Weight-based Dosing Strategies for Factor Replacement Therapy in Hemophilia A and B

Participant Request

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Center for Evidence-based Policy

Medicaid Evidence-based Decisions Project (MED)

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Objective

To summarize the evidence on comparative effectiveness and costs of factor replacement dosing strategies based on ideal body weight (IDW), rather than actual body weight (ABW).

Background

Hemophilia is an inherited clotting disorder characterized by recurrent bleeding episodes. The most common types of hemophilia are hemophilia A, also known as factor VIII deficiency, and hemophilia B, or factor IX deficiency. Both are X-linked inherited disorders that manifest in male children of carrier females. Hemophilia A is the more common type, occurring in about 1 in 5,000 live male births, compared to hemophilia B, which occurs in about 1 in 30,000 live male births (Hoots & Shapiro, 2016). Hemophilia is classified as mild, moderate, or severe based on factor activity level. Those with severe hemophilia are more likely to have spontaneous bleeding and be younger when they experience their first bleeding episode. Hemophilia A is more likely to be severe than is hemophilia B (Hoots & Shapiro, 2016).

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Factor Replacement Therapy

Factor VIII and IX products are used to treat hemophilia A and B, respectively. Factor products are derived from human plasma or produced from cell lines (recombinant products). Factor replacement is used to treat acute bleeding episodes, or as prophylaxis to prevent bleeding. Prophylactic factor replacement therapy is further classified as primary, secondary, tertiary, or intermittent (periodic) (Table 1) (Srivastava et al., 2013). The goal of prophylaxis is to prevent bleeding and to preserve normal musculoskeletal function.

Table 1. ***Description of Factor Replacement Therapy Protocols***

Protocol	When Initiated
Episodic treatment	At the time of clinically evident bleeding; to treat pain and serious bleeding
Primary prophylaxis	Before second joint bleed, in the absence of documented joint disease
Secondary prophylaxis	After second joint bleed and before onset of joint disease
Tertiary prophylaxis	After onset of joint disease
Intermittent prophylaxis	Given to prevent bleeding for periods not exceeding 45 weeks in a year

Source: Adapted from Srivastava et al., 2013

Dosing of factor replacement is based on the patient's weight. For example, the dose of Factor VIII is calculated by multiplying the patient's weight in kilograms by the factor level in IU/dl desired, multiplied by 0.5. The factor IX dose is calculated by multiplying the patient's weight in kilograms by the factor level desired. The factor level desired varies based on duration of treatment and type of hemorrhage (Srivastava et al., 2013). The effectiveness of factor replacement therapy is assessed by measuring factor levels, with the target plasma level based on observations of better outcomes in patients with mild hemophilia.

Because factor dosing is based on patient weight, overweight and obese patients receive a higher dose compared to patients of similar height who are not overweight. However, since fatty tissues contains less blood volume than muscle of the same weight, dosing factor based on the patient's weight overestimates total blood volume (Wong et al., 2011). If dosing is based on IDW, rather than ABW, this could reduce the amount of factor used without increasing risk of bleeding or other adverse events.

A 2005 survey found that 34.5% of adults with hemophilia ages 20 and older in the United States were overweight and 23.5% were obese (Wong et al., 2011). The same survey found that 16.4% of children with hemophilia were overweight, compared to 13.7% in the general population. A more recent study from the Netherlands found an increase in obesity that paralleled that of the general population. Inactivity may contribute to obesity in patients with hemophilia, and hemophilia care guidelines stress the importance of promoting safe exercise and good nutrition (Srivastava et al., 2013). In addition to higher factor usage, obesity puts more pressure on joints and can contribute to bleeding into joints and arthropathy (Wong et al., 2011).

PICO and Key Questions

Populations

- Adults or children with hemophilia A or B receiving factor replacement treatment

Interventions

- Factor dosing based on IBW

Comparator

- Factor dosing based on ABW

Outcomes

- Pharmacokinetic measurements
- Total factor use
- Long-term joint outcomes (arthropathy)
- Cardiovascular events
- Cost-effectiveness

Key Questions

1. What is the comparative effectiveness and cost-effectiveness of factor dosing based on IBW versus ABW?
2. Does the comparative effectiveness of factor dosing based on IBW vary by:
    a. Patient characteristics (age, ethnicity, hemophilia type, presence of inhibitors)
    b. Prophylactic use vs on-demand use
    c. Type of factor replacement

Methods

To identify evidence and clinical practice guidelines, Center for Evidence-based Policy (Center) staff searched Medicaid Evidence-based Decision Project core sources and Ovid MEDLINE® using terms for factor replacement and dosing (Appendix A). Center staff also searched reference lists of included review articles and Google Scholar for articles citing included and/or relevant studies.

