

Treatment of Dialysis Access Puncture Wound Bleeding with Chitosan Dressings

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Background. Bleeding from coagulopathic hemodialysis puncture sites can contribute to anemia in dialysis patients, and current compressive dressings may contribute to graft thrombosis. We studied the safety and efficacy of a new chitosan-based bandage with an active clotting surface and compared its time to hemostasis and compression strap usage in dialysis access puncture wounds with that of conventional gauze dressings.

Methods. Fifty patients received both the chitosan-based and conventional gauze dressings in random order on 2 successive visits. Time to hemostasis and compression strap usage were compared between the visits. Time to hemostasis was analyzed using the binary response variable at 2 and 4 minutes. A compression strap was used if dressing application was unsuccessful at 4 minutes. Covariates included coagulation state as measured by laboratory analysis and anticoagulation therapy.

Results. Hemostasis was achieved by 2 minutes in 30% of the chitosan-based and 38% of the conventional dressings ($p = 0.608$) and by 4 minutes in 86% of the chitosan-based and 72% of the conventional dressings ($p = 0.040$). Compression strap usage was reduced by 50% in the chitosan-based group compared to the conventional group (7 vs. 14 patients; $p = 0.052$). No adverse events were reported with either dressing.

Conclusions. The chitosan-based bandage from HemCon is a safe and effective hemostatic agent to reduce prolonged post-hemodialysis puncture site bleeding and may reduce the use of occlusive compression straps.

Bleeding at dialysis puncture sites is a source of chronic blood loss that can contribute to the chronic anemia seen in hemodialysis-dependent patients with renal failure. Hemodialysis patients have coagulopathies associated with chronic renal failure and iatrogenic coagulopathy as a result of systemic heparinization and the common use of oral anticoagulant drugs to treat comorbid conditions. These factors can contribute to occasional difficulties achieving prompt hemodialysis-site hemostasis, which contributes to further blood loss and consumes valuable staff time treating and monitoring these patients. In patients with prolonged

post-dialysis bleeding, compression devices are frequently used that are effective but may create trauma or stasis and subsequent graft thrombosis.

Stenosis and thrombosis of the arteriovenous fistulas are the most frequent complications of vascular access¹ accounting for 20% of hospital admissions of dialysis patients.² The cost of access procedures and complications has been estimated at \$1 billion annually, the single greatest categorical expense for dialysis patient care.² Although repeated access to these sites with catheters is considered the most common traumatic insult, occlusive pressure dressings and compression devices also contribute.³

Improved hemostasis dressings with active clotting surfaces and components have been recently reported in trauma and other literature to accelerate hemostasis in moderate to severe bleeding.^{4,5} We investigated the safety and efficacy of a chitosan-based dressing (HemCon Bandage, HemCon, Portland, Ore.) to improve hemostasis at dialysis site punctures and to reduce the need for compressive devices.

Chitosan is a naturally occurring substance whose molecular makeup and preparation have been discussed previously.⁶ Chitosan hemorrhage control dressings have been shown to be effective in animal models of severe hemorrhage.⁴ Preclinical studies in swine surgical spleen trauma, carotid lacerations, liver lacerations, and aortic perforation have been successfully treated with

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the HemCon Bandage.⁴ The HemCon Bandage is a lyophilized chitosan-acetate-based hemostatic dressing. U.S. military personnel in the conflicts in Iraq and Afghanistan have successfully used the HemCon Bandage to stop severe hemorrhage not controlled by conventional bandages in more than 64 patients without adverse effects.⁷ The HemCon Bandage is also an FDA-cleared hemostatic dressing suitable for use in hemodialysis-associated bleeding. Clinical characteristics and efficacy, though, have not yet been studied in randomized fashion in this population.

The treatment of post-hemodialysis bleeding at our center uses regular gauze with manual pressure or compression straps, with most vascular access sites being occluded for 8–12 minutes. For refractory bleeding, Gelfoam (RxMed, Louisville, KY.) is often used, with repeated vascular access occlusion using a strap. If bleeding is still not achieved, transfer to the emergency department for more definitive treatment may be required. A more effective hemostatic agent in this setting may decrease time to hemostasis, as well as reduce the need for occlusive compression devices. We studied the time to hemostasis and usage of compression devices in 50 patients using both routine treatment and the HemCon Bandage.

