

Does Recombinant Human Factor VIIa Control Bleeding Episodes in Children with Glanzmann's Thrombasthenia

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Citation

M Moffitt. *Does Recombinant Human Factor VIIa Control Bleeding Episodes in Children with Glanzmann's Thrombasthenia*. The Internet Journal of Academic Physician Assistants. 2006 Volume 6 Number 1.

Abstract

This review is important because it addresses a lifelong disease that, although it effects a small percentage of the population, is seen and dealt with every day. Recombinant Factor VIIa has been shown to help control bleeding episodes in patients suffering from various inherited bleeding disorders including Glanzmann's Thrombasthenia. There have been shown to be limitations on the benefits of rVIIa. Hemostasis has a better chance of being achieved if the bleeding is not excessive and if the patient presents in a window of less than 12 hours after bleeding began. The benefits of rVIIa are many. The children affected with such rare bleeding disorders such as Glanzmann's thrombasthenia face a lifelong battle of increased risk of possibly life threatening bleeding episodes. Recombinant factor VIIa does in fact help to stop bleeding episodes in these patients. The efficacy continues to be studied. Recombinant factor VIIa is a valuable treatment alternative.

The first study selected, "The Use of Recombinant Factor VIIa in Children with Inherited Platelet Function Disorders" is considered a Level II study with regard to the amount of evidence provided by the controlled case study. The second study selected, "Use of Recombinant Factor VIIa for Bleeding in Children with Glanzmann Thrombasthenia" is also considered a Level II study with regard to the amount of evidence provided by the controlled case study. The third study selected, "Recombinant Factor VIIa : A Review of its Use in Congenital or Acquired Hemophilia and Other Congenital Bleeding Disorders" is considered a Level I with regard to the amount of evidence provided by the systematic review.

INTRODUCTION

The question examined in this paper is whether treatment with recombinant human factor VIIa helps to control bleeding in children with Glanzmann's Thrombasthenia. This review is important because it addresses a lifelong disease that, although it effects a small percentage of the population, is seen and dealt with every day. When a child presents to the physician's office covered in petechia or purpura or has nose bleeds more often than typical children of the same age, the child should first be examined to determine whether child abuse is possibly occurring in the home. The child then must be exposed to a series of tests to determine the cause. Once the etiology has been found to be that of Glanzmann's Thrombasthenia, the family and the health care providers should review and discuss the prognosis. Glanzmann's is not necessarily a life threatening disease, but it is a lifelong disease. Bleeding episodes are difficult to control and can progress to severe morbidity or mortality quickly. Bleeding episodes can lead to arthritis, muscle atrophy or neuropathy . If left untreated, bleeding episodes can result in death. Bleeding episodes are inevitable; therefore, treatment

focuses on preventative medicine with regards to morbidity and mortality.

METHODS

A search was performed using Academic Search Premier and CINAHL website.

The search was then refined using only "full text" articles and scholarly journals. The search was performed using the keywords, "Glanzmann's Thrombasthenia", "recombinant factor VIIa" and "children". Gender was not included in the search. The search brought up relevant articles which were reviewed and the most relevant and current articles were chosen that examined the use of recombinant factor VIIa to achieve homeostasis in children with Glanzmann's thrombasthenia. Glanzmann's is a rare disorder and studies are limited. The search was broadened to include treatment with recombinant factor VIIa in populations regardless of age.

The first study selected, "The Use of Recombinant Factor VIIa in Children with Inherited Platelet Function Disorders"

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BACKGROUND

Glanzmann's Thrombasthenia is a very rare autosomal recessive inherited platelet function disorder. It affects populations that are observed to have the highest incidences of consanguinity. The disease is characterized by a deficient platelet glycoprotein IIb/IIIa (GP IIb/IIIa) complex or present but dysfunctional which causes an extended bleeding time. Clotting does not occur normally as it would in someone who has an undamaged GPIIb/IIIa complex. This is due to a type of platelet membrane defect; a disorder of aggregation inherited along with afibrinogenemia. The platelets do not aggregate with any of the agonists that require fibrinogen binding, such as adenosine diphosphate (ADP), thrombin or epinephrine. Clotting can not occur without platelets binding fibrinogen and the formation of aggregates ₂.

