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Visualization of Efficacy of Recombinant Factor FVIIa in a Pelvic Fracture Patient

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The studies that report that administration of recombinant Factor VIIa for perioperative and trauma patients with or without existing coagulopathy was effective increased recently.[1–4] The efficacy of recombinant activated coagulation factor VII (rFVIIa; NovoSeven, Novo Nordisk) has been assessed by indirect parameters only, such as the amount of blood transfusion, fresh frozen plasma, platelets, or change in blood pressure.[5,6] However, the evidence heretofore of rFVIIa efficacy for hemostasis on the basis of decrease of blood transfusion volume or change in blood pressure does not necessarily indicate immediate arrest of arterial bleeding.

We attempted to visualize the direct and objective evidence of the efficacy of rFVIIa for hemostasis in patients with blunt injuries using a digital mobile imaging system for angiography.

On angiography, arterial bleeding appears as the extravasation of contrast medium. We could objectively and directly prove the efficacy of rFVIIa for arterial bleeding by visualizing diminished extravasation of contrast medium after rFVIIa administration on angiography findings.

In our institution, angiography is performed if stability of circulatory dynamics is previously obtained by initial fluid resuscitation and vital organ injuries are detected by enhanced helical computed tomography (CT). When angiography shows extravasation of contrast medium extending or pseudoaneurysm from arterial injuries caused by injury to solid organs, pelvic fractures, or other injuries (e.g., facial injury or injury of the extremity), transarterial embolization is performed. For hemodynamically stable trauma patients with pelvic injury, angiography is performed when contrast medium extravasation is observed in an extrapelvic hematoma or a large hematoma compressing the bladder is observed even if extravasation is not apparent on CT findings. We also perform angiography when the fracture is determined on pelvis X-ray examination even though the circulatory dynamics are unstable. Written informed consent was obtained from the patient or from the guardian before the initiation of any study procedure.

CASE REPORT

A 36-year-old man was admitted after falling from the fourth floor of a building at the emergency department in our tertiary emergency center. The patient's presenting blood pressure was 130/80 mm Hg with a heart rate of 96/min and a respiratory rate of 25/min. After admission, the patient received an initial fluid administration of 2 L of Ringer's lactate according to the Advanced Trauma Life Support and subsequently maintained hemodynamically stable.[7] Focused assessment with sonography for trauma and chest roentgenogram were interpreted as normal. On pelvis X-ray examination, he had pelvic fractures in the sacrum and the left pubic rami and femur fracture. Enhanced helical CT of the chest, abdomen and pelvis was performed for this patient according to Advanced Trauma Life Support because he was hemodynamically stable and had pelvic fracture. Hematoma was found on the left side of the pelvis that compressed the bladder in the obturator internus, the iliacus, and in the gluteus medius muscle of the fracture area on CT scan. The hemodynamic condition was stable during the primary trauma care.

At admission, hemoglobin concentration, hematocrit, and platelet count were 14.6 g/dL (normal, 11.0–17.0 g/dL), 42.4% (normal, 34.0–49.0%) and 214,000/mm^3 (normal, 140,000–340,000/mm^3), respectively. His fibrinogen concentration, prothrombin time and activated partial thromboplastin time were 116 mg/dL, 11.0 and 58.3 seconds, respectively.

In accordance with the indications and guidelines of our institution, we performed angiography immediately after admission because pelvic hematoma with extravasation of contrast medium was shown on admission CT scans, indicating active bleeding. In this case, after insertion of a 5-F cobra catheter transfemorally in the main trunk of internal iliac artery, we performed digital subtraction angiography twice in the emergency department.

