

## Variability in Response to Cryoprecipitate Treatment for Hemostatic Defects in Uremia

DARRELL J. TRIULZI, M.D.,<sup>a</sup> AND NEIL BLUMBERG, M.D.<sup>b</sup>

<sup>a</sup>*Chief Resident, Department of Pathology and Laboratory Medicine, Strong Memorial Hospital, University of Rochester Medical Center, Rochester, New York;*

<sup>b</sup>*Associate Professor and Director, Transfusion Medicine Unit, Department of Pathology and Laboratory Medicine, Strong Memorial Hospital, University of Rochester Medical Center, Rochester, New York*

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Cryoprecipitate is frequently administered as treatment for hemostatic defects in patients with uremia. The only published data supporting this approach however, involves seven patients described by Janson and colleagues in whom bleeding times were shortened and bleeding complications reduced after cryoprecipitate infusion. We retrospectively reviewed our institution's experience with cryoprecipitate in this setting. Five patients had sufficiently complete data for evaluation of the efficacy of therapy with cryoprecipitate, including pretreatment bleeding time > 15 minutes, normal coagulation studies, and platelet count > 100,000/ $\mu$ l. Two patients had normalization of their bleeding time and a favorable clinical outcome after cryoprecipitate infusion. Three patients failed to shorten their bleeding time after cryoprecipitate infusion or, in one case, multiple infusions. One of these latter patients had correction of his abnormal bleeding time after subsequent administration of deamino-8-D-arginine vasopressin (DDAVP). We conclude that the hemostatic response to cryoprecipitate therapy is variable, and that cryoprecipitate therapy does not achieve restoration of normal hemostasis in some patients with uremic bleeding.

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### INTRODUCTION

Bleeding and hemostatic defects are common complications of uremia. Multiple abnormalities in laboratory tests of hemostasis have been reported [2-4]. These abnormalities include defects in platelet aggregation, platelet retention, platelet factor 3 availability, and prostaglandin synthesis. These defects may contribute to the frequently observed prolongations of the bleeding time found in uremic patients [5]. The exact mechanism underlying these abnormalities remains obscure. Not surprisingly, therapy is also problematic in many cases. Dialysis has been the standard therapy for uremic bleeding, although at times it is ineffective [6,7]. Recently, cryoprecipitate and deamino-8-D-arginine vasopressin (DDAVP) have emerged as therapeutic alternatives [1,8-10].

While cryoprecipitate is widely used for hemostatic alterations or bleeding secondary to renal failure, very little data exist to support this approach. Janson and associates reported seven patients in whom the bleeding time shortened and bleeding

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*Abbreviations:* BUN: blood urea nitrogen DDAVP: deamino-8-D-arginine vasopressin PT: prothrombin time PTT: partial thromboplastin time

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Address reprint requests to: Neil Blumberg, M.D., University of Rochester Medical Center, 601 Elmwood Avenue—Box 608, Rochester, NY 14642

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complications were reduced after cryoprecipitate therapy [1]. To our knowledge, there have been only two other case reports on the use of cryoprecipitate in uremia [11,12]. While many hematologists believe that cryoprecipitate works only in some uremic patients, there are no reported data contradicting the initial uniformly positive findings. We performed a retrospective review of uremic patients who received cryoprecipitate therapy in our institution in order to determine whether laboratory abnormalities or bleeding were consistently ameliorated by this therapy, as suggested in the original report.

## MATERIALS AND METHODS

### *Patients*

The medical records of 82 consecutive patients discharged from Strong Memorial Hospital, Rochester, New York, between April 1984 and January 1987 with a diagnosis of renal failure (acute or chronic), who had received cryoprecipitate therapy were reviewed. For unambiguous evaluation of efficacy from the standpoint of this study, we felt that the following information or situations were required: (1) platelet count  $> 100,000/\mu\text{l}$  so that patients whose bleeding time abnormality or bleeding might be on the basis of thrombocytopenia would not be included, (2) normal prothrombin time (PT) and/or activated partial thromboplastin time (PTT) so that patients whose bleeding was on the basis of deficiencies of coagulation factors measured in these assays would not be included, and (3) prolonged template bleeding time with at least one post-infusion bleeding time. Five of 82 patients met all these criteria (four males and one female). Many of the patients were not evaluable simply because no post-infusion bleeding time had been performed.

