CASE REPORT

Recombinant factor VII (rFVII) can be useful for massive hemorrhage during radical nephrectomy

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ABSTRACT
Radical nephrectomy for renal tumors can be associated with serious complications, e.g. massive bleeding or even table deaths. Various regimens like normovolemic hemodilution, autologous transfusion, hypotensive anesthesia, etc have been used in anticipation of hemorrhage in these operations. In our case there was not only massive hemorrhage but also a failure to clot and disseminated intravascular coagulation. All the routine regimens failed to stop bleeding and the generalized ooze. Recombinant Factor VII (rFVIIa) was used and it saved the day!

Key words: Nephrectomy; Recombinant FVIIa; Hemorrhage; Blood loss; Massive blood transfusion; Disseminated intravascular coagulation

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INTRODUCTION
Renal cell carcinoma is the 8th most common malignant tumor of adults, with an incidence of 80 to 90% of all primary malignant adult renal tumors.1,2 It is more common in males and is found to be a highly vascular tumor which can lead to catastrophic hemorrhage.1 In a Japanese survey conducted in 2004 – 2008 it was found that hemorrhage was the most important factor of on table cardiac arrest.3 To fight this massive hemorrhage various methods of transfusions have been applied like early donor directed transfusion, normovolemic hemodilution, hypotensive anesthesia, tranexamic acid, autologous transfusion, etc. Although FDA has approved recombinant factor-VIIa (rFVIIa) only for patients suffering from hemophilia but its off-label use is in practice. It has proved to be a miraculous agent saving lives in various cases of uncontrolled hemorrhage, like gun shots and post-partum hemorrhage, but so far no such case has been published to our knowledge from Pakistan. Therefore, we report this case in elective use of rFVIIa helped us save a life.

CASE REPORT
A 37 years old male patient with left renal tumor presented for radical nephrectomy. Preoperative hemoglobin was 9.7 g/dl, TLC 22000, hematorcrit 30%, platelet count 485,000, INR 1.2, and mallampati score 1. Intraoperatively following parameters were monitored; SpO2, CVP, ECG, NIBP, temperature, urine output, EtCO2, and blood gas analysis. Patient was induced with propofol 100 mg titrated slowly until patient went to sleep, followed by nalbuphine 20 mg, rocuronium 50 mg, and dexamethasone 4 mg. Intubation was done followed by an epidural catheter placement at T12-L1, and insertion of a central venous pressure line, two 16G cannulas, and a radial arterial line. The patient was maintained on 40% oxygen, isoflurane
and rocuronium. Mechanical ventilator was set on pressure control ventilation (PCV) mode.

Packed red cell transfusion was initiated on incision along with 0.9% normal saline. Inj. tranexamic acid 750 mg was given prophylactically. The tumor was friable and highly vascular; massive bleeding started as the surgeon tried to mobilize the kidney. Approximately one liter of pus and blood clots was suctioned out. The blood pressure fell from 120 mmHg systolic to 45 mmHg within seconds. Five units of red cell concentrate (RCC) were pushed in less than 20 minutes along with one liter of Gelafundin 4% (B Braun), 6 pints of fresh frozen plasma (FFP), 5 pints of cryoprecipitate and 5 pints of platelets. After 30 minutes when the bleeders were controlled and the tumor was removed the blood pressure stabilized back to 120 mmHg systolic. Total blood loss was approximately 6 liters, and a total of 10 pint RCCs, 7 pint cryoprecipitates, 16 pints FFP, 10 pints of platelets, calcium gluconate 2 g, inj. hydrocortisone 250 mg, 3 liters of normal saline, 02 liters of Gelafundin 4% (B Braun) were infused per-operatively.

After removal of tumor generalized oozing continued with failure to clot. The wound was packed with multiple laparotomy swabs. Blood complete picture showed hemoglobin 6.6 g/dl and platelet count 106,000. Clotting profile was repeated (INR was 1.78). After 15 minutes wound was re-examined, the swabs were found to be fully soaked with serous fluid. DIC was suspected because of huge amount of pus suctioned, malignant tumor manipulation and near normal platelet count (which ruled out dilutional coagulopathy). As the generalized oozing remained uncontrolled, on the basis of laboratory reports and clinical judgment 7 mg rFVIIa (90 µg/kg) was administered IV. After 15 min swabs were removed and wound was re-examined. This time the swabs were found to be mildly soaked as compared to before. His blood pressure was 118/56 mmHg, heart rate 115 beats/min, and urine output 60 ml/hr. The wound was repacked with laparotomy swabs, coagulation profile was repeated (INR 1.48) and the patient was shifted to the surgical intensive care unit on mechanical ventilation. Next morning the wound was explored and no active oozing or hemorrhage was seen. INR was 1.29, Hg 9.5 g/dl, hematocrit 24% platelet 146,000 and TLC 14,000. So the wound was closed and the patient was successfully weaned off the ventilator. On the third post-operative day he was shifted to general ward and later on discharged.

