The Efficacy and Safety of Hypertonic Citrate as Catheter-Locking Solution in Hematopoietic Stem Cell Transplant Recipients

Hipertonik Sitratın Hematopoetik Kök Hücre Transplant Alıcılarında Kateter Kapatma Solüsyonu Olarak Etkinlik ve Güvenirliği

Özlem ŞAHİN BALÇIK, MD,[a]
Çiğdem AKKAYA, MD,[b]
Burak UZ, MD,[c]
Cafer AKSOY, MD,[b]
Birol GÜVENÇ, MD,[d]
Süleyman DİNÇER, MD[b]

[a]Department of Hematology, Fatih University Faculty of Medicine, [b]Bayındır Hospital Bone Marrow Transplantation Unit, [c]Department of Hematology, Hacettepe University Faculty of Medicine, Ankara [d]Department of Hematology, Çukurova University Faculty of Medicine, Adana

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Yazışma Adresi/*Correspondence:*
Özlem ŞAHİN BALÇIK, MD
Fatih University Faculty of Medicine, Department of Hematology, Ankara, TÜRKİYE/TURKEY
drozlembalcik@yahoo.com

ABSTRACT Objective: Central venous catheters are frequently used for vascular access in hematopoietic stem cell transplant recipients. Prophylactic locking with heparin is still a standard procedure despite its associated risks. Trisodium citrate has been advocated in recent years because of its antimicrobial properties. Additional advantages of trisodium citrate are that it prevents systemic anticoagulation and is less expensive than heparin. The objective was to determine the clinical effectiveness and safety of trisodium citrate 46.7% as a locking solution for central venous catheters in hematopoietic stem cell transplant recipients. **Material and Methods:** Twenty three patients with various hematologic malignancies were enrolled to the study. They had received hypertonic citrate (46.7%) locking solution at least 1/week instead of standard dose heparin in their outpatient period. The clinical characteristics of the patients, side effects of the relevant solution and catheter related complications were evaluated retrospectively. **Results:** Median catheter using time was 68 days (range: 25-252) for all catheters. Median using time of catheter lock solution was 20 days (range: 3-222). Of 23 eligible patients, 3 had catheter related thrombosis and one had hypocalcemic symptoms that improved after calcium infusion. Catheter infection, cardiac symptoms, embolic events and hypernatremia did not occur in any of the patients. **Conclusion:** It seems safe and effective to use high concentrations of trisodium citrate for catheter locking in hematopoietic stem cell transplant recipients. Randomized trials comparing these anticoagulants with a control group would definitively determine the optimal locking solution.

Key Words: Catheterization, central venous; venous thrombosis; catheter-related infections

ÖZET Amaç: Santral venöz kateterler, hematopoetik kök hücre transplant alıcılarında sıklıkla kullanılan bir vasküler yoldur. Heparinle profilaktik kapatma, risklerine rağmen, halen standard prosedürdür. Son zamanlarda antimikrobiyal özelliklerinden dolayı bu amaçla trisodyum sitrat kullanımı önerilmektedir. Bu sayede sistemik antikoagülasyondan kaçınma ve daha az maliyet de sağlanmış olacaktır. Çalışmamızın amacı bu hasta grubunda %46.7 trisodyum sitrat kullanımının klinik etkinlik ve güvenirliğini belirlemektir. **Gereç ve Yöntemler:** Çeşitli hematolojik malinite tanıları olan 23 hasta çalışmaya alınmıştır. Bu hastalara nakil işlemi sonrası ayaktan takip edildikleri dönemde en az haftada bir kez hipertonik sitrat kapatma solüsyonu (%46.7) uygulanmıştır. Hastaların klinik özellikleri, kateter solüsyonuna bağlı yan etkiler ve kateterle ilişkili komplikasyonlar geriye dönük olarak değerlendirilmiştir. **Bulgular:** Tüm kateterler için ortalama kullanım süresi 68 (25-252) gün, ortalama kateter kapatma solüsyonu kullanım süresi ise 20 (3-222) gündü. 23 hastanın 3'ünde katetere bağlı tromboz, birinde ise kalsiyum infüzyonu ile düzelen hipokalsemik semptomlar meydana geldi. Hiçbir hastada kateter ilişkili enfeksiyon, kardiyak semptomlar, embolik olaylar ve/veya hipernatremi gelişmedi. **Sonuç:** Hematopoetik kök hücre alıcılarında kateter kapatma solüsyonu olarak yüksek konsantrasyonlu trisodyum sitrat kullanımı güvenli ve efektif bir yöntem olarak görülmüştür. Optimal kapatma solüsyonunu belirlemek üzere bu antikoagülanların karşılaştırılacağı randomize kontrollü çalışmaların yapılmasına ihtiyaç vardır.