The GP IIb/IIIa complex plays an important part in the binding of platelets to endothelium as well as to each other. The complex binds fibrinogen and/or von Willebrand factor. Adjacent platelets are also cross-linked through GP IIb/IIIa-fibrinogen-GP IIb/IIIa complexes. The membrane of the platelet contains the GP IIb/IIIa complex. This complex binds with fibrinogen to form aggregates. This impairs hemostasis and causes recurrent bleeding episodes. Platelets of the thrombasthenic patient will bind and aggregate with ristocetin, but not with the agonists required for fibrinogen binding. In patients with Glanzmann's Thrombasthenia, the platelet count, morphology and platelet functions unrelated to the GP IIb/IIIa complex are normal.

The discovery of Glanzmann's usually occurs early in childhood. The child presents with mucocutaneous bleeding. This can occur in infancy or even at birth. Males are usually diagnosed after being circumcised. The patient may present somewhat later in childhood with excessive bleeding from a seemingly innocent injury. The child may also present with

multiple ecchymoses and petechiae. The initial evaluation of the patient is going to be a complete physical exam looking for any occult blood or obvious current bleeding. The initial work up should include the complete blood count (CBC), the prothrombin time (PT), the partial thromboplastin time (PTT) and bleeding times. The platelet count and morphology should be normal. The bleeding times should be prolonged. Bleeding times are variable depending on the lab, but anything over 10 minutes is considered prolonged ₃. When bleeding times are this prolonged, a platelet dysfunction is present. The platelet studies should show normal platelet count and normal morphology. Platelet aggregation studies should then be performed. These tests show a normal aggregation with ristocetin and a decreased aggregation with adenosine diphosphate, epinephrine and collagen ₄. These results will diagnose the presence of Glanzmann's thrombasthenia.

The differential diagnosis of Glanzmann's includes Wiskott-Aldrich Syndrome which always causes a persistent thrombocytopenia. Von Willebrand Disease should also be ruled out. Other possible conditions include afibrinogenemia, autoantibodies to GP VIIa/IIb, and Bernard-Soulier syndrome. These conditions can be ruled out after the bleeding times, the PT and PTT, the platelet count and morphology and the platelet aggregation studies are performed.

Severe bleeding episodes are the greatest concern with Glanzmann's thrombasthenia. There are treatments available to help achieve homeostasis when these episodes inevitably occur. Treatments such as desmopressin, steroids, and antifibrinolytic agents can be useful. Bleeding is very difficult to control in patients with Glanzmann's thrombasthenia and treatment progresses to platelet transfusions. The patient will undoubtedly need to have at least one transfusion at some point in his or her life. The patient should be immunized against hepatitis B due to the increased risk of exposure as a result of the transfusions. The other main concern is that, since the patient will receive multiple platelet transfusions throughout his or her lifetime, he or she can develop platelet alloimmunization which is a reaction of antibodies against the GP IIb/IIIa complex. This causes the newly transfused platelets to be destroyed. The subsequent treatment is to use recombinant human factor VIIa. Factor VIIa increases thrombin generation on the activated platelet surfaces as a result of the direct activation of factors IX and X. The use of recombinant factor VIIa

bypasses any platelet alloimmunization that may have occurred from previous platelet transfusions. The treatment inevitably turns to the use of recombinant human factor VIIa for the bleeding episodes since platelet transfusions can become problematic even after the initial transfusion.