Patients and Methods

Patients

Patients who underwent routine outpatient hemodialysis at the Providence Outpatient Kidney Dialysis Center between July 18 and October 15, 2005, were considered for inclusion in the study. Exclusion criteria were: cognitive inability to provide informed consent; participation in another IRB-confirmed clinical trial; allergy to shellfish, shrimp, chitin, or chitosan; and central line-based hemodialysis access.

All aspects of the research, including patient consent forms, were approved by the Providence Health System IRB committee. All patients were given a copy of the consent form to review both before and after consent was obtained. Once written consent was obtained, each patient was assigned a unique identifying number used in all paperwork related to the study in order to maximize confidentiality.

Dressings

Sterilized pieces of HemCon Bandage 20 mm in diameter and 5.5 mm thick were used. The control dressing was standard surgical 2'×2' gauze (Kendall Versalon by Tyco; Mansfield, Mass.) folded twice to make a 1'×1' gauze dressing (the standard of care at this dialysis center).

All patients had either an arteriovenous fistula or nylon graft as access on an upper extremity. Hemodialysis was initiated after the nurse placed both needle-based catheters into the access site. Blood flowed out one catheter to the hemodialysis device and back to the patient through the other (Figure 1). The placement of these catheters within the access site was random and varied from visit to visit in order to distribute the

trauma throughout the graft. The distance between the 2 catheter sites during any visit typically varied from 1 to 3 inches. Simply by convention, the first catheter removed was labeled catheter A and the second removed was labeled catheter B.

The pressure differential across the access site was considered negligible despite each site having both arterial and venous anatomic origins. Given the proximity of the sites to each other, bleeding from one site could influence interpretation of bleeding from the next. That is, any attempt to look at the sites individually was considered difficult in practice, compromising the independence of the observations. Because of this, the final analysis combined data from sites A and B, with the longer of the 2 times (2, 4, or > 4 minutes) recorded as the bleeding time for a visit. Accordingly, if a compression strap was needed for either puncture site during a visit, then bleeding control during that visit was designated as requiring a compression strap.

Procedure

Patient data were collected on 3 consecutive hemodialysis visits. Patients were randomized to receive



Figure 1. Vascular access site of hemodialysis.

either the HemCon Bandage or a routine gauze dressing during visit 1 and to get the treatment not received the first time at visit 2. They were interviewed about side effects at visits 2 and 3. Patient demographic data, including age, sex, access type, and anticoagulation status, were recorded at visit 1 (anticoagulation status was rechecked at visit 2 in order to document any new medications).

The study protocols employed in visits 1 and 2 were identical for all patients, except for the dressing used. On arrival at the dialysis unit, the patients had blood drawn for both a complete blood count and an international normalized ratio (INR). During the last 15 minutes of each hemodialysis run, blood was drawn to determine the activated clotting time (ACT).

Following dialysis, blood pressure was measured and recorded. One catheter (catheter A) was removed from each patient, immediately followed by placement of the appropriate dressing. A hemodialysis staff member manually applied pressure at the site for 2 minutes. (Because inconsistently applying pressure could have confounded the results, the performance of this procedure was standardized by having all participating staff undergo training in which they repeatedly practiced generating approximately 500 mmHg of force as measured on a standard pressure gauge.)

After 2 minutes, pressure was removed to look for evidence of bleeding around the dressing. If no bleeding was noted, a 4-inch piece of paper tape was placed over the dressing. If any bleeding was observed, a new dressing was placed over the catheter site, which on average took less than 3 seconds, and pressure was applied at the site for another 2 minutes. Then pressure was again released and bleeding assessed. If no evidence of bleeding was observed, a 4-inch piece of paper

tape was placed over the dressing simply to keep it in place. If bleeding was again observed, the dressing was replaced once more, and a compression strap was positioned over the site. Every 4 minutes for the next 12 minutes the site was evaluated for evidence of rebleeding.

