Title: Elevated Blood Ion Levels from Metal-on-Metal Hip Implants: Biological and Adverse Effects

Date: 03 March 2008

Context and Policy Issues:

Total hip arthroplasty (THA) or hip replacement typically involves replacing the head of the femur with a cobalt-chromium metal alloy prosthesis that articulates onto a prosthesis placed in the acetabular cup of the hip joint.\(^1,2\) In the majority of THAs the acetabular prosthesis is made of ultra-high molecular weight polyethylene (UHMWPE).\(^1,2\) Wear particles are generated at the articulating surfaces and polyethylene debris collects in the joint space where it elicits an immune response. The immune response is ineffective against the polyethylene debris leading the body’s defenses to attack the bone adjacent to the prosthesis. The resulting bone loss (osteolysis) leads to loosening of the prosthetic and its failure.\(^1,3\)

Extending the life of hip prostheses is viewed as important given a trend to perform THA on younger, more active patients and the complexities of revision surgery (i.e., the replacement of hip prostheses).\(^1\) Lower wear rates are viewed as central to achieving this objective. Metal-on-metal (MOM) prostheses are a promising alternative, with some first generation MOM prostheses functioning well after 20 years.\(^1\) MOM prostheses reportedly wear at rates 20 to 100 times lower than metal-on-polyethylene (MOP) prostheses.\(^1,4\)

Despite lower wear rates, the amount of particulate debris produced by MOM prostheses is estimated to be 13 to 500 times greater than is the case with MOP prostheses.\(^4\) As with MOP prostheses, particulate matter results from corrosion, abrasion and differential micromovement,\(^5\) but unlike MOP prostheses, the resulting debris rarely triggers osteolysis thus contributing to superior survivorship for MOM prostheses.\(^4\)

MOM wear particles are in the nanometer size range, much smaller than polyethylene wear particles.\(^1,4\) These small particles can distribute throughout the body in both solid and ionic...
Metal particles have been identified in periprosthetic tissue as well as organs such as the liver and spleen. Elevated metal ion levels (e.g., cobalt, chromium and nickel) have been identified in the blood, urine, hair and regional lymph system of patients with metallic implant components.

The systemic distribution of metal particles and/or metal ions gives rise to a number of concerns including metal ion hypersensitivity, toxicity and carcinogenesis. In patients with well-functioning MOM prostheses the prevalence of metal sensitivity is about 25%, twice that of the general population and prevalence climbs to 60% among patients with failed MOM prostheses. High concentrations of cobalt and chromium particles have been shown to be cytotoxic to human fibroblasts and macrophages in vitro and are reportedly also genotoxic. Elevated cobalt and chromium levels have also been associated with cancers in animal models and at least 25 case reports exist of cancers in humans, 84% being sarcomas associated with hip or knee prostheses.

The concerns associated with MOM prostheses are complex and have been described as theoretical by some sources. Policy/decision makers will be concerned with the absence of well defined safety parameters for blood and urine metal concentrations in patients who have received MOM prostheses for THA or hip resurfacing, the validity of the identified concerns and the impact these have on the relative advantage MOM prostheses seem to confer over MOP prosthesis in terms of device longevity.

Research question:

1. What are the biological effects associated with elevated blood ion levels in patients with metal-on-metal hip implants?

Methods:

A limited literature search was conducted on key health technology assessment (HTA) resources, including Pre-Medline, Medline, Embase, Biosis, CINAHL, Pubmed, UpToDate, the Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 1997 and February 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

Summary of findings:

No reports or trials specifically addressing the biological effects associated with elevated blood ion levels in patients with MOM prostheses were identified.

Two HTAs addressing MOM hip resurfacing were identified that touch on the issue of blood ion levels.