Recombinant human factor VIIa is a vitamin K dependent glycoprotein. The structure of the recombinant factor VIIa is similar to the human plasma derived factor VIIa. The therapy works and is usually very well tolerated. The standard dose of recombinant factor VIIa is 90micrograms/kilogram intravenously every 2-3 hours. With continued therapy, the dose can be given every 4-12 hours once homeostasis is achieved^{1, p.1172}. Unlike platelet transfusions, there is no exposure to human blood products which makes it safe from transfusion transmitted infections. There are possible side effects, but they are rarely seen. Side effects can range from myocardial infarction, cerebrovascular thrombosis/accident, deep vein thrombosis/pulmonary embolism, and disseminated intravascular coagulation to angina, acute renal failure, nausea or fever. The incidence of these side effects occurring from treatment with recombinant factor VIIa is less than 1%^{1, p.1171}. The mechanism of action is still being studied, but is proposed that recombinant factor VIIa activates factors IX and X which increases the thrombin produced on the platelet surface. This results in faster platelet activation. This raises the issue of whether to begin the treatment of achieving hemostasis with recombinant human factor VIIa initially rather than to use it as a subsequent treatment after the platelet alloimmunization has already begun. Multiple studies were examined to determine if this is a possible and logical next step in the treatment of Glanzmann's thrombasthenia and other platelet disorders affecting children.

DISCUSSION

STUDY 1

The first article chosen entitled, "The Use of Recombinant Factor VIIa in Children with Inherited Platelet Function Disorders" by Almeida, Khair, Hann, Liesner is a cohort study of the use of recombinant factor VIIa in the treatment of acute bleeding episodes and surgical interventions among 7 children aged 2 ½ -5 with inherited platelet function disorders were studied over a period of 2 years⁵. Of the 7 children, 5 had Glanzmann's thrombasthenia. The other 2 had other inherited platelet disorders. A total of 33 bleeding episodes were recorded during the study period.

Recombinant factor VIIa (rVIIa) was used as first line treatment in all cases. The time between the start of the bleed and the presentation were noted. The prothrombin time was measured pre and post rVIIa treatment at least once in each child. The efficacy of the rVIIa at achieving hemostasis was noted using the International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders. "Excellent" responses were noted if bleeding stopped within 6 hours of treatment, "Good" responses were noted if bleeding slowed within 6 hours of treatment, "Poor" responses were noted if bleeding slowed more than 6 hours after treatment and "Ineffective" responses were noted if there was no slowing or stopping of bleeding within 6 hours of treatment. Recurrences within 24 hours of treatment were also noted. Subsequent transfusions requiring platelets or red blood cells were also noted and the amount needed was recorded.

The planned dose for effective treatment was 3 doses of a minimum 100 micrograms/kilogram at 90 minute intervals. There was a total of 33 episodes recorded, 5 of which were planned procedures. In only 9 of the 28 episodes did bleeding cease with rVIIa alone and in 3 of those 9 episodes it recurred. All but 7 of the 28 episodes had blood products transfused in order to achieve hemostasis. Therefore, it appears that the use of rVIIa did not significantly reduce the use of platelet transfusions. There were a few possible reasons that the results were less than desirable. There are three main factors that would affect the outcome of treatment. First, the underlying condition. Patients with Bernard-Soulier syndrome and patients with storage pool disease had better responses to treatment than patients with Glanzmann's thrombasthenia. Second, the severity of bleeding affected the response to treatment. The more severe the episode, the less efficacious the treatment. Finally, the time from onset of bleeding to treatment affected the response. Presentation greater than 12 hours from onset of bleeding episode had an unfavorable outcome. Another aspect of the study that could affect results was that the population only contained children. True epistaxis is much more common among children and may be harder to achieve hemostasis with rVIIa.

This article had some flaws. The study population size was very small, including only seven children. Since the diseases being studied are so rare, it is very difficult to achieve a large enough population size for an adequate study. The study did a very good job of treating each patient and providing the doses and times between each dose and start

and end time of each bleeding episode. The dose given was slightly more than the standard adult dose. The adequate dose for children is still being studied. The study also used the same person to evaluate the patient which eliminated possible observer variability. The study also showed that no serious side effects were seen with the use of the rVIIa in these children. There was a variable effect of the recombinant factor VIIa. The treatment regimen required the addition of platelet transfusions in many of the episodes. This could be because the population being evaluated was limited to children. The time of presentation after onset of bleeding episode seems to be variable among children. The treatment alone of recombinant factor VIIa did not cause any serious side effects among the studied population.

