Commentary

Developments in Blood Management: The Potential Therapeutic Role for Epoetin alfa in Orthopedic Trauma

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ABSTRACT

Orthopedic trauma is a major source of morbidity and mortality in the United States and other countries. Major orthopedic trauma often results in significant blood loss, which is the most common cause of shock in the trauma setting. Transfusion of allogeneic blood and blood products may be used to maintain blood pressure but may not be the most effective therapy for the acute anemia that results from trauma-induced hemorrhage. Because acute anemia can interfere with successful and timely rehabilitation of these patients, it is important to be aggressive in treating anemia. One approach is to administer Epoetin alfa to stimulate erythropoiesis. A pilot study is currently in progress to test the efficacy of this approach in major trauma patients.

INTRODUCTION

Orthopedic trauma is a major source of morbidity and mortality in the United States and other developed countries. One spectrum of the problem is minor trauma, primarily involving falls during walking or while transferring from a bed or chair. Low-energy fractures in the elderly population are generally attributed to impaction on osteopenic bone; they include fractures of the vertebrae, distal radius, ankle, pelvis, and hip. The incidence of hip fractures in the elderly has been estimated at 238,000 per year in the United States and continues to increase. Hip fractures account for the occupancy of over 20% of all surgical hospital beds and present a formidable socioeconomic threat, as billions of dollars are spent yearly in their treatment.

Another spectrum of orthopedic trauma is major trauma sustained from motor vehicle accidents, falls from heights, and industrial injuries. Major trauma includes fractures of the pelvis, femoral shaft, and multiple extremities, and is associated with a high rate of mortality. The explosive increase in the elderly population in recent years accounts for a marked shift in the typical victims of traumatic injuries; the elderly now suffer a greater proportion of major trauma. Whereas major trauma accounts for only 2% of deaths among persons over the age of 65 years, over one third of trauma care expenditure is accounted for in the care of people in this age group. Major trauma is typically associated with life-threatening hemorrhage, although a hip fracture in a chronically anemic elderly person can cause significant loss of blood as well. Despite these data, trauma management principles for the elderly are not well defined.

ORTHOPEDIC TRAUMA

Sources of Blood Loss. Intertrochanteric and femoral neck hip fractures can rapidly deplete the blood volume of an anemic elderly person. Diminished physiologic reserve and comorbidities such as hypertension decrease the ability of the elderly to replenish blood volume. Osteopenic bone presents a challenge to the orthopedic surgeon because it makes stable fixation and good bone purchase difficult to achieve. Surgery on osteopenic bone results in longer operative time and increased need for blood transfusion.

Major orthopedic trauma is associated with significant blood loss.
Bleeding can be external from open fractures or internal from severe pelvic fractures, bilateral femur fractures, and multiple-extremity closed fractures. The surrounding vasculature, soft tissues, and fractured bony edges are typical sources of bleeding. Arterial bleeding, such as bleeding from the hypogastric artery in pelvic fractures, leads to substantial blood loss and hemodynamic instability. In a landmark study, Burgess et al found that pelvic fractures require an average of 5.9 units of blood replacement, with a range of 3.6 units (lateral compression injuries) to 14.8 units (anteroposterior compression injuries).

In major trauma, prolonged extrication time and delay in instituting resuscitation contribute to blood loss. Failure to tamponade and immobilize wounds promptly and delays in operative management due to intensive care treatment of more life-threatening injuries (e.g., closed head injury) result in continued bleeding from the fracture site. The type of surgical reconstructive procedure also affects blood loss. Open reduction and internal fixation of pelvic fractures, periarticular fractures, and femoral fractures cause significant hemorrhage, whereas percutaneous pinning and other minimally invasive techniques are associated with minimal hemorrhage. In an effort to curtail surgical blood loss, definitive treatment of a complex fracture might be postponed in favor of temporary stabilization.

Classification of Hemorrhage. Hemorrhage is the most common cause of shock in a trauma setting. Inadequate organ perfusion and tissue oxygenation secondary to diminished blood supply may result in arrhythmia, myocardial infarction, stroke, multiple-system organ failure, and death. Normal blood volume is approximately 7% of body weight and decreases with age. In an average 70-kg male with 25 units (or 5000 cc) of circulating blood volume (1 unit of packed red blood cells = approximately 200 cc), hemorrhage is rated as class I through class IV. In class I, up to 4 units of blood are lost and minimal resuscitation is required. In class II, 4 units to 8 units of blood volume are lost. These patients are generally stabilized with intravenous fluids but often require transfusion of blood as well. In class III, 8 units to 10 units of blood are lost and a transfusion is almost always mandated. Finally, in class IV, more than 10 units of blood volume are lost. This situation is life threatening and generally requires rapid transfusion and/or immediate surgical intervention to control hemorrhage.