In accordance with our protocol of using rFVIIa that our institution approved, the informed consent was obtained from

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the patient and families. Immediately after the first angiography, rFVIIa was injected, and then 10 minutes later, angiography was performed once more. The entire time sequence lasted less than 30 minutes. Angiography before administration of rFVIIa showed extravasation of contrast medium from the left internal iliac artery of the lateral sacral, iliolumbar, superior gluteal, internal pudendal and obturator and an intimal defect (Figs. 1 and 2). A bolus of 90 μg/kg of rFVIIa was given intravenously as the initial treatment for bleeding before transcatheter arterial embolization (TAE). Ten minutes after rFVIIa injection, angiography, performed again in the same position, with the same dose and same timing of the contrast medium, showed that the extravasation had diminished markedly. The extravasation from the lateral sacral artery had diminished, and that from the iliolumbar artery, superior gluteal artery, internal pudendal artery, and obturator artery had disappeared (Figs. 3 and 4). After checking the post-rFVIIa findings, we performed TAE with gelatin sponge in the conventional way to secure the hemostasis.

After TAE, this patient had hemodynamically stable and admitted to our trauma intensive care unit, and physical examination and monitoring of vital signs were repeated. His hemoglobin concentration, hematocrit, and platelet count were 8.0

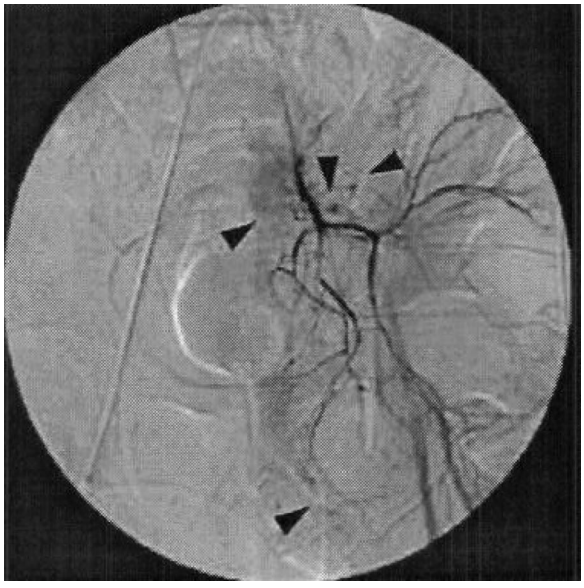

Fig. 1. *Arterial phase of angiography before administration of rFVIIa. Anteroposterior aortagram shows multiple areas of extravasations from left internal iliac artery (*block arrowheads*).*

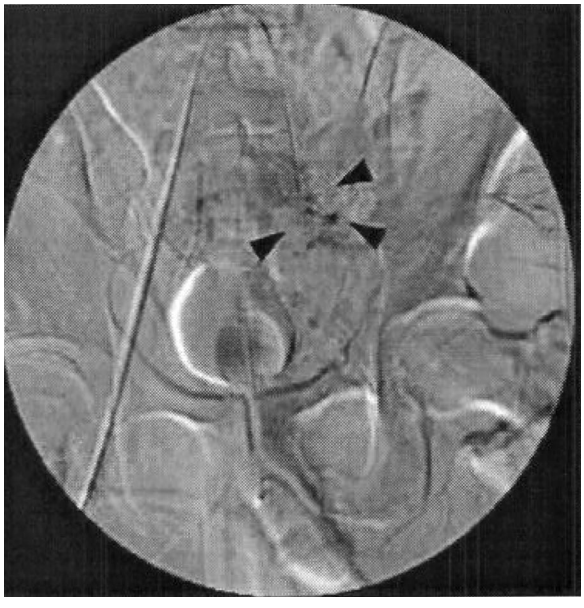

Fig. 2. *Capillary phase of angiography before administration of rFVIIa. Anteroposterior aortagram still shows the extravasations from left internal iliac artery (*block arrowheads*).*

