Use of Ultrasound to Diagnose Hemarthrosis and Monitor Joint Health in Hemophilia

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 current evidence on effectiveness and costs of using ultrasound in the management of hemophilia A and B.

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).

Bleeding can occur at any site, but hemarthrosis, or bleeding into a joint, is the most common manifestation, accounting for about 80% of bleeding episodes in ambulatory patients (Hoots & Shapiro, 2016). Bleeding may occur as the result of a trauma, but spontaneous bleeding may also occur in severe disease. Hemarthrosis causes pain and may be physically debilitating. Once a joint has been damaged by hemarthrosis, it is more susceptible to recurrent bleeding and is referred to as a "target joint." Advanced joint degeneration, or hemophiliac arthropathy, may develop over time with recurrent hemarthroses. Therefore, the goals of therapy are prevention, early diagnosis, and prompt treatment of hemarthroses to preserve joints.

Diagnosis of hemarthrosis is usually made based on clinical findings of pain and reduced mobility. Magnetic resonance imaging (MRI) is the most accurate method for diagnosing hemarthrosis (Khan et al., 2010). Although MRI is the "gold standard" for diagnosis of joint bleeding, its routine use is not practical due to lack of widespread availability, time requirements, need for sedation in young children, and expense. Ultrasound has been proposed as a quicker, simpler, and less costly imaging technique for the diagnosis of hemarthrosis.

Various scoring systems are used to assess hemophilic arthropathy based on radiologic and/or clinical findings. These systems are not sensitive to early joint changes, however, and may underestimate the severity of joint damage (Di Minno et al., 2013). Ultrasound may be an option to detect early changes and guide treatment.

PICO and Key Questions

Populations

- Adults or children with hemophilia A or B

Interventions

- Use of ultrasound for diagnosis of acute hemarthrosis or routine assessment of joint health

Comparator

- Usual care (clinical assessment, goniometry, patient questionnaires)
- MRI

Outcomes

- Long-term joint outcomes (arthropathy)
- Change in management
- Total factor use
- Diagnostic accuracy or time to diagnosis
- Cost-effectiveness

Key Questions

1. What is the comparative effectiveness and cost-effectiveness of ultrasound vs usual care or MRI to diagnose acute hemarthrosis?
2. What is the comparative effectiveness and cost-effectiveness of ultrasound vs usual care or MRI to assess joint health longitudinally?
3. Does the effectiveness of ultrasound in the management of hemophilia vary by:
    a. Patient characteristics?
    b. Presence of degenerative joint changes?
    c. History of prior joint bleeding?
    d. Severity and location of acute joint bleeds?
    e. Operator experience?

Methods

Center for Evidence-based Policy (Center) staff searched Medicaid Evidence-based Decision Project core sources and Ovid MEDLINE® using terms for hemophilia and ultrasound (Appendix A).

Findings

Center staff identified no systematic reviews or randomized controlled trials of the use of ultrasound in patients with hemophilia A or B. Three observational studies (Di Minno et al., 2013; Doria et al., 2015; Sierra Aisa et al., 2014) and one cost effectiveness analysis (Khan et al., 2010) were identified and used to address the key questions for this report.

Effectiveness of Ultrasound to Diagnose Hemarthrosis

We identified no studies comparing clinical examination to ultrasound for diagnosing hemarthrosis. One prospective cohort study compared ultrasound to MRI for diagnosis of joint lesions in 61 patients with hemophilia in two regions of Spain (Sierra Aisa et al., 2014). All patients had a physical examination, but only those with severe disease (n = 30) underwent MRI and ultrasound scans. There was good agreement (Kappa=1.0) between MRI and ultrasound in cases of observed bleeding. Hemarthrosis was detected in 100% of severe cases with both MRI and ultrasound (Sierra Aisa et al., 2014). The authors received editorial support from Dr. Blanca Piedrafita of Medical Statistics Counseling, which was funded by Pfizer. However, they reported no significant conflicts of interest that would potentially bias their findings.

Effectiveness of Ultrasound to Assess Joint Health

A prospective cohort study compared ultrasound to MRI to detect joint changes in asymptomatic patients with severe hemophilia (Di Minno et al., 2013). The cohort was small, consisting of 20 boys. In evaluations by blinded assessors, MRI and ultrasound scores correlated significantly for effusion (r = 0.819, P = 0.002), synovial hypertrophy (r = 0.633, P = 0.036), and cartilage erosion (r = 0.734, P = 0.010) (Di Minno et al., 2013). The researchers concluded that ultrasound was able to identify early-onset subclinical joint alterations. Because this study did not include an assessment of symptomatic joints, it does not provide evidence on the comparison of ultrasound to clinical findings. The authors noted no significant conflicts of interest.

The study by Sierra Aisa and colleagues discussed above (Sierra Aisa et al., 2014) also compared ultrasound to MRI for assessment of arthropathy in patients with severe hemophilia. Ultrasound assessment was not statistically significantly different than MRI for detecting the presence of synovial hyperplasia and erosion of margins. For detection of bone cysts or cartilage loss, however, MRI had better accuracy.

A small observational study included imaging of ankles (n = 34) or knees (n = 25) of boys with hemophilia ages 5 to 17 years in Canada and India (Doria et al., 2015). Ultrasound was sensitive and had good agreement with MRI when performed by experienced radiologists. For this study, financial support was provided by Bayer Healthcare Canada. The authors did not list conflicts of interest.

Effectiveness by Patient Characteristics and Other Factors

We identified no direct evidence addressing this key question. Observational studies discussed above found that ultrasound was comparable to MRI in detecting acute joint bleeding in patients with severe hemophilia (Sierra Aisa et al., 2014), and in detecting subclinical arthropathy in children with severe hemophilia A (Di Minno et al., 2013).

Cost Effectiveness of Ultrasound

A cost effectiveness analysis published in 2010 examined different imaging strategies for the diagnosis of hemophilic arthropathy in children (Khan et al., 2010). The study's objective was to compare costs and effectiveness of usual care (physiotherapy and radiography) to usual care plus ultrasound. This was a small study of only 31 patients that used retrospective data from medical records at a single center in Canada. The researchers found that the strategy including ultrasound was more costly, but increased diagnostic effectiveness compared to usual care. Because this analysis considered only the cost of diagnosing arthropathy and not the cost of management of hemophilia, or variations in treatment as a result of different diagnostic strategies, it does not provide information on longer term cost effectiveness.

Conclusions and Limitations

Observational studies have shown that there is good agreement between ultrasound and MRI for detecting acute bleeds and assessing joint damage in adults and children with hemophilia. However, no studies compared outcomes of treatment in patients assessed with ultrasound, usual care, or other imaging techniques. Clinical practice guidelines do not address the routine use of ultrasound in diagnosing hemoarthroses or monitoring joint health in patients with hemophilia. In part because hemophilia is a relatively rare disorder, studies are small and the evidence base is limited. Longer-term, prospective studies are needed to evaluate the place of ultrasound in the management of hemophilia.

Appendix A: *Search Strategy*

Database: Ovid MEDLINE(R) <1946 to February Week 4 2016>

1 hemophilia.mp. or exp Hemophilia A/

2 exp Hemophilia B/

3 exp Ultrasonography/ or ultrasonography.mp.

4 *Ultrasonography/

5 *Magnetic Resonance Imaging/

6 exp Hemarthrosis/di [Diagnosis]

7 1 or 2 or 6

8 3 or 4 or 5

9 7 and 8

10 limit 9 to (english language and humans)

11 limit 10 to yr="2010 -Current"

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