STUDY 2

The second article chosen, "Use of Recombinant Factor VIIa for Bleeding in Children with Glanzmann Thrombasthenia" is a case report of 2 children treated with recombinant factor VIIa to achieve hemostasis in acute severe bleeding episodes³. The first case was a 5 year old boy diagnosed with Glanzmann's thrombasthenia. The patient's bleeding time was recorded to be 10 minutes. The patient was seen previously at 15 months for severe epistaxis. The patient was treated with platelet transfusions at that point. The child was seen again at age 5 following a circumcision. The bleeding episode was severe. Treatment was as follows: 27 bags of platelet concentrate, 6 bags of platelet from apheresis, and 7 bags of red blood cell units. Fibrin glue was also used with no cessation of bleeding. A dose of 120 micrograms/kilograms of recombinant factor VIIa was administered. The dose was repeated 11 times at 3 hour intervals. As a result, bleeding then began to decrease. A dose of 75 micrograms/kilograms of recombinant factor VIIa was given 3 more times and bleeding stopped within 30 minutes.

The second case was a 6 year old girl with Glanzmann's thrombasthenia. The patient had severe epistaxis. She had a history of previous epistaxis requiring platelet transfusions. This epistaxis episode was treated as follows: initially spongostan absorbable hemostatic gelatin tampons with no improvement, then the patient was transfused with 5 bags of platelet concentrate. After 15 hours and continuous bleeding, the patient was given a dose of 90 micrograms/kilogram of recombinant factor VIIa. The same dose was repeated in 2 hours and the bleeding ceased completely.

The study shows that bleeding in patients with Glanzmann's

thrombasthenia is very serious and difficult to control. The study showed that epistaxis was quickly treated with recombinant factor VIIa. The patient with the bleeding episode following the circumcision had greater bleeding which made treatment more difficult. The treatment took more doses to achieve hemostasis. The study suggests that recombinant factor VIIa is an effective treatment in achieving hemostasis among Glanzmann's thrombasthenia patients.

This study was well done. The patients' previous transfusion history was obtained and the treatment administered was well documented. The study did not appear to be biased. The population size was very small. The study only examined 2 patients. The results were favorable for the treatment with recombinant factor VIIa to achieve hemostasis in thrombasthenic patients, but the population size is too small to be significant. The study is able to give an intimate look at the treatment of 2 specific children with Glanzmann's thrombasthenia, but further studies are needed to achieve more significant results.

STUDY 3

The third article chosen, "Recombinant Factor VIIa : A Review of its Use in Congenital or Acquired Haemophilia and Other Congenital Bleeding Disorders" is a systemic review of bleeding episodes in patients with bleeding disorders achieving homeostasis with recombinant factor VIIa treatment¹. The main focus of the review was to examine the use of intravenously administered recombinant factor VIIa for the treatment of bleeding episodes and as coverage during surgery in patients with hemophilias, Glanzmann's thrombasthenia, and factor VII deficiency.

In the first study reviewed, patients with Glanzmann's thrombasthenia were eligible for studies if the patients became refractory to platelet transfusion because of alloimmunization. The studies examined showed effective hemostasis in 94% (29/31 episodes) of surgical procedures and in 75% (77/103 episodes) of non-surgical bleeding episodes in a total of 59 patients. There was one failure seen in minor and one in major surgery. There were 8 reoccurrences of bleeding episodes and 26 failures in achieving hemostasis.

The median dose of recombinant factor VIIa the patients received was 74-150 micrograms/kilograms in 23 surgical procedures and 28-238 micrograms/kilograms in 68 bleeding episodes. The other successes were achieved with infusion

of recombinant factor VIIa.

