

International Prophylaxis Study Group Final Report

Chair: Victor Blanchette, Chief, Division of Hematology/Oncology, Hospital for Sick Children, Professor of Pediatrics, University of Toronto, Toronto, ON, Canada.

Overview of the International Prophylaxis Study Group
Victor Blanchette, Canada

The International Prophylaxis Study Group (IPSG) was formed in 2001 by 10 experts from Canada, the United States, Sweden, Italy, Germany, and the Netherlands. Its goal is to promote the generation and communication of new information on the administration and outcome of factor prophylaxis in individuals with hemophilia, Dr. Victor Blanchette said.

The IPSG established expert working groups in four domains: physical examination, imaging (ultrasound/magnetic resonance imaging, or MRI), economics, and health-related quality of life (HRQoL). The physical therapy working group has been developing the international Hemophilia Joint Health Score (HJHS). The imaging working group has been developing an MRI scale for global use. The economics working group has published a report detailing the ideal elements that should be collected, from a health economics viewpoint, in prospective trials of prophylaxis. The HRQoL working group focused on a review of the best HRQoL measures for application in hemophilia.

Hemophilia Joint Health Score

Brian Feldman, Head, Division of Pediatric Rheumatology, The Hospital for Sick Children, Professor of Pediatrics, University of Toronto, Toronto, ON, Canada, and Sharon Funk, Physiotherapist, Department of Pediatric Hematology, University of Colorado Denver, Mountain States Regional Hemophilia and Thrombosis Center, Denver, CO, United States

Musculoskeletal measurement tools help quantify outcomes such as whether interventions are working and whether treatment is preventing joint disease, said Sharon Funk. The tools also provide criteria by which physiotherapists, hematologists and orthopedists can decide whether current treatment is still effective and determine whether surgical or other interventions are needed.

The ultimate goals of musculoskeletal measurement tools are to quantify the minimum amount of factor required to prevent joint disease, and to use this information in encouraging governments to fund prophylaxis programs in countries where it is not available.

The first hemophilia joint scale (World Federation of Hemophilia scale) was developed more than 20 years ago by orthopedists from Germany, Venezuela, Israel, England, and the United States. The tool consisted of a physical examination and pain scale to evaluate and score joint arthropathy. Ms. Funk noted some limitations of the WFH scale. Although it was appropriate for measuring the more severe degrees of hemophilic joint degeneration (arthropathy) present at the time, it was insensitive to the earliest signs of joint disease in young children. In addition, psychometric criteria were never established for the scale.

In 1992, Ms. Funk began modifying the scale to increase its sensitivity (her version became known as the "Colorado Scale"). In 1994, under the direction of Dr. Marilyn Manco-Johnson,

Ms. Funk started working on a joint outcome study that used a pediatric version of the Colorado Scale to measure joint status in children with hemophilia from age 1 - 6 years every six months, incorporating functional activities appropriate for very young children. This scale was also used by the Hospital for Sick Children in Toronto, Canada in the Escalating Dose Prophylaxis Study. Not long after, Stockholm researchers suggested modifications to the original WFH joint scale as well. In 2002, the Colorado and Stockholm researchers, along with experienced hemophilia physiotherapists from Canada and The Netherlands, began working together to design and test a new joint scale for use in persons with hemophilia: the Hemophilia Joint Health Score (HJHS).

Their goals were to develop a hemophilia physical examination assessment tool sensitive enough to pick up the subtle early signs of joint damage and the differences among patients with mild, moderate, or severe hemophilia. Ms. Funk said that they also wanted their score to be appropriate for screening children on both prophylactic treatment and on-demand regimens.

Modifications made in the development of the HJHS included adding several new items as well as redefining and increasing the sensitivity of some of the existing items from the original WFH and Colorado Joint Scales. There are very specific criteria by which each item is assessed. Changes include:

- Addition of the items of strength, gait and duration of swelling
- Redefinition of the range of motion item to be expressed as flexion and extension loss
- Assessment of pain objectively rather than subjectively

A reliability study was carried out in September 2003, and strong construct validity was established through an international cross-sectional study in 2006-07. The use of the HJHS should be considered for studies on prophylaxis as well as for clinically monitoring joint change over time or assessing efficacy of treatment regimens, Ms. Funk said.

Dr. Brian Feldman described the findings of the HJHS reliability study, which were published in *Haemophilia* in 2006 (Hilliard et al. *Haemophilia* 2006; 12: 518 - 525). The study objectives were to ensure the score's reliability, i.e. that it yielded the same score when an individual patient was assessed twice by the same physiotherapist and also when assessed by two different physiotherapists. Four physiotherapists and eight patients of varying ages and degrees of disease severity participated in the study. Findings indicated that the HJHS had excellent reliability.