Treatment Principles. Major orthopedic trauma is often associated with life-threatening injuries of the cardiopulmonary, neurologic, and gastrointestinal organ systems. Injuries should be prioritized and treated according to the guidelines on Advanced Trauma Life Support. Tscherne et al divided trauma management into four periods: resuscitation (1 to 3 hours), stabilization (1 to 72 hours), regeneration (3 to 8 days) and rehabilitation (after 8 days). In the resuscitation period, the focus is on ventilation, circulation, and assessment of neurologic status. Life-threatening issues are addressed and emergent intervention is planned for hemodynamic instability. For example, a pelvic fracture warrants transfusion, embolotomy, and external or internal fixation of the pelvic ring for uncontrolled hemorrhage. In the stabilization period, adequate ventilatory and hemodynamic stability is achieved and diagnostic procedures are instituted. However, substantial blood may still be lost from bleeding vessels, bone, or from a reconstructive procedure. During this period, surgical treatment is performed on unstable spine injuries, closed-shaft fractures, pelvic ring injuries, and fractures complicated by an open wound, compartment syndrome, intra-articular injury, or vascular injury. The priority pattern in fixation of multiple closed fractures is as follows: tibia, femur, pelvis, spine, and upper extremity. Studies have shown that prompt surgical fixation (within 48 hours) of long-bone fractures in the polytrauma patient reduces bleeding, fat embolization, and the incidence of adult respiratory distress syndrome, and decreases hospitalization time.

During the regeneration period, blood volume is replenished to some extent by endogenous erythropoiesis. Orthopedic procedures done at this time include secondary wound closure, soft-tissue reconstruction, osteosynthesis of upper-extremity fractures, and complex joint reconstructions. By the rehabilitation period, hemorrhage subsides and erythropoiesis gradually ensues. However, the erythropoietic response is modulated by volume of blood loss, injury severity, metabolic stress, and the overall health of the patient. During the rehabilitation period, final operations may be performed, including definitive closure of amputation sites and bone-grafting procedures.

Therapeutic Measures to Control Hemorrhage

Emergency Control of Blood Loss. Efforts to control bleeding are initiated at the scene of an accident. Tamponade, splinting, traction, and immobilization are simple techniques used to reduce subacute bleeding from fractured bone and surrounding structures. In the emergency room, aggressive crystalloid and colloid intravenous fluid resuscitation assists in maintaining blood volume. Warming of intravenous fluids to 39°C is critical to optimize response to resuscitation and prevent hypothermia and coagulopathy. Massive bleeding can be controlled through nonoperative measures. For example, arterial embolization is a rapid and effective means to control massive hemorrhage from large arteries torn in pelvic fractures. Persistent, life-threatening bleeding from an orthopedic injury warrants urgent surgical exploration to identify and correct the source of hemorrhage. In certain instances, emergent external and internal fracture fixation is performed to prevent hemodynamic instability.
Almost invariably, however, major trauma patients require transfusion of blood products to maintain blood pressure and prevent compromise of tissue perfusion.

**Allogeneic Blood Transfusion.** Approximately 20 million blood products are transfused in the United States each year.\(^4\) The decision to transfuse allogeneic blood is a clinical judgment based on several variables, including symptomatology (shortness of breath, fatigue, lightheadedness, angina), hemoglobin (Hb) level, patient age, the likelihood of further blood loss, and the comfort level and aggressiveness of the physician. Most elderly patients have chronic anemia secondary to comorbidities and diminished erythropoietic capabilities. Diminished blood volume in patients with cardiovascular disease results in an increased risk of arrhythmia, stroke, and myocardial infarction.\(^5\) For these reasons, elderly patients and patients with cardiovascular disease are more likely to receive transfusions.

The life span of a transfused erythrocyte is highly variable, ranging from a few days to a few weeks, whereas the shelf life has been quoted as 42 days\(^14\) — a relatively short life span compared with the average 120-day life span of endogenous red blood cells. Thus, transfusion effectively restores blood volume in the acute setting, but it will not correct chronic anemia or enhance erythropoiesis.

Several risks are associated with allogeneic transfusion of blood products, including transmission of infectious disease,\(^6\) transfusion reactions,\(^7\) and immunosuppression.\(^8\) Koval et al\(^14\) showed that blood transfusion in hip fracture patients increased the risk of postoperative infection, primarily urinary tract infection, from 14.9% to 26.8%. The study also verified that infection rate is proportional to the number of units of blood transfused. Transfusion products, such as fresh frozen plasma, platelets, and/or cryoprecipitate, require blood from multiple donors and, thus, increase the risks associated with allogeneic blood. Despite the risks, allogeneic blood is currently less expensive and more widely accepted than many other treatment alternatives.