Anahtar Kelimeler: Kateterizasyon, santral venöz; venöz tromboz; kateter kaynaklı enfeksiyonlar

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Many intravenous treatments including high-dose chemotherapy, antibiotics or intravenous replacement therapies are applied during and after hematopoietic stem cell transplantation.

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The early complications of transplantation such as cytopenias, infections or graft-versus host disease also make the need for central vascular access more evident. Long-term indwelling central venous catheters have eased the administration of drugs, blood products, and hyperalimentation to patients with cancer. However, catheters are associated with a number of recognized complications, including infection, catheter-related sepsis, catheter-associated fibrin sheath and thrombus leading to malfunction.[1]

Catheter malfunction due to occlusion can have a significant impact on patient quality of life and patient morbidity while thrombolytic and diagnostic interventions add additional financial burden to the already escalating costs of hematopoietic stem cell transplantation process. Some clinical studies showed that an interdialytic lock with trisodium citrate (TSC) is more effective than interdialytic locking with heparin in reducing morbidity and mortality due to catheter-related infections.[2-4] In addition, citrate can also be used in the case of confirmed or suspected heparin-induced thrombocytopenia (HIT),[5] or where the use of heparin could be potentially dangerous. However, sodium citrate has not gained wide acceptance for use in intermittent haemodialysis in the US primarily because of fear of accidental infusion of highly concentrated solutions of sodium citrate during the lock procedure.

Colonization and formation of a biofilm produced by bacteria are thought to be major risk factors for both catheter-related infections and intraluminal thrombosis.[3] A recent prospective study by Martín-Peña et al. showed that, in patients with allogeneic hematopoietic stem cell recipients, the second most common cause of infectious complication was found to be catheter related bloodstream infections.[6] Catheter-related infections (CRI) are associated with a substantial morbidity, mortality, and additional cost per infective episode.[7] In this point, heparin has no antibacterial properties and, may help to promote the biofilm layer on catheter surfaces.[8]

Recently, it has been demonstrated that trisodium citrate has superior antimicrobial effects over heparin for catheter locking.[9] Sodium citrate has an intrinsic antibacterial activity at higher concentrations. In fact, the osmolality of 47% citrate is 6400 mOsm, and it is well known that solutions of very high osmolality are, at least, bacteriostatic. Citrate has also added advantage of being compatible with almost every type of antibiotic drug, even in high concentrations.[10] Many dialysis centers have turned from traditional heparinized catheter locks to antiseptics, including various concentrations of citrate and/or antibiotics in heparin solutions.[3] Both types of locks have been shown to reduce the risk of catheter-associated bacteremia.[4]

Currently, there is limited experience with high concentrations of TSC in clinical practice, and the efficacy and the safety of these solutions for improving catheter outcome have yet to be established.[10,11] The studies of citrate about this issue are limited mainly with hemodialysis patients. Therefore, we decided to demonstrate the efficacy and safety of hypertonic citrate as a catheter lock solution in hematopoietic stem cell recipients.