In the second study reviewed, recombinant factor VIIa was used to achieve hemostasis within 48 hours in 97% (28/29 episodes) in non-surgical bleeding episodes in 5 children with Glanzmann's thrombasthenia. The dose administered was 90 micrograms/kilogram every 2 hours until bleeding ceased. Another study reviewed with a population of 5 patients had less impressive results. Hemostasis was achieved in only 48% (12/25 episodes). Hemostasis was achieved in 5 surgical bleeding episodes included in these two studies.

This review was a very thorough examination of the use of recombinant factor VIIa in the treatment of bleeding episodes among congenital or acquired bleeding disorders. The review was unbiased. The review shows a significant improvement of hemostasis with the use of recombinant factor VIIa. Side effects were rarely seen among the patients. Incidence was approximately less than 1%. The review states that there were 7 thrombotic events, including 3 disseminated intravascular coagulation during clinical trials of treatment with recombinant factor VIIa in the bleeding disorders. These side effects were seen in patients that had predisposing factors, such as diabetes mellitus, obesity and cancer. Therefore, it is difficult to attribute these events solely to the recombinant factor VIIa treatment. Throughout the studies reviewed in this article, there was an overall incidence of 0.6% of other serious side effects. The side effects include angina, tachycardia, ataxia, acute renal failure, anaphalactic shock and liver function abnormality. In patients specifically with Glanzmann's thrombasthenia, 2 serious side effects were seen. There was one case of deep vein thrombosis with pulmonary embolism and one case of clotting in a ureter. Both patients had received high dose and prolonged infusion of recombinant factor VIIa while also being treated with antifibrinolytic medication. Less severe side effects such as nausea, fever, increase of alkaline phosphatase, and lactate dehydrogenase were seen less than 0.01% of the time. Overall, recombinant factor VIIa seemed to be well tolerated and effective in the studies reviewed in this article.

CONCLUSION

There is a lack of direct studies over a wide population because Glanzmann's thrombasthenia is such a rare disease. The findings, although somewhat limited, show how well recombinant factor VIIa achieves hemostasis in these patients. The treatment can be used for planned procedures

such as surgeries, or in an emergent situation where the patient can not achieve hemostasis on his or her own or with the aid of transfused platelets. As with any treatment, there are always possible side effects. As shown in the studies examined, there are possible serious side effects with the use of recombinant factor VIIa, but the overall occurrence of side effects is less than 1%. The occurrences of DVTs or PE's are very rare. Recombinant factor VIIa is never exposed to human blood products during its production, thus making it safe from transfusion-transmitted infections unlike platelet and blood product transfusions. A major downfall to the rVIIa treatment is the cost. The treatment for recombinant human factor VIIa ranges from \$2,000.00 to \$8,000.00 per treatment. The treatments are expensive, but in the end any treatment that can stop a child from progressing to a life threatening bleed is worth the cost. Another disadvantage to the use of recombinant factor VIIa is the need for frequent dosing due to a short half life ^{p1174}.

Recombinant Factor VIIa has been shown to help control bleeding episodes in patients suffering from various inherited bleeding disorders including Glanzmann's Thrombasthenia. There have been shown to be limitations on the benefits of rVIIa. Hemostasis has a better chance of being achieved if the bleeding is not excessive and if the patient presents in a window of less than 12 hours after bleeding began. The benefits of rVIIa are many. The patient does not have to worry about alloimmunization occurring as with platelet transfusions. The risk of transfusion infections is also diminished when rVIIa is used instead of other blood products. The children affected with such rare bleeding disorders such as Glanzmann's thrombasthenia face a lifelong battle of increased risk of possibly life threatening bleeding episodes. Recombinant factor VIIa does in fact help to stop bleeding episodes in these patients. The efficacy continues to be studied. Recombinant factor VIIa is a valuable treatment alternative.

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