Findings

Clinical Practice Guidelines

Center staff identified hemophilia treatment guidelines from the United States, United Kingdom, Italy, and Australia (Australian Haemophilia Centre Directors' Organisation, 2016; Collins et al., 2013; National Hemophilia Foundation, 2015; Rocino et al., 2014). With one exception, these guidelines recommend using the patient's ABW to calculate factor

replacement dose and do not address different factor dosing strategies based on ABW versus IBW.

Australian guidelines, still in draft form, differ from the World Federation of Hemophilia guidelines and others in that they recommend factor dosing of obese patients based on IBW (Australian Haemophilia Centre Directors' Organisation, 2016). The final guidelines are expected to be released by June 30, 2016. The citation for this recommendation is an observational study of only six patients, discussed below (Graham & Jaworski, 2014).

Evidence

Searches did not identify systematic reviews or randomized controlled trials (RCTs) comparing dosing strategies based on actual versus ideal body weight. Center staff identified only uncontrolled observational studies addressing the key questions.

A study of six obese patients with hemophilia A (5 of whom had severe disease) used IBW rather than ABW to calculate dose of their usual factor VIII replacement prophylaxis (Graham & Jaworski, 2014). This regimen resulted in a mean 48.9% reduction in factor product usage over 3 months compared to ABW-based dosing. This translated to an annual mean savings of $133,000 per patient, based on average wholesale price. The regimen was not associated with an increase in bleeding frequency or other adverse events during the study period. Despite the positive results, caution should be taken with the findings of this study. There were only six patients in the sample, which limits both the results and generalizability of the study. Additionally, no control group was used, which may significantly bias the findings by inflating the results in a positive direction. Further research should be done to replicate these findings in a larger sample with a more rigorous study design.

Three pharmacokinetic studies by the same author have found that dosing based on BMI resulted in higher factor VIII recovery levels in overweight patients (Henrard & Hermans, 2015; Henrard, Speybroeck, & Hermans, 2011, 2013). An analysis of data from eight pharmaceutical industry-sponsored RCTs examined the effect of being overweight or underweight on factor VIII recovery in 201 adults with hemophilia A (Henrard et al., 2013). Less than 5% of patients were underweight, 25.9% were overweight, and 17.4% were obese. In a regression analysis, BMI was the strongest predictor of Factor VIII recovery (citation). The researchers concluded that the assumed standard rise of 2%/IU in factor VIII /kg infused dose does not apply do those with a BMI in either underweight or obese BMI categories, and recommended that IBW be used to calculate dosing in underweight and overweight patients. Median factor recovery was 1.60, 2.14, and 2.70 IU^{-1} dL^{-1} IU kg^{-1}, respectively, for those with BMI below 20.3, 20.3 to 29.5, and 29.6 or more. A more recent study (Henrard & Hermans, 2015) used the same methods to examine the impact of being overweight on factor VIII dosing among 66 children with hemophilia A, and found a similar relationship between BMI and factor VIII recovery.

A recent pharmacoeconomic analysis used chart review data from the entire hemophilia population living in Mississippi to identify children ages 2 to 18 years on factor prophylaxis who exceeded their IBW (n = 20) (Majumdar et al., 2011). The analysis concluded that an IBW dosing strategy would result in a projected monthly cost savings of over $120,000 if 20 overweight/obese pediatric patients were dosed at their IBW. This translated to nearly $1.5 million per year. The study's authors did not address whether an ABW-based dosing strategy should be used in overweight/obese patients, but rather highlighted the importance of obesity prevention in patients with hemophilia.

Trial in Progress

A Phase 2 RCT to assess whether IBW is more accurate than ABW in calculating factor VIII dosing in adults is in progress, with an estimated completion date of August 2017.

Conclusions and Limitations

Center staff did not identify any RCTs or systematic reviews on the comparative effectiveness of dosing factor replacement based on ABW or IBW. One very small observational study concluded that a strategy based on IBW would result in a reduction in prophylactic factor usage of almost 50% over 3 months, and generate significant cost savings. The long-term effect of this strategy has not been evaluated, however. A trial in progress will evaluate this question. Obesity prevention and treatment efforts aimed at patients with hemophilia may lead to reduced factor usage even if an IBW strategy were not implemented, and may also lead to better general health outcomes and quality of life for patients.

Appendix A: *Search Strategy*

Database: Ovid MEDLINE(R) without Revisions <1996 to February Week 4 2016>

1 exp Factor VIII/ or factor replacement.mp.
2 weight-based dosing.mp.
3 1 and 2
4 Factor VIII/ad [Administration & Dosage]
5 Factor IX/ad [Administration & Dosage]
6 4 or 5
7 limit 6 to (english language and humans)
8 limit 7 to (meta analysis or systematic reviews)

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