MATERIAL AND METHODS

CATHETERS

Two models of catheters were used during the study period; Hickman Catheters (double-lumen, tunneled and cuffed, 11 F) were 90 cm in lenght and temporary juguler catheters (double-lumen, untunneled and noncuffed, 14 F) were 15 cm in lenght. The proximal and distal priming volumes of Hickman catheters were 2.1 cc. For the temporary dialysis catheters these volumes were 1.1 cc and 1.3 cc respectively. All the catheters were inserted by experienced radiologists under direct image guidance and were dual-lumen. In our centre, the choice between insertion of a tunnelled or untunnelled catheter is primarily based on the expected duration of catheter use.

SELECTION OF PATIENTS

Patients were excluded from the study if any of the following criteria were present: suspected HIT or heparin-induced thrombosis, systemic bacterial infection, localized infection requiring systemic antibiotics, proven or suspected allergy to heparin or TSC. Written informed consent was obtained from all patients before enrollment.

CATHETER LOCK SOLUTION (CLS)

LOXXIT TM Catheter Lock Solution (46.7% Trisodium Citrate), 5 mL (Citra Anticoagulants, Inc., Braintree, MA 02184 USA) was used for CLS.

STUDY DESIGN

Heparin 5000 IU/ml was used for locking the catheters in the hospitalization period (inpatient period). The patients were discharged without removing their catheters and the TSC solution was used in their outpatient interval (outpatient period). The process for locking catheters with TSC was identical to the process previously used when catheters were locked with heparin. Application of TSC solution was restricted to only bone marrow transplantation unit nurses which were skilled and experienced on their areas. TSC was used at least 1/week for each patient. No drugs or intravenous treatments were administered via the catheters. At the each nurse visit, the lumens of the catheter were flushed with 10 ml of normal saline. Next, sodium citrate was instilled into each lumen as a locking agent in volumes corresponding to luminal capacity. Catheters and connectors are inspected for leaks or evidence of damage during treatment. Exit-site care involved inspection of the catheter exit site at each nurse visit, cleaning with chlorhexidine or iodine and covering with a new transparent dressing. Connecting and disconnecting of the catheter to the bloodlines was done under strict aseptic conditions, with nurses wearing facial masks, sterile gloves and a sterile gown.

RESULTS

The results given in this study include only the outpatient period while the patients were receiving TSC. The study included 23 patients (16 male, 7 female) with various hematologic malignancies (Table 1). Their median age was 42 (19-61 years). Twenty patients were conditioned for allogeneic stem cell transplantation while 3 patients underwent autologous stem cell transplantation (Table 2).

Hickman catheters were used in 21 patients (91.3%) while temporary juguler catheters were used in 2 patients (8.7%). All catheters were inserted via the juguler vein. Median catheter using time was 68 days (range: 25-252) for all catheters. Median using time of CLS was 20 days (range: 3-222).

TABLE 1: The diagnosis of the patients.

Diagnose	n
AML	13
AA	3
ALL	3
HL	1
MDS	1
SCA	1
MM	1

AML: Acute myeloblastic leukemia; AA: Aplastic anemia; ALL: Acute lymphoblastic leukemia; HL: Hodgkin's lymphoma; MDS: Myelodysplastic syndrome; SCA: Sickle cell anemia; MM: Multiple myeloma.

TABLE 2: Patients' clinical characteristics.

Median Age (range)	42 (19-61)
Gender (Female/Male)	7/16
Allogeneic/Autologous	20/3
Hickmann/Temporary	21/2
Median catheter use (range)	68 (25-252)
Median CLS use (range)	20 (3-222)
Catheter thrombosis	3
Catheter infection	None
Cardiac symptoms	None
Embolic events	None
Hypocalcemia symptoms	1
Hypernatremia	None

CLS: Catheter lock solution.

The protocol specified that the infusion be stopped immediately if the patient reported a symptom that should be related to CLS allergy or toxicity. During the whole study period only one patient complained from hypocalcemic symptoms (paresthesia) which improved after calcium infusion. Catheter infection, cardiac symptoms, embolic events and hypernatremia did not occur in any of the patients. Catheter thrombosis was detected in 3 patients. Of 3 thrombosis patients, 2 had Hickman catheters whom did not receive catheter care with TCS regularly. One thrombose patient with temporary jugular catheter was an old and diabetic patient.