Once bleeding had stopped at catheter puncture site A, the catheter at site B was removed, and the type of dressing used at site A was applied immediately at site B. If site A had not required a compression strap, site B was treated identically and also did not get a strap. However, if catheter site A had required a compression strap, then site B automatically received one as well. There were 3 reasons for this:

1. A significant change in pressure to the access site occurred at that time;
2. A visit was categorized as having more than 4 minutes of bleeding if a strap had been used at either site, regardless of there being 2 sites; and
3. This would reduce the impact on staff and patient time.

If either site started to bleed after placement of the tape (4–12 minutes after removal of the catheter), the dressing was replaced, and a compression strap was used to hold pressure on the site. If rebleeding was noted after placement of a strap, the dressing was removed and the patient was crossed over to the other dressing, with a strap used immediately to maintain adequate pressure.

During either visit, once complete hemostasis had been achieved for at least 12 minutes, each dressing was gently removed and replaced with 2' × 2' piece of gauze that was taped in place (a routine practice at our center). This was done so patients would leave with the standard-of-care treatment of their access sites.

At the beginning of visits 2 and 3, each access site was assessed for evidence of thrombosis, and each

patient was asked about any side effects observed outside the dialysis center since the last visit, including evidence of a rash or delayed bleeding (this was the only intervention during visit 3).

Statistical Analysis

The 2 primary efficacy variables considered were compression time required for hemostasis and use of a strap compression device. The secondary efficacy variables were crossover rate and evidence of short-term (within 48 hours) thrombosis of the vascular access site (observed at the following hemodialysis run).

Compression times (<2 minutes, 2–4 minutes, >4 minutes) were compared using the Stuart-Maxwell test,^{8,9} which tested the marginal homogeneity of all 3 categories simultaneously, taking the pairing between observations into account. The use of strap compression (yes/no) in the 2 groups (HemCon vs. control) was compared using the McNemar test¹⁰ in order to ensure proper pairing.

Covariates included systolic and diastolic blood pressure, coagulation state of the patient as measured by ACT, INR, and platelet count, as well as anticoagulation state with heparin, Coumadin, or platelet inhibitors (aspirin, Plavix, Aggrenox). The paired *t* test was used to compare the means of the continuous variables, and the Wilcoxon signed-rank test was used to compare the medians of the continuous variables.

Results

Fifty patients were enrolled in the study, 26 men and 24 women, aged 24–85. Among them, 34 patients had an arteriovenous fistula and 16 patients had a nylon graft. All patients were heparinized; most were on heparin only, and the others were also on Coumadin, Aggrenox, Plavix, or ASA (Figure 2). There were no significant differences between

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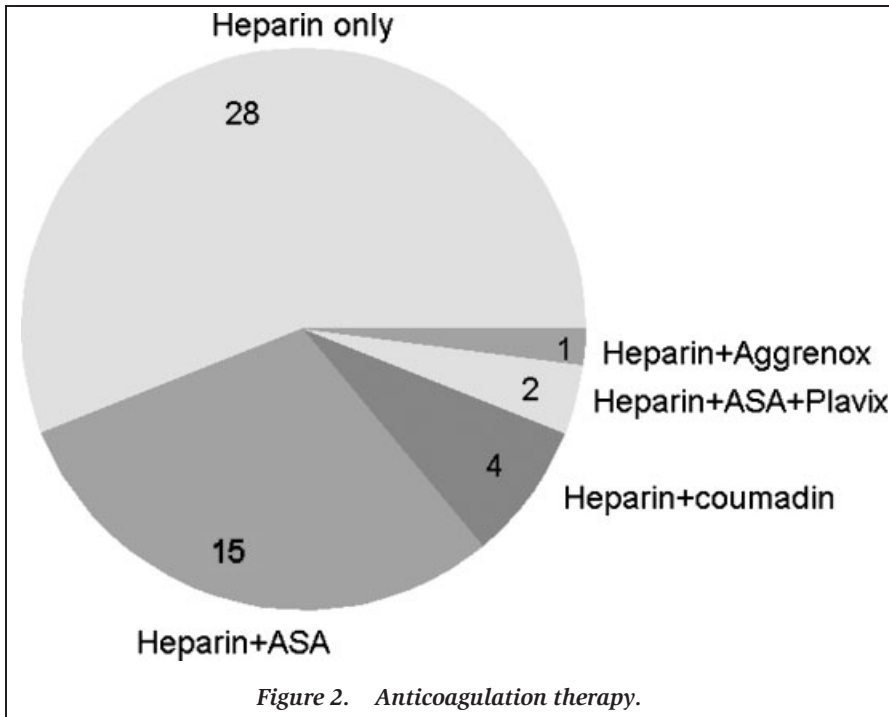