All five patients had an elevated template bleeding time  $> 15$  minutes (normal, four to nine minutes) prior to therapy, and an elevated blood urea nitrogen (BUN) ranging from 41 to 99 mg/dl. None had taken platelet function-altering drugs. Three patients (patients 2, 3, and 5) were dialyzed within 24 hours prior to their cryoprecipitate infusions, and two patients received additional pre-infusion blood transfusions (patient 3 received fresh frozen plasma; patient 4 received red blood cells). The abnormal bleeding times were measured after administration of these components. None received platelet transfusions. Table 1 summarizes the clinical and laboratory data for the five patients immediately prior to cryoprecipitate therapy.

### *Laboratory*

Platelet counts were done on a Coulter Counter S-Plus STKR or S Plus Jr. (Coulter Electronics Inc., Hialeah, FL). Prothrombin time and activated partial thromboplastin time employed an automated Simplastin reagent and automated methods (General Diagnostics, Durham, NC), respectively. Bleeding times were performed by inflating an arm blood pressure cuff to 40 mm Hg and making a vertical forearm incision with a Simplate II (General Diagnostics) kit. Blotting with filter paper was performed every 30 seconds. The normal range in our hospital for this method is four to nine minutes. Bleeding times extending past 15 minutes are shown as  $> 15$  minutes. Cryoprecipitate was obtained from the Strong Memorial Blood Bank as prepared by the American Red Cross Services, Rochester Region, Rochester, New York, by accepted methods [13]. Our standard dose of cryoprecipitate for a uremic adult patient is 10 units infused intravenously over approximately 30 minutes.

TABLE 1  
Clinical Information

	Patient 1 (CW)	Patient 2 (JK)	Patient 3 (VW)	Patient 4 (FG)	Patient 5 (SM)
Age/Sex	24/Female	23/Male	32/Male	20/Male	21/Male
Diagnosis	Medullary cystic disease	Reflux hydronephrosis	Toxic shock syndrome	Lupus nephritis	Reflux hydronephrosis
BUN	59	41	99	48	49
Creatinine	5.2	13.5	10.2	7.7	14.1
Platelet count	207,000	223,000	258,000	204,000	104,000
Hematocrit	25	23	27	27	21
PT/PTT	12.9 25.5	12.9 28.5	11.1 31	10.8 27.1	12.7
History of bleeding	Easy bruising	Hemoptysis bleeding gums and teeth	None	None	None

Normal ranges: BUN, 8–22 mg/dl; Creatinine, 0.5–1.0 mg/dl; PTT, 25.0–37.0 sec; PT, 9.5–12.5 sec

## RESULTS

The effects of cryoprecipitate therapy on bleeding time and clinical outcome for the five patients are summarized in Table 2.

### *Patients Who Responded Satisfactorily to Cryoprecipitate Therapy*

Two patients (patients 1 and 3) achieved normal bleeding times after cryoprecipitate infusion. In the bleeding patient (patient 3), this laboratory improvement was accompanied by cessation of bleeding from a subclavian vein dialysis catheter site. This bleeding gradually subsided over a four-day period, during which cryoprecipitate therapy (10 U daily or 0.95 U/10 kg) had failed to correct the bleeding time initially, improved to 12.0 minutes after the third dose, and normalized 16 hours after the last dose (fourth day) of cryoprecipitate therapy.

The asymptomatic patient (patient 1) received two preoperative cryoprecipitate doses that were six hours apart and consisted of 10 U (1.6 U/10 kg) each. The bleeding time corrected to 8.5 minutes, five hours after the second dose. Open renal biopsy was performed without complications. An additional similar dose of cryoprecipitate was given during the procedure. Repeat bleeding time seven hours after this last dose had returned to > 15 minutes.

