



## Efficacy, Safety, and Synovial Effects of Intra-articular Hyaluronic Acid in Treating Recalcitrant Hemophilic Arthropathy of Knee Joint

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**Background and Aim:** Recurrent hemarthrosis results in synovitis and destructive arthropathy in hemophilic patients. The aim of our study was to investigate the efficacy and synovial changes with viscosupplementation therapy in treating hemophilic arthropathy of the knee. **Subjects and Methods:** Twenty hemophilic patients who had painful arthropathy of the knee with synovitis were enrolled. Patients received three weekly intra-articular injections of 2 mL hyaluronic acid (HA). The synovial thickness and vascularity determined by ultrasonography, visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Short Form 36 (SF-36) were compared initially and at 1, 2, 3, and 6 months after the first injection. Statistical analysis was performed using SPSS version 20 software (Armonk, NY, USA: IBM Corp). **Results:** There were 19 hemophilia A patients and 1 hemophilia B patient. A total of 26 knees received viscosupplementation therapy. Significant improvement in VAS, SF-36, WOMAC score, hyperemia, and thickness of suprapatellar recess synovium from baseline was seen up to 6 months after intra-articular HA injection. No severe injection-related adverse event was observed. **Conclusions:** This study suggests that three weekly intra-articular HA injections are safe and effective in treating hemophilic arthropathy of knee with synovitis for a period up to 6 months. The treatment not only improved quality of life, pain and knee function but also reduced synovial thickness and hyperemia. HA viscosupplementation therapy could serve as an adjunctive therapy before arthroscopic synovectomy or total knee arthroplasty.

**Key words:** Hemophilia, hemophilic arthropathy, hemophilic synovitis, hyaluronic acid, intra-articular injection, viscosupplementation

### INTRODUCTION

Hemophilia is an X-linked recessive bleeding disorder caused by a deficiency of coagulation factor VIII (hemophilia A) or IX (hemophilia B). Hemophilia affects 1 in 5000 male births. The classification of severity was determined by measuring factor clotting activity level (<1%, severe; 1%–5%, moderate; 5%–30%, and mild). Severe hemophilia patients may have frequent spontaneous bleeding episodes such as joint and muscle bleeding, but mild hemophilia patients only have bleeding episodes after trauma, surgery, or tooth extraction. More than 60% of bleeds

occurring into joints in severe hemophilia.<sup>1</sup> Repeated joint bleeding leads to chronic synovitis, cartilage damage and bony destruction, which is associated with the limitation of range of motion (ROM), pain, muscle atrophy, functional impairment and poor quality of life.<sup>2</sup> Around 80% of all spontaneous joint bleeds occur in the ankles, knees, and elbows. Prophylactic replacement, physical therapy, COX2 inhibitors,<sup>3</sup> corticosteroids, radionucleotide synovectomy,<sup>4</sup> and joint arthroplasties<sup>5</sup> are some of the typical modalities used in the managements hemophilic synovitis and arthropathy.

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The onset of joint bleedings in severe hemophilia occurs approximately 2 years of age<sup>6</sup> and arthropathy could be worsening in adolescents or young adults. Some hemophilia patients may either not be good candidates for surgery or may not prefer to have surgery. Hyaluronic acid (HA) has been shown to be safe and effective for the treatment of pain associated with mild-to-moderate osteoarthritis<sup>7</sup> since 1989. The research investigating the therapeutic effect of HA in patients with hemophilic arthropathy is rare because bleeding tendency is concerned, and hemophilic arthropathy is often severe and troublesome. Fernández-Palazzi *et al.* first used intra-articular HA injection for hemophiliacs with arthropathy since 1994 and reported its good response in 2002.<sup>8</sup> Following two studies also showed a similar result.<sup>9,10</sup> However, the definite effect of intra-articular HA injection for hemophilic arthropathy of the knee in current published studies are insufficiently proved because they enrolled small patient numbers and lack of controlled group. Moreover, all the measured outcomes of above-mentioned studies are all based on patients' subjective symptom, functional activity or working condition, and no objective measurement such as synovial thickness and vascularity by image study, the intervention-related bias would overstate its clinical effect.