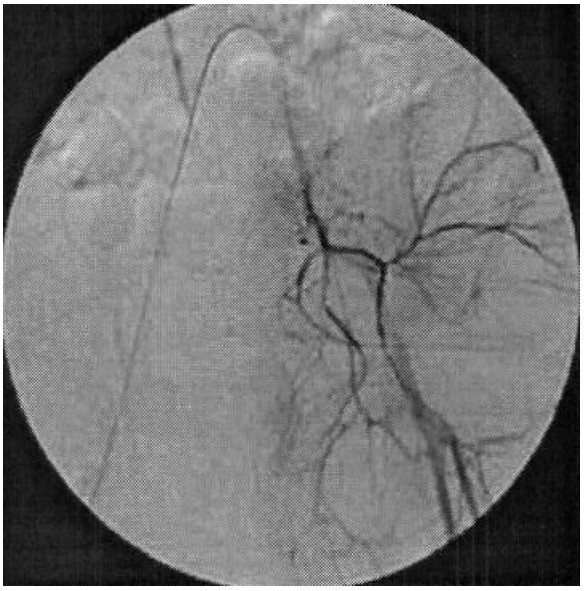

Fig. 3. *Arterial phase of angiography after administration of rFVIIa.*

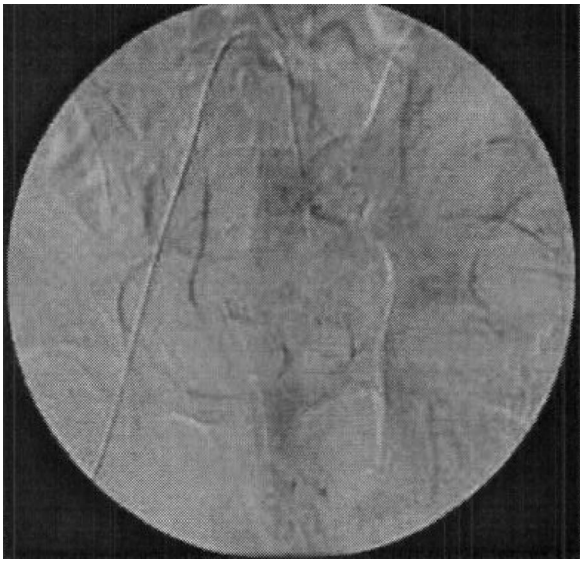

Fig. 4. *Capillary phase of angiography after administration of rFVIIa.*

g/dL, 23.2%, and 64,000/mm^3, respectively, on admitted trauma intensive care unit. This patient received a total of two units of packed red blood cells in the first 24 hours.

One month after admission, the patient made a good recovery and was transferred to psychiatry department.

DISCUSSION

This is the first report on the visualized efficacy of rFVIIa as direct visual evidence of hemostasis. In this case, the 90 μg/kg of rFVIIa given intravenously diminished the extravasation of contrast medium on pelvic angiography. This patient was admitted after falling from the fourth floor of a building, which lead to a high-energy and serious injury. Hagiwara et al.[8] have previously reported that arterial hemorrhage from injuries to solid organs and pelvic injury can be controlled by TAE in patients who can be stabilized by fluid resuscitation and nonoperative treatment 80% to 100% of the time. TAE performed for bleeding from solid organs and pelvic arterial hemorrhage can make it possible to avoid the additional trauma of laparotomy in some cases. In this case, angiography was performed immediately after admission because of the determination of the large hematoma with extravasation on CT scan, then rFVIIa injection was performed and 10 minutes later, angiography was performed again in the same condition to confirm the effect of rFVIIa. We would submit that the twice sequence of two angiography procedures, the first followed immediately by rFVIIa injection, within a period of 30 minutes, is much more likely to point to the result being a treatment-related than a natural phenomenon. It is unlikely that the extravasation diminished spontaneously resulted from the tamponade effect during this short period. Thus, in this case, the marked decrease in extravasation recognized 10 minutes after rFVIIa injection suggests that the hemostatic effect was relevant to the treatment.

The role of rFVIIa in the trauma population has not been studied. Proinflammatory cytokines show an increase in severe trauma. Increased cytokines induce tissue factor mediated activation of coagulation in vascular endothelium and endothelial damage.[9] It would therefore seem reasonable to assume that the administration of rFVIIa under conditions of severe trauma, such as increased proinflammatory cytokines, may enhance the thrombotic predisposition. However, an in vitro study suggests that rFVIIa does not produce or enhance a hypercoagulable state.[10] In accordance with these experimental findings, there is a growing number of clinical reports in which rFVIIa has been administered to patients with severe trauma, diffuse intravascular coagulation, or sepsis, resulting in successful hemostasis with no significant increase of thromboembolic events.[1,11] In our case, after administration of rFVIIa there was no thrombotic predisposition or multiple organ dysfunction syndrome.

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