### *Patients with No Evidence of Response to Cryoprecipitate Therapy*

Two patients (patients 2 and 5) were given cryoprecipitate, but the bleeding time remained abnormal. Patient 2 had been admitted for bilateral nephrectomy required for reflux hydronephrosis. The initial bleeding time was > 15 minutes. Ten units of cryoprecipitate (1.4 U/10 kg) were infused, with one hour and seven hours post-infusion bleeding times remaining > 15 minutes. Two additional similar doses of cryoprecipitate were given five hours apart, and repeat bleeding time five hours after the last dose was still > 15 minutes. A fourth dose (1.4 U/10 kg) of cryoprecipitate was given on the day of surgery, with a two-hour post-infusion bleeding time > 15 minutes. The patient was vigorously dialyzed and started on estrogen therapy (20 mg premarin intravenously) on the day prior to surgery. Despite a persistently elevated bleeding

TABLE 2  
Results of Cryoprecipitate (Cryo) Infusion

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
BT before infusion	>15 minutes	>15 minutes	>15 minutes	>15 minutes	>15 minutes
BT after infusion	8.5 minutes	>15 minutes	8 minutes	8 minutes	>15 minutes
Post-infusion BT interval	5 hours	1 hour and 7 hours	16 hours <sup>b</sup>	2 days <sup>a</sup>	3 hours
Procedure	Open renal biopsy	Bilateral nephrectomy	Subclavian vein catheter placement	Renal biopsy prior to therapy	Cadaveric renal transplant
Bleeding complications prior to cryo	None	None	Oozing from catheter	Gross hematuria	Perirenal and scrotal hematoma
Outcome	Continued free of complications	Continued free of complications	Bleeding decreased after cryo	No improvement after cryo; decreased with DDAVP therapy	No improvement after cryo

<sup>a</sup>Post-infusion BT was obtained two days after the last cryo dose while two doses of DDAVP were given in that interval. The BT of eight minutes likely reflected the DDAVP, not the cryo.

<sup>b</sup>There was a gradual diminution of BT after several cryo doses given over a 36-hour period with the BT of eight minutes obtained 16 hours after the last dose. No other BT was performed in the 36-hour interval.

time, the patient underwent bilateral nephrectomy with satisfactory intraoperative hemostasis. Premarin and 10 units of cryoprecipitate (1.4 U/10 kg) were given every 12 hours postoperatively, and no complications developed. No further bleeding times were performed.

Patient 5 had been admitted for a cadaveric renal transplant and had a preoperative bleeding time of > 15 minutes. No specific therapy was given for this hemostatic abnormality. Postoperatively, perirenal and scrotal hematomas developed. Three days postoperatively, 10 units of cryoprecipitate (1.8 U/10 kg) were given, and at three hours post-infusion the bleeding time remained > 15 minutes. The patient continued to have bleeding at the incision and required a transfusion of two units of red blood cells for anemia.

Patient 4, after failing to respond to cryoprecipitate, had a correction of bleeding time after DDAVP treatment. This patient had undergone a renal biopsy and developed gross hematuria. A bleeding time done postoperatively was > 15 minutes. Ten units of cryoprecipitate (1.1 U/10 kg) were infused with continued severe hematuria over the next 16 hours, requiring 2 units of red blood cells for anemia. No bleeding time was performed at this point. The lack of clinical improvement in bleeding prompted a trial of DDAVP (27 mg intravenously). This first dose was given approximately one day after the cryoprecipitate infusion. The patient improved, with decrease in hematuria noted within one hour after DDAVP. A second dose of DDAVP was given 24 hours later, resulting in yet further decrease in hematuria. A bleeding time done 13 hours after this dose of DDAVP was eight minutes. This check of bleeding time was performed approximately two days after the cryoprecipitate ther-