DISCUSSION

In this one center limited experience, we found that hypertonic citrate lock solution should be used in

hematopotietic stem cell transplantation recipients safely. Semi-permanent tunneled silicone rubber Hickman catheters are widely used to provide durable central venous access for patients undergoing stem cell transplantation. We preferred Hickman catheters in the majority of the patients. Only 2 patients had temporary juguler catheters. Three patients had catheter thrombosis and 1 patient had hypocalcemic symptoms during the study period. To our knowledge, hypertonic citrate lock solution was firstly used in this spesific patient group.

Considering possible antimicrobial mechanisms of citrate, it is likely that the most important effect of TSC is chelation of the divalent cations Ca^2 and Mg^2.[9] It is also not clear whether the antimicrobial potency of a solution depends on the level of hyperosmolality or not.[12] Presumably, this is because the construction and maintenance of a biofilm depends on cations, mainly Mg^2 and Ca^2.[13,14] On the other hand, heparin manifested no antimicrobial effect of any significance.[12] Moreover, it has been previously shown that sodium heparin in clinically relevant concentrations enhances *Staphylococcus aureus* biofilm formation.[15] Sodium citrate at concentrations above 0.5% efficiently inhibits biofilm formation and cell growth of *S. aureus* and *Staphylococcus epidermidis*. High (30%) concentrations of citrate have been noted to reduce catheter related bacteriemia rates up to 73%[16] compared with conventional heparin. Furthermore, the incidence of bacteriemia decreased from 4.32% episodes per 3000 patient-days to 0% with 47% citrate locks.[10]

Most central vein catheters develop a bacterial biofilm on their surface that can already occur within 24 h after placement.[17,18] In a prospective study, it was shown that 68% of dialysis catheters became colonized after a mean time of 27 days after placement.[17] The presence of bacterial biofilms on catheter surfaces can serve as a nidus for infection and bacteraemia.[2,19-23] Even in individuals with excellent cellular and humoral immune reactions, biofilm infections are rarely resolved by the host defense mechanisms. In addition, antibiotics are not very useful because they have been shown to penetrate poorly into a biofilm.[24] In our study, the median catheter and CLS usage time were 68 and 20 days respectively, and no catheter infection was reported. Although 2 patients with Hickman catheters developed catheter-related thrombosis, no catheter infection was detected. So, one can estimate that TSC may have a long-term antimicrobial activity.

A few small trials have suggested that replacing heparin with sodium citrate results in comparable catheter patency rates while avoiding exposure to systemic heparin.[11,25,26] These studies included either a small number of patients or were conducted over a short period of time. In more comprehensive studies, interdialytic locking with TSC 4% had promising outcomes compared with heparin with regards to the frequency of catheter exchanges, intraluminal thrombolytic usage and access-associated hospitalizations.[27,28] TSC 30% also improved overall patency rates and reduced catheter-related infections and major bleeding episodes for both tunneled and untunneled hemodialysis catheters. There were no differences in catheter flow problems and thrombosis. Moreover, fewer patients died from catheter related bleeding (CRB) in the TSC group.[3]

Citrate in combination with gentamicin or taurolidine has been shown to decrease the rate of catheter-related infections.[8,29,30] Adding gentamicin to TSC (7.5%) provided superior bacterial growth inhibition but had no effect on yeast growth.[12] The increasing concentrations of citrate were correlated with decreased incidence of symptomatic bacteriemia. With the using of 47% citrate as catheter lock the incidence of bacteremia was 0%.[10] However, aminoglycoside-related ototoxicity still remains to be a matter.[7] An other alternative, taurolidine-containing solutions have shown promising results. Catheter filling with a solution containing the antimicrobial taurolidine (1.35% taurolidine and 4% sodium citrate) may significantly reduce the incidence of catheter related sepsis. Their limited availability and high costs, however, preclude their usage in clinical practice so far.[30] The development of bacterial resistance and sensitization of the patient can also be an undesirable consequence. Addition of aminoglycosides or other antibiotics to locking solutions for long-term

using is therefore not advisable. In our opinion, CLSs with alternating concentrations of citrate seems better than antibiotic plus citrate solutions without the risk of developing resistant strains of bacteria (as will occur with antibiotic lock solutions).