Health technology assessments

The Medical Advisory Secretariat (MAS) of the Ontario Ministry of Health and Long Term Care published an assessment of MOM total hip resurfacing arthroplasty in February 2006. The assessment reviewed literature published between January 1, 1997, and October 27, 2005, that addressed the relative effectiveness and safety of hip resurfacing versus THA.
addressing carcinogenicity and cobalt cardiotoxicity. One cited source, an evaluation by the International Agency for Research on Cancer (IARC), found inadequate evidence for the carcinogenicity in humans of metallic implants and metallic foreign bodies, including orthopedic implants of complex composition. The IARC concluded that foreign bodies of metallic chromium or titanium and of cobalt-based, chromium-based and titanium-based alloys, stainless steel and depleted uranium are not classifiable as to their carcinogenicity in humans. The MAS also summarized an epidemiological study, the sole study of its kind, that examined the incidence of cancer after MOM (n=698) and MOP (n=1831) THA. Mean follow-up was 15.7 years after MOM THA and 12.5 years after MOP THA. The incidence ratios for all cancers were 0.95 (95% CI, 0.79 – 1.13) after MOM THA and 0.76 (95% CI, 0.29 – 1.05) after MOP THA. The combined incidence ratios for lymphoma and leukemia were 1.59 (95% CI, 0.82 – 2.77) after MOM THA and 0.59 (95% CI, 0.29 – 1.05) after MOP THA. The MAS assessment stated that MOM THA patients had a significantly increased risk of leukemia. With regard to cardiotoxicity, a number of epidemiological studies were cited linking cobalt exposure to an unusual type of myocardiopathy. Overall, the MAS authors concluded that longer-term follow-up data are required to resolve inconsistent reports regarding the carcinogenicity and toxicity of cobalt-chromium alloy prostheses used in MOM total hip resurfacing arthroplasty.

In November 2006, the Alberta Bone & Joint Institute (ABJI) published an assessment of MOM hip resurfacing for young adults with degenerative hip disease. The authors discussed metal ion release and safety but the discussion adds nothing to the material presented in the MAS assessment. The ABJI assessment recommended that women of child-bearing age and patients with renal failure should not be eligible for MOM hip resurfacing procedures. The report also stated that all patients receiving MOM resurfacing should sign a consent acknowledging the unknown risks associated with MOM hip resurfacing and should undergo annual toxicology tests.

Limitations:

The Ontario MAS assessment appears to be a well documented and thorough assessment of MOM total hip resurfacing arthroplasty. It is difficult to assess whether the literature search for material addressing the safety of MOM hip resurfacing was as thorough as that addressing the effectiveness of the procedure itself but it is notable that the discussion of safety concerns did not touch on metal ion hypersensitivity or genotoxicity. In addition, the statement regarding the statistically significant increased risk of leukemia in the MAS study is unclear. Other studies that cite this study also highlight this finding but note that the confidence intervals are wide which may indicate that this is not statistically significant. The MAS authors did not identify any limitations of their assessment.

The ABJI assessment presents a good discussion of MOM hip resurfacing but the discussion of safety issues is cursory. The authors noted that their assessment was based on a limited review of the evidence and it was not subject to external review.

Conclusions and implications for decision or policy making:

The concerns related to systemic distribution of metal particles and/or metal ions in patients with MOM hip prostheses are widely acknowledged but also highly theoretical. A wealth of narrative reviews address the topic and numerous trials examine the impact of MOM prostheses on serum and urine ion levels, but little or no research documents the in vivo impact of metal particles/ions associated with MOM hip prostheses in humans. The issue is made more complicated by the fact that elevated blood ion levels are not unique to MOM prostheses. While
blood ion levels appear to be most elevated with MOM prostheses, elevated ion levels are common to MOP and other prostheses having metal components as well, thus implicating to varying degrees most, if not all, hip prostheses.4,10,11

The challenge for policy/decision makers rests in weighing the relative advantage MOM prostheses seem to confer in terms of device longevity against the potential risks associated with these prostheses. Separating theoretical from real risks will be complex and require long term follow-up given, for example, the latency period associated with metal-induced cancers. In the short term, policy/decision makers may be limited to mitigating the potential risks for certain patient groups by researching and identifying possible contraindications such as child-bearing potential and impaired renal function.

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