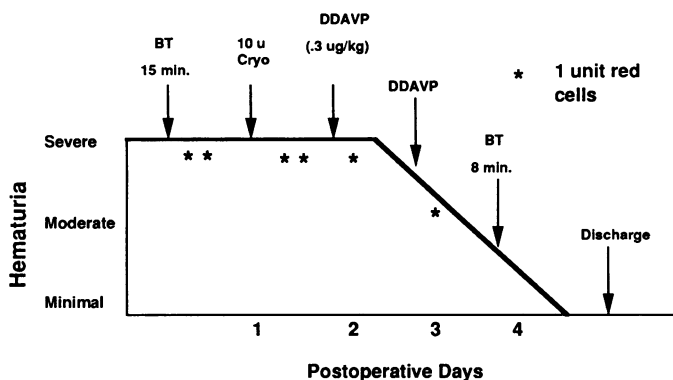


FIG. 1. The clinical course of patient number 4 is shown, depicting the continued severe hematuria after cryoprecipitate infusion. The bleeding time and severity of hematuria decreased after doses of DDAVP. Asterisks show administration of red blood cells. BT, bleeding time; cryo, cryoprecipitate.

apy. Figure 1 displays the clinical course of this patient in terms of therapy and response.

## DISCUSSION

Janson and colleagues reported seven patients, all of whom had improvement in their bleeding time by four hours after cryoprecipitate treatment [1]. The nadir value of bleeding time occurred one to 12 hours after infusion. Consonant with the anecdotal, contrary experience of many, only one of our five patients responded in a comparable fashion (patient 1). One other patient had a beneficial effect of cryoprecipitate therapy (patient 3). This recipient showed a gradual decrease in bleeding time over 36 hours with multiple doses of cryoprecipitate. A normal bleeding time of eight minutes was finally obtained 16 hours after the fourth and last cryoprecipitate dose. Concomitantly there was a gradual decrease in bleeding from a subclavian vein catheter site. These data support the clinical usefulness of cryoprecipitate, although with a different time course of correction than that previously reported, and with one patient requiring several doses prior to improvement.

Three patients, similar to those previously reported, had no apparent response to cryoprecipitate therapy. Cryoprecipitate did not correct the bleeding time in patients 2, 4, and 5, nor did it ameliorate bleeding complications in patients 4 and 5. Patient 4 is of special interest in that his severe hematuria from a renal biopsy was not reduced after a single dose of cryoprecipitate therapy but did improve after two doses of DDAVP, with a bleeding time shortened to eight minutes. While no post-cryoprecipitate infusion bleeding time was obtained before DDAVP was started, the normal bleeding time occurred two days after the infusion of cryoprecipitate and therefore was most likely due to DDAVP rather than to the cryoprecipitate. The efficacy of DDAVP in the setting of uremia has been described [8,9].

While our case reports are limited by lack of a standardized treatment protocol, some conclusions are possible. Contrary to the original report of uniform success, correction of bleeding time within a few hours after a single dose of cryoprecipitate was the exception rather than the rule in these five patients. Some patients may respond only after multiple doses of cryoprecipitate. For practical purposes, some patients do not respond at all, when urgent clinical interventions are required. The time course of correction of bleeding time in patients responding to cryoprecipitate therapy appears to be much more variable than that seen in the originally reported seven patients. At least

one and occasionally more post-infusion bleeding times are necessary in order to identify these patients.

The apparent efficacy of DDAVP in patient 4, in whom cryoprecipitate was ineffective, is interesting in that it suggests that the mechanisms of action of DDAVP and cryoprecipitate may be different. In addition, patient 4 received multiple red cell transfusions. Several investigators have found a negative correlation between bleeding time and hematocrit in uremic patients [14,15]. Abnormal bleeding times have improved, but not necessarily normalized with red cell transfusion [14,15] or erythropoietin therapy [16] in anemic patients with renal failure. The relative contribution of red cell transfusion and DDAVP to the normalized bleeding time in this patient is impossible to quantitate, but the rapid clinical response to DDAVP suggests that this was the primary therapeutic agent. We, and most others, would favor use of DDAVP in most patients as initial treatment, due to its lower risk and possibly more rapid onset of action. The risks associated with cryoprecipitate include post-transfusion hepatitis, HIV infection, allergic or, rarely, anaphylactic reactions, and serologic incompatibility due to red cell isoagglutinins. Cryoprecipitate should be reserved for those failing to respond to DDAVP, for whom DDAVP is contraindicated, and perhaps when massive bleeding or emergent operative intervention is required.