The using of thrombolytic therapy did not differ when using low dose citrate or standard dose heparin for locking the catheters.[5,25,31] Similarly, Weijmer et al.[3] did not find a difference in thrombolytic effect between citrate 30% and heparin locks. In contrast to these studies, Allon[29] found an increased requirement for thrombolytic interventions to maintain catheter patency among patients receiving citrate (4%)-taurolidine (1.35%) solution, indicating a less effective anticoagulant activity of 4% sodium citrate compared with heparin. However, Betjes et al. did not observe such a difference with the same CLS in a larger number of patients.[30] Despite the presence of the aforementioned biases, a study by Ash et al. showed that after implementation of 20% citrate/gentamicin for locking, the usage of urokinase reduced by half. When 47% citrate was used to lock the clotted catheters, no urokinase was used for any catheter.[10] In our study, the thrombosed catheters were removed without thrombolytic usage.

On the other hand, hypertonic citrate usage has been shown to have some adverse effects. Ash et al.[10] reported that 10% of patients had a 'metallic' taste shortly after injection of the exact fill volume of 47% sodium citrate. It has been recently observed that a number of cases of symptomatic emboly from hemodialysis CVCs in patients in whom hypertonic citrate (43%) was used as the locking solution, causing pulmonary and cerebral emboly and symptomatic hypotension during hemodialysis.[1] Case reports of fatal cardiac arrest following the mistaken bolus injection of trisodium citrate (46.7%) led to the withdrawal of a commercially marketed product, Tricitrosol licenced by the US Food and Drug Administration in 2000.[33] In this particular case, however, a large amount of TSC (10 ml) was injected in a previously unstable patient with severe electrolyte disturbances.[32] We did not observe such adverse reactions in our patients.

Citrate usage also associated with electrolyte imbalances, especially hypocalcemia and hypernatremia. Citrate inadvertently entering the circulation of the patient will chelate calcium ions and depress the ionized calcium level. If infused very rapidly, this citrate might cause transient hypocalcemic symptoms.[10] Serious symptoms have been reported when the ionized calcium blood level decreases to 0.6 mmol/l.[33] This may prolong the QT interval,[34] which may lead to ventricular dysrhythmias and torsade de pointes.[35] In our study, one patient with hypocalcemia suffered from paraesthesia at the time of catheter locking, and treated with slow calcium infusion. Cardiac dysrhythmia was not observed. The sodium concentration also showed a strong linear correlation with citrate.[35] For every 10 ml of Citra-Lock added, the sodium concentration increased by approximately 20 mmol/litre.[36] However, we did not observe sodium level abnormalites in our patients.

The last several years, many dialysis departments have experienced the benefits of TSC 30% without reports of major complications. The safety of trisodium citrate 30% was confirmed in a large clinical trial, where no serious adverse events were encountered.[3] But it is clear that the use of these solutions should be restricted to authorized and skilled health-care professionals.

Citrate lock solutions also seem to be more appropriate than heparin in terms of cost-effectivity. It is approximately 10-fold less expensive than heparin.[3] There was an 85% reduction in the costs associated with catheter-locking therapy during the citrate (4%) period.[28]

Our study has some limitations. We acknowledge that the retrospective nature of the study is a weakness and that a prospective randomized study is needed for confirmation of the results. We were unable to make a cost-effectivity analysis for TSC versus heparin. Finally, the findings of this study must be interpreted in the context of its small size.

CONCLUSION

We conclude that high concentrations of trisodium citrate lock solutions should be used safely in outpatient hematopoietic stem cell transplant recipients.

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