For knee imaging, magnetic resonance imaging (MRI) and ultrasonography (USG) are more sensitive tools than conventional radiography for determining the involvement of the synovium, effusion, bursa, cartilage, tendons, and ligaments. USG is useful in detecting joint bleeds, synovial hyperplasia, and joint erosion in hemophilic arthropathy, with efficacy comparable to those of MRI.<sup>11</sup> With the advancement of USG techniques, such as Power Doppler, it appears that this modality can provide the detailed assessment of vascularity and disease activity.<sup>12,13</sup> The use of MRI is limited by its lack of widespread availability and high cost, and it is also unsuitable for nonsedated pediatric patients or claustrophobic adults. Thereafter, musculoskeletal USG has been coming a very useful complementary tool for the detection of hemophilic arthropathy or synovitis<sup>14</sup> because of its good performance in detecting synovial hypertrophy and hyperemia, cartilage change, joint effusion, and bony destruction.<sup>15</sup> It may provide a viable alternative to MRI, especially in settings where the latter, is not readily available or where there is a need for frequent assessments for close monitoring.

The aims of the study were (1) to investigate the efficacy, safety and effective duration of three weekly intra-articular injections of HA in patients with hemophilic arthropathy of knee (2) to evaluate changes in synovial thickness and vascularity by USG after intra-articular HA injection.

## SUBJECTS AND METHODS

### Patients

The study was approved by the Institutional Review Board of our institution (No. 099--05-152), and all the enrolled patients provided their written informed consents that fully disclosed the risks and benefits of study participation. A total of 61 hemophilia patients with hemophilic arthropathy of knee joints were managed at our hemophilia center. Twenty-four of the 61 patients (39%) who were found to have painful (visual analog scale [VAS]  $\geq 5$ ) hemophilic arthropathy for at least 6 months and had no significant response to conservative treatment (including medication with analgesic or anti-inflammatory agents and physical therapy) were screened for this study. Synovial hypertrophy was determined by USG, and the thickness of the synovium had to be more than 2 mm for inclusion in the study. The exclusion criteria were as follows: the presence of joint infections, any surgery on the knee joint in preceding 12 months, intra-articular corticosteroid or HA injection within the past 6 months, treatment with systemic steroids, history of rheumatoid arthritis, or gouty arthropathy, history of chicken or egg allergy, presence of neoplasm, acute hemarthrosis, paresis, or recent trauma. Based on the above-mentioned criteria, four patients were excluded, including two patients with previous surgeries and the other two with synovial thickness of  $<2$  mm. Therefore, 20 patients were eventually enrolled in this study. We collected clinically relevant information including age, gender, body mass index (BMI), hemophilia type, disease severity, inhibitor titre, and the average number of joint bleeds per month.

### Intervention

Patients received three weekly intra-articular injections of 2 mL of sodium hyaluronate (Hyalgan, Fidia Farmaceutici S. p. A., Abano Terme, Italy) with prophylactic factor replacement before each injection to prevent joint bleeding. Before starting this course of treatment, a baseline USG evaluation was performed. Before injection, the hemophilia patients received 25 IU/kg factor replacement therapy to protect them from hemarthrosis. After injection, the joint was rested for 20 min, and the compression was applied with an elastic bandage to minimize any injection-related bleeding. All outcome measurements were performed initially at baseline and at 1, 2, 3, and 6 months after the first injection. The primary outcome measure was the reduction of pain intensity measured by the VAS, whose scale ranged from 0 (no pain) to 10 (extremely severe pain). Secondary clinical outcome measures included synovial thickness by USG, hyperemia by Power Doppler, ROM, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Short Form 36 (SF-36).

The patients self-administer clotting factor for perceived knee joint bleeds were based on their own judgment. The only investigator supplied paracetamol was allowed for additional pain relief. The administration of analgesic, joint bleeding episodes, and adverse events during the study was also recorded in diary by the patients themselves.