Figure 2. Anticoagulation therapy.

treatment groups in platelet count, INR, ACT, and systolic and diastolic blood pressures (Table I). No thrombosis or other vascular access site complications were reported in either treatment arm. Rebleeding 6 hours post-hemodialysis while at home was reported by 1 patient after use of the HemCon Bandage. This stopped spontaneously.

The comparison of time to hemostasis is depicted in a 3×3 table (Table II). Hemostasis was achieved by 2 minutes in 30% of the patients

who had a HemCon dressing and 38% of the patients who had a control dressing ($p = 0.608$), and by 4 minutes in 86% of those with HemCon and 72% of those with a the control ($p = 0.040$). Compression straps were used in 14 of 50 patients (28%) in the control group and 7 of 50 patients (14%) in the HemCon group ($p = 0.052$; Figure 3). An insignificant number of patients required crossover to stop bleeding beyond 4 minutes (2 gauze, 4 HemCon: $p > 0.05$).

Discussion

Many factors contribute to the high morbidity and mortality associated with end-stage renal disease, including complications from hemodialysis. These complications include chronic anemia, vascular access-site thrombosis and failure, and life-threatening bacteremia. Although the exact causes of these complications are not always well understood, anything that would minimize their frequency should be considered. How long it takes and the technique used to stop post-hemodialysis bleeding are areas worthy of such consideration.

The current standard of care at our center is to use regular gauze, manual pressure, and a plastic compression device to control hemorrhage. For prolonged bleeding, Gelfoam is used with direct pressure, and if necessary, the patient is transferred to the emergency department for more definitive treatment. Although it is unusual for vascular access puncture sites to bleed severely enough for transfusion to be required and no one has died at our center, we investigated an alternative mechanism for achieving hemostasis.

In animal studies, chitosan dressings were found to be effective in controlling major arterial bleeding.¹¹ Recent data have also demonstrated that chitosan is bactericidal.¹³ Prospective, randomized clinical research in hemorrhage control is challenging because of the variability in patient characteristics and presentation. In fact, no prospective, randomized human studies in which a chitosan dressing was used have been done. The HemCon Bandage is a chitosan-based hemorrhage-control dressing already approved for use in the hemodialysis setting. Therefore, we developed a prospective, randomized study to evaluate whether or not the HemCon Bandage improved post-hemodialysis hemorrhage control and reduced excessive compression.

Table I. Coagulation status by group.

Variable	HemCon	Control	<i>p</i> Value*
platelet count (mean ± SD)	244 ± 77	243 ± 79	0.773
activated clotting time (mean ± SD)	175 ± 36	168 ± 33	0.138
systolic blood pressure (mean ± SD)	138 ± 26	134 ± 24	0.248
diastolic blood pressure (mean ± SD)	68 ± 16	68 ± 14	0.946
international normalized ratio (INR)	1.1 (median)	1.1 (median)	0.129

**p* Value for paired *t* test for all variables except INR, for which Wilcoxon signed-rank test was performed.

Table II. Time to hemostasis and usage of strap by group.

	Control Group			Total
	<2 minutes/strap-	2-4 minutes/strap-	>4 minutes/strap+	
HemCon Group				
<2 minutes/strap-	12	2	1	15
2-4 minutes/strap-	6	13	9	28
>4 minutes/strap+	1	2	4	7
Total	19	17	14	50

The dressings used to control vascular access bleeding vary from center to center, as do the techniques used to augment this control. The HemCon Bandage used in this study was small enough to facilitate easy manipulation within the vascular access site yet large enough to ensure adequate coverage of the puncture site. The size and thickness of the HemCon Bandage made its use by the staff simple and straightforward after only minimal training.

Previous clinical results showed that the HemCon Bandage works most effectively if the chitosan sur-

face is in contact with blood. Our protocol called for pressure to be applied immediately after removal of the catheter, which may have limited the amount of blood available for contact below the dressing site. This may have contributed to the observed lower efficacy of the HemCon Bandage after 2 minutes of applied pressure.