Our review also demonstrates that cryoprecipitate is frequently used without evaluation of whether it has decreased the patient's risk of bleeding (i.e., correcting the bleeding time). This use may be a necessary approach in some urgent situations; however, in many instances where cryoprecipitate was given to reduce the risk of bleeding, it appeared that the procedure would be done whether improvement occurred or not. Having decided that a hemostatic defect constitutes sufficient danger to expose the patient to the risks of homologous transfusion, it seems inconsistent not to determine that the desired benefit has been accomplished. Our data do suggest that cryoprecipitate use in uremic patients in our institution is probably providing no hemostatic improvement in a substantial number of patients, and that failure to measure the bleeding time post-transfusion leaves the physician unaware of its lack of efficacy.

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#### REFERENCES

1. Janson PA, Jubelirer SJ, Weinstein MJ, Deykin D: Treatment of the bleeding tendency in uremia with cryoprecipitate. *N Engl J Med* 303:1318-1322, 1980
2. Rabiner SF: Uremic bleeding. *Prog Hemostasis Thromb* 1:233-249, 1972
3. Di Minno G, Martizen J, McKean M, De La Rosa J, Burke JF, Murphy S: Platelet dysfunction in uremia. *Am J Med* 79:552-558, 1985
4. Rabiner SF, Hrodek O: Platelet factor 3 in normal subjects and patients with renal failure. *J Clin Invest* 47:901-912, 1968
5. Steiner RW, Coggins C, Carvalho ACA: Bleeding time in uremia: A useful test to assess clinical bleeding. *Am J Hematol* 7:107-117, 1979
6. Rabiner SF: The effect of dialysis on platelet function of patients with renal failure. *Ann NY Acad Sci* 201:234-242, 1972
7. Stewart JH, Castaldi PA: Uremic bleeding: A reversible platelet defect corrected by dialysis. *Quart J Med* 36:409-423, 1967
8. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, Zimmerman TS: Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 308:8-12, 1983

9. Watson AJS, Keogh JAB: Effect of 1-deamino-8-D-arginine vasopressin on the prolonged bleeding time in chronic renal failure. *Nephron* 32:49–52, 1982
10. Gotti E, Mecca G, Valentino C, Cortinovis E, Bertani T, Remuzzi G: Renal biopsy in patients with acute renal failure and prolonged bleeding time. *Lancet* ii:978–979, 1984
11. Maierhofer W, Adams MB, Kleinman JG, Roth DA: Treatment of the bleeding tendency in uremia with cryoprecipitate (letter). *N Engl J Med* 305:645, 1981
12. Liu Y, Kasfeld R, Marcum S: Treatment of uremic bleeding with conjugated oestrogen. *Lancet* ii: 887–889, 1984
13. Widman FK (ed): *Technical Manual*. 9th edition. Arlington, VA, American Association of Blood Banks, 1985
14. Livio M, Marchesi D, Remuzzi G, Gotti E, Mecca G, Gaetano G: Uremic bleeding: Role of anemia and beneficial effect of red cell transfusions. *Lancet* ii:1013–1015, 1982
15. Fernandez F, Goudable C, Sie P, Ton-That H, Durand D, Suc JM, Boneu B: Low hematocrit and prolonged bleeding time in uremic patients: Effect of red cell transfusion. *British J Hem* 59:139–147, 1985
16. Moia M, Vizzotto L, Cattaneo M, Mannucci PM, Casati S, Ponticelli C: Improvement in the hemostatic defect of uraemia after treatment with recombinant human erythropoietin. *Lancet* ii: 1227–1229, 1987