D., Milani, S., Frassati, C., Cossu, S., . . . Rasero, L. (2014).

Flushing the central venous catheter: Is heparin necessary? *Journal of Vascular Access*, 15, 241–248. <https://doi.org/10.5301/jva.5000225>

Goossens, G.A., Jérôme, M., Janssens, C., Peetermans, W.E., Fieuws, S., Moons, P., . . . Stas, M. (2013). Comparing normal saline versus diluted heparin to lock non-valved totally implantable venous access devices in cancer patients: A randomised, non-inferiority, open trial.

Annals of Oncology, 24, 1892–1899. <https://doi.org/10.1093/annonc/mdt114>

Heidari Gorji, M.A., Rezaei, F., Jafari, H., & Yazdani Cherati, J. (2015). Comparison of the effects of heparin and 0.9% sodium chloride solutions in maintenance of patency of central venous catheters. *Anesthesiology and Pain Medicine*, 5(2), e22595. <https://doi.org/10.5812/aapm.22595>

Jonker, M.A., Osterby, K.R., Vermeulen, L.C., Kleppin, S.M., & Kudsk, K.A. (2010). Does low-dose heparin maintain central venous access device patency?: A comparison of heparin versus saline during a period of heparin shortage. *Journal of Parenteral and Enteral Nutrition*, 34, 444–449. <https://doi.org/10.1177/0148607110362082>

Julious, S.A. (2005). Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics*, 4, 287–291. <https://doi.org/10.1002/pst.185>

Keeler, M. (2014). Central line practice in Canadian blood and marrow transplant. *Canadian Oncology Nursing Journal*, 24, 67–77.

López-Briz, E., Ruiz Garcia, V., Cabello, J.B., Bort-Marti, S., Carbonell Sanchis, R., & Burls, A. (2014). Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults. *Cochrane Database of Systematic Reviews*, 10, CD008462. <https://doi.org/10.1002/14651858.CD008462.pub2>

Mayo, D.J., Cullinane, A.M., Merryman, P.K., & Horne, M.K., III. (1999). Serologic evidence of heparin sensitization in cancer patients receiving heparin flushes of venous access devices. *Supportive Care in Cancer*, 7, 425–427.

Mitchell, M.D., Anderson, B.J., Williams, K., & Umscheid, C.A. (2009). Heparin flushing and other interventions to maintain patency of central venous catheters: A systematic review. *Journal of Advanced Nursing*, 65, 2007–2021.

O'Grady, N.P., Alexander, M., Burns, L.A., Dellinger, E.P., Garland, J., Heard, S.O., . . . Saint, S. (2011). Guidelines for the prevention of intravascular catheter-related infections. *Clinical Infectious Diseases*, 52, e162–e193. <https://doi.org/10.1093/cid/cir257>

Schiffer, C.A., Mangu, P.B., Wade, J.C., Camp-Sorrell, D., Cope, D.G., El-Rayes, B.F., . . . Levine, M. (2013). Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology*, 31, 1357–1370. <https://doi.org/10.1200/JCO.2012.45.5733>

Stephens, L.C., Haire, W.D., Tarantolo, S., Reed, E., Schmit-Pokorny, K., Kessinger, A., & Klein, R. (1997). Normal saline versus heparin flush for maintaining central venous catheter patency during apheresis collection of peripheral blood stem cells (PBSC). *Transfusion Science*, 18, 187–193.