According to the results of an informal survey prior to the study, time to hemostasis in our patient population averaged 8-15 minutes. The results reported for patients who received the regular gauze would demonstrate a profound reduction in

time to hemostasis if the results of this informal survey were, in fact, accurate. The effectiveness of gauze alone at 2 and 4 minutes was surprising, knowledge of which may promote improvements in the standard of care. Regardless, the HemCon Bandage was shown to be as effective at 2 minutes and more effective at 4 minutes ($p=0.04$). There were no significant adverse reactions reported in either group. Furthermore, these results were obtained from patients anticoagulated with heparin, some of them with additional anticoagulants, a finding not previously reported in human subjects.

Despite these findings, the study had several methodological limitations. Sample size was restricted by limited patient availability because of the small size of our center and by patient inclusion in other studies. Many staff members were trained and subsequently participated in the study, certainly contributing to variability in technique and possibly in outcomes. The time taken to remove failed dressings was considered negligible yet may have influenced placement and adhesion of the next bandage. Substituting unsuccessful dressings with fresh replacements at the 2-minute interval may have disrupted clot formation, whereas continuing pressure with the same dressing may have more effectively reduced hemorrhage in both groups.

Future studies, which may answer these and other questions, are

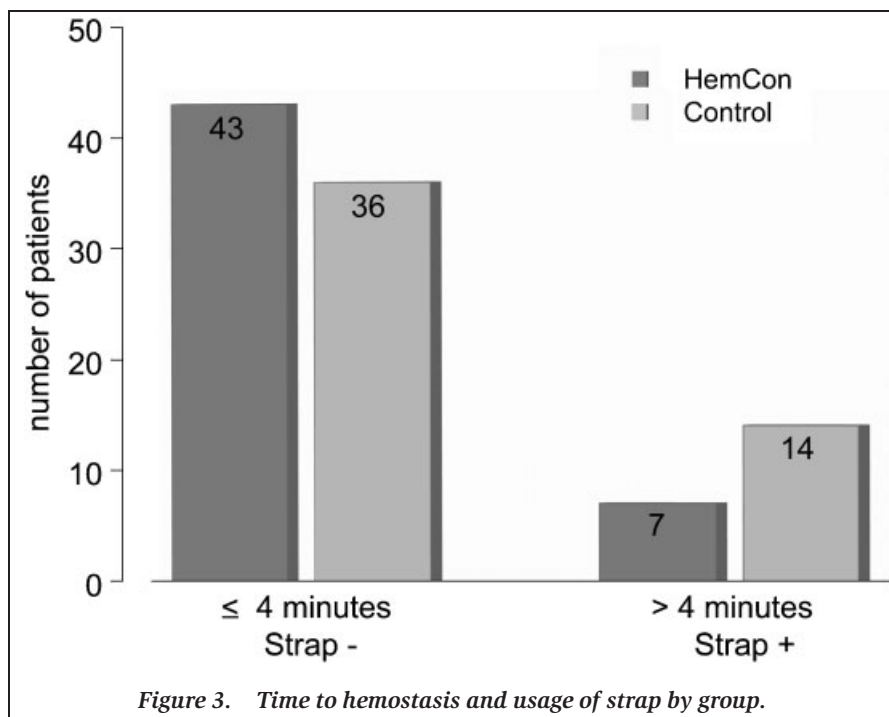


Figure 3. Time to hemostasis and usage of strap by group.

needed. Any impact on the development of access malfunction, including thrombosis, would require a larger study population and longer-term follow-up. Other clinical applications related to needle puncture bleeding should also be considered for study given the risks associated with blood-borne infections.

Conclusions

The HemCon Bandage is currently FDA cleared for use in hemodialysis. Prolonged bleeding and excessive compression at vascular access sites may contribute to unnecessary morbidity, including anemia and thrombosis of the access site. We have demonstrated that the HemCon Bandage was effective in hemorrhage control, did not cause adverse events, and may reduce the use of compression straps in anticoagulated patients. The limitations of this study warrant further study of the use of chitosan-based dressings in controlling bleeding from hemodialysis.

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