## Evaluation

### Ultrasonography

The USG assessment was performed according to a standard technique using Terason t3000 machines (Teratech™, Burlington, Massachusetts, USA) with a 5–12 MHz linear transducer. The probe scanned the joint in the longitudinal view with the knee in full extension [Figure 1]. Synovium thickness and hyperemia were evaluated from the lateral, middle, and medial aspects of the anterior suprapatellar recess.<sup>13,16</sup> Power Doppler assessment of selected synovial sites was carried out with settings standardized to a pulse repetition frequency of 700 Hz. The power Doppler gain was adjusted to a level just below the disappearance of artifacts under the bony cortex.<sup>16,17</sup> The intensity of the blood flow in the synovium was scored into 0–3 (0 = No flag; 1 = 1 flag; 2 = 2–3 flags; 3 ≥ flags) adapted from Klukowska *et al.* and Melchiorre *et al.*<sup>16,18</sup> Averages of synovium thickness and score of hyperemia in lateral, middle, and medial aspects of the anterior suprapatellar recess were calculated.

### Radiological evaluation

Anteroposterior and lateral plain radiographs of knees were performed and scored according to Pettersson classification<sup>19</sup> by the designated orthopedic specialist at our hemophilia

center. The Pettersson score ranges from 0 to 13 and is based on the following radiographic features of joints: osteoporosis, osteophytes, narrowing of joint space, subchondral irregularity, subchondral cyst formation, erosion of joint margins, and bone remodeling. A totally normal joint has a score of zero. This Pettersson scoring system has been adopted by the World Federation of Haemophilia as the preferred radiographic classification system for hemophilic arthropathy.

### Assessment of knee function

ROM of the knee was measured in degrees with a goniometer according to the American Academy of Orthopaedic Surgeons guidelines. All ROM measurements were performed by the same assessor. The pain intensity of knee was evaluated subjectively on a VAS (0–10 cm).

### Short Form 36

The SF-36 is a generic measure of health status and has gained popularity as a measure of outcome in a wide variety of patient groups and surveys.<sup>20</sup> The SF-36 is a 36-item assessment tool that measures eight general health concepts including physical functioning, role limitation due to physical health problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problems, and mental health. The SF-36 is filled out taking into account the person's condition in the last 1 month, and scores range from 0 to 100, with higher scores indicating better health-related quality of life.

### Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC index was developed in the early 1980s as a disease-specific measure for lower limb arthritis and arthropathy.<sup>21</sup> It consists of 24 items: five pertaining to pain, two to stiffness, and 17 to physical function. We used 100 mm VAS formats. Individual question scores were then added up to form a raw score ranging from 0 (best) to 2400 (worst). Finally, raw scores were normalized by multiplying each score by 100/2400. This produces a reported WOMAC Score of between 0 (best) to 100 (worst).

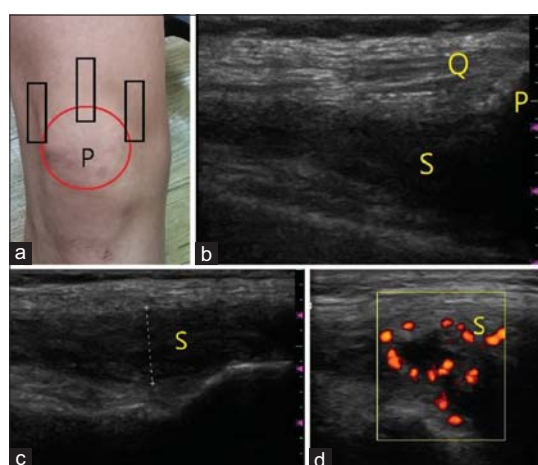
## Statistical methods

Continuous variables were expressed as mean values and standard deviations. The repeated measures analysis of variance was used to test for significant difference between baseline and various follow-up measures.  $P < 0.05$  was considered statistically significant. Statistical analysis was performed using SPSS version 20 software (Armonk, NY, USA, IBM Corp