A validation study was then undertaken to establish that the HJHS accurately measures joint status in patients with mild, moderate, or severe hemophilia A or B. The original WFH scale was also evaluated at that time. The study involved 226 patients from five centres (Stockholm, Utrecht, Denver, Montréal, and Toronto). The six-joint HJHS was found to correlate highly with the WFH scale; however, the HJHS was better able to distinguish between mild, moderate, and severe disease. In addition, the HJHS correlated moderately with the total number of joint bleeds and scores recorded by the treating physicians, who were blind to the HJHS, but less moderately for individual joints, Dr. Feldman said. Although more than half of the patients had severe factor deficiency and several had a history of inhibitors, most had a low bleeding risk; one-third of patients were on primary prophylaxis, and the rest were on secondary prophylaxis.

Further revisions and reliability and validity studies are ongoing, said Dr. Feldman, and include a follow-up study and international translation and distribution of the HJHS.

Role of MRI for Detection of Early Arthropathy: A Proposed New International MRI Score

Bjorn Lundin, Radiologist and Chief of musculoskeletal MRI at the department of Radiology, University Hospital of Lund, Sweden, and Andrea Doria, Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, ON, Canada.

Given the number of magnetic resonance imaging (MRI) scoring systems for hemophilic arthropathy presented in the literature, one of the main objectives of the International Prophylaxis Study Group (IPSG) in initiating an international MRI score was to develop a single common scale that could be used globally, said Dr. Bjorn Lundin.

The IPSG imaging working group began with a step-by-step approach to analysing the breadth and varying complexities of existing MRI scales, particularly the Denver (progressive design: the final score represents the worst joint changes) and the European (additive design: the final score represents all joints changes seen on imaging) scales. It concluded that the best scoring system for MRI assessment is a simple, additive scale. The group has developed a preliminary scoring system, which is being tested over the summer (2008).

The preliminary IPSG MRI scale has the capacity to measure musculoskeletal changes (particularly, soft tissue and osteochondral) in the six most commonly affected joints by assessing aspects such as:

- Effusion/hemarthrosis
- Synovial hypertrophy
- Hemosiderin deposition
- Changes of the subchondral bone or joint margins
- Subchondral cysts
- Cartilage loss

MRI is highly sensitive and can yield detailed information about joint changes. The standard procedure in MRI is to acquire several images at a number of planes and sequences (with different echo and repetition times), which are reconstructed to acquire an image of different structures of the body.

However, MRI use for hemophilia joint assessment presents a number of challenges; Dr. Lundin stated how it is difficult to investigate multiple joints, particularly given the time constraints. The standard procedure in MRI is to acquire sets of images with different types of contrast (weighting), but if six index joints (elbows, knees, and ankles) are to be investigated this is too time-consuming. The use of a single sequence protocol with images of only one type of weighting makes the procedure feasible, although still lengthy.

Some may consider that MRI is not useful for the evaluation of hemophilic arthropathy, because it is too expensive and complicated. However, it is the most sensitive imaging tool available. "MRI is not easy to use, but it is already used today and will gradually become more practical,"

Dr Lundin said. "It is one of several imaging options for evaluation of hemophilic arthropathy and it will contribute to further improvement of hemophilia care."

Dr. Andrea Doria said that the ultimate goals of the IPSPG imaging working group are to:

- develop sensitive imaging tools for the assessment of hemophilic arthropathy.
- validate a single scoring system (additive or progressive) for hemophilic joint assessment based on comparative results from previous research.
- gain a better understanding of the role of imaging modalities in the management of hemophilic arthropathy.

The imaging working group developed a preliminary MRI scale that incorporated both progressive and additive scales. In 2006–07, the scale underwent a reliability study to determine the extent to which repeated assessments by different radiologists yield similar results. In addition, a construct validity study was performed to determine the extent to which the MRI score relates to other clinical measures. The study showed high reliability for MRI assessment of the knees, ankles, and elbows. However, there was poor validity for assessment of early changes in some joints. The scale was also shown to favour assessment of osteochondral aspects of joints. The scale clearly needed refining, Dr. Doria said, and changes have been made to both the osteochondral and the soft tissue scoring elements in the scale.

The final MRI scale should be simple, have the ability to evaluate early changes in joints, and be applicable in different clinical settings – including the evaluation of early osteochondral changes in individuals receiving prophylaxis, and for pre-intervention assessment (before surgical or radiosynovectomy). The imaging working group's future objectives include exploring adjunct imaging modalities (ultrasound), weighting items in the MRI scale according to clinical/functional correlations, and tailoring the total MRI score to the assessment of single or multiple joints at a point in time.