**Alternatives to Allogeneic Blood Transfusion.** When significant blood loss is anticipated in elective orthopedic surgery, alternative blood management techniques can be used, such as preoperative autologous blood donation and preoperative normovolemic hemodilution. Due to the acute nature of orthopedic trauma, these techniques are not possible. Alternatives that are possible are intraoperative and postoperative blood salvage, which can recover about 30% to 50% of blood salvaged from surgical drains. Recently, the perioperative use of recombinant human erythropoietin (Epoetin alfa) has gained popularity as an alternative to allogeneic blood transfusion in elective orthopedic surgery.\(^19\)-\(^22\)

**Epoetin alfa.** Epoetin alfa is a safe and well-tolerated drug that stimulates a sustained increase in red blood cell levels, unlike the transient increase that occurs with transfusion.\(^23\) Multicenter, randomized, prospective studies have demonstrated that Epoetin alfa reduces allogeneic blood transfusion in elective orthopedic surgery.\(^19\)-\(^22\) Epoetin alfa is a practical option for chronically anemic patients, elective surgery patients, and Jehovah’s Witness patients.\(^19\)-\(^24\) Although Epoetin alfa has not been tested in major orthopedic trauma, Goodnoh and St. John investigated its use in minor orthopedic trauma.\(^25\) In that study, 9 patients who underwent operative fixation of hip fractures received an average of 5 daily doses of 150 International Units/kg of Epoetin alfa and 100 mg of parenteral iron. The study noted that only 3 of 9 (33%) patients received allogeneic transfusion, and reticulocyte counts increased in 6 of 8 (75%) patients for whom the values were available. These results demonstrate that Epoetin alfa may have a role in orthopedic trauma therapy.\(^25\)

**REHABILITATION**

Rehabilitation of the orthopedic trauma patient focuses on early patient mobilization to achieve a rapid return to a preinjury level of function. A study by Seekamp et al\(^26\) documented that 79 of 104 (76%) multiply injured patients were able to return to a daily routine and to work. In the elderly, however, compromised cardiopulmonary and cardiovascular function, poor nutritional status, and psychosocial factors often limit the ability to participate in rehabilitation. Factors related to successful rehabilitation in an elderly person include age (> 60 versus > 85 years), gender, American Society of Anesthesiologists fracture classification,\(^27\) fracture type, comorbidities, and preinjury ambulatory and functional status.\(^28\) Koval et al\(^29\) found that patients younger than 85 years with three or fewer medical comorbidities who were ambulating independently at the time of hospital discharge were more likely to regain their independent living status following surgery. The rehabilitation process can be delayed by acute anemia that results from trauma-induced blood loss when superimposed on preexisting chronic anemia.

**DISCUSSION**

Research on Epoetin alfa in the orthopedic setting has focused primarily on elective surgery patients, such as those undergoing hip or knee replacement. In these studies, Hb levels increased by 0.5 g/dL to 1.4 g/dL within 7 to 10 days after beginning therapy.\(^19\)-\(^22\) This effect may also be beneficial in major trauma patients; however, a treatment protocol with Epoetin alfa for major orthopedic trauma patients remains to be established, and is likely to vary from the protocol used for elective orthopedic surgery patients. For example, the urgent nature of major trauma treatment will require delaying the initiation of Epoetin alfa treatment until the postoperative period. Also,
because major trauma patients often spend several days in the intensive care unit and may be unconscious, an appropriate dosing schedule for these patients will need to be determined.

Because injury severity, excessive hemorrhage, and trauma-induced metabolic stresses blunt the endogenous erythropoietic response, it is not yet clear if major trauma patients will elicit a robust erythropoietic response to Epoetin alfa. This is one issue that must be addressed in a well-controlled study of Epoetin alfa in major orthopedic trauma patients.

We have begun to investigate the use of Epoetin alfa in trauma patients with pelvic and acetabular fractures who require reconstructive surgery. We will test the hypothesis that Epoetin alfa therapy, in combination with the judicious use of blood products, has a role in the management of major orthopedic trauma. Patients will be monitored for transfusion requirements and ability to achieve preinjury level of function. We expect Epoetin alfa to have the greatest impact on patients with class I to class III trauma who lose ≤ 10 units of blood. For patients with class IV trauma who lose > 10 units, an aggressive blood management strategy will be employed in conjunction with Epoetin alfa treatment.

If Epoetin alfa treatment is initiated early in the course of trauma management, it may improve rehabilitation by supporting Hb levels and may reduce the need for transfusion, especially in the chronically anemic, elderly patient. A substantial reduction in transfusion frequency would justify the routine use of Epoetin alfa in orthopedic trauma.

**CONCLUSION**

The safety and efficacy of Epoetin alfa treatment in elective orthopedic surgery and in minor trauma suggest that Epoetin alfa may have a role in treating major trauma patients with orthopedic injuries. Further research is needed to establish guidelines for the use of Epoetin alfa in major orthopedic trauma.

**REFERENCES**