**DISCUSSION**

While operating a case of radical tumor nephrectomy the foremost thing to be taken care of is ‘massive bleeding’. So, an arterial line was passed to keep an eye on beat to beat blood pressure variation, central venous line was passed to monitor fluid volume status and fight air embolism and wide bore cannulas were placed in anticipation. Where there is massive bleeding there has to be massive blood transfusion which is defined as need to transfuse one to two times the patient’s blood volume within 24 hours. So we kept 6 units of RCCs, FFP and platelet concentrates each ready and donors were on standby for added blood requirements. There are various regimens of blood transfusion but the most appropriate in such cases is the ATLS guideline of 1:1:1, e.g. 01 pint of RCC + 01 pint of FFP and 01 pint of platelet. This strategy was developed by US Army in Iraq and Afghan wars. Massive blood transfusion has its complications like hypocalcemia, citrate toxicity, hemolytic reactions, dilutional coagulopathy, metabolic derangements, electrolyte imbalance, transfusion related acute lung injury (TRALI) and DIC.

In anticipation of probable massive hemorrhage, we injected tranexamic acid before incision. It prevents the conversion of plasminogen to plasmin thus preventing fibrinolysis, it being one of the key factors for successful homeostasis. Cryoprecipitates are derived by thawing FFP at 4° C, contain factor VIII, XIII, von Willebrands factor and fibrinogen, and are an excellent blood product given prophylactically in the management of massive hemorrhage. One unit per 10 kg body weight raises plasma fibrinogen concentration approximately 50 mg/ml in absence of ongoing DIC. In our case, early cryoprecipitate administration was initiated along with RCC and platelet concentrate because of the expected massive blood loss and its replacement.

One of the most common side effect following massive blood transfusion is dilutional coagulopathy. There is both dilution of clotting factors and dilutional thrombocytopenia. Investigations like PT, APTT, INR, and platelet count should be sent and replacement should be done accordingly. In the recent years thromboelastography (TEG) has gained much popularity. In our case chances of dilutional coagulopathy were remote because we not only followed the 1:1:1 ATLS regimen, but also blood complete picture and clotting profiles were monitored on hourly basis.
Disseminated intravascular coagulation (DIC) is a consumptive coagulopathy, resulting in generation of fibrin clots, consumption of all clotting factors along with platelets and microthrombi formation which results in multi-organ failure. PT, APTT, BT, CT and INR becomes deranged. DIC can be seen in various conditions including malignancies, sepsis, trauma, obstetric cases, massive blood transfusion, heat stroke, hyperthermia etc. In our case two solid reasons led us to believe that DIC was in fact the primary differential diagnosis; a) a collection of pus was found in the tumor which could have been the cause of sepsis and (b) possible migration of the malignant cells into intravascular space. The surgical field showed generalized oozing which at times is the only way to diagnose DIC. The best cure for DIC is prevention, early recognition, targeting the cause, followed by transfusion of blood products. If not treated timely it can lead to inevitable death.

Factor VIIa is marketed as Novo Seven (Distributor: Novo Nordisk, Clifton, Karachi (Pakistan); Phone no. +92 21 35839611). Though very expensive but it is a miraculous agent approved by FDA for patients with hemophilia and inhibitory antibodies who are having uncontrolled bleeding. It is also being used “off-label” in cases of massive bleeding due to trauma and surgical bleed. Factor VIIa binds with tissue factor only at the site of injury, thus initiating coagulation locally at the site. Then it directly activates factor X by-passing the need of activation of Factor VIII and Factor IX. Factor X then in turn activates pro-thrombin to thrombin and thus leads to a stable clot formation. The prescribed dose is 90-120 µg/kg to be injected in 02 - 05 min. If hemorrhage persists for the next 15-20 min the dose should be repeated, with a maximum of up to 200 µg/kg.

In May 2006 a case report was published by Tahir Shamsi at el, in which they reported a gunshot case who kept on bleeding postoperatively until rFVIIa was injected which led to rapid recovery and later on successful discharge of the patient from hospital. Also in 2012 an article was published by an Indian gynecologist where she described 3 cases of postpartum hemorrhage which recovered speedily after injecting rFVIIa.

So far there are few methods to test factor VII efficacy but prothrombin time (PT), INR and hemostasis in the surgical field can give a quick idea. Other than these, a factor VIIa:c assay is done to check the therapeutic levels of factor VIIa.

When to inject rFVIIa is an important decision. In our setup we offer it to any age group in such condition and always keep factor VIIa in quantity sufficient for two patients in emergency. We believe that rFVIIa should always be an integral part of the emergency drugs list in every tertiary care hospital. As this drug has the potential to challenge death and bring a new hope of life to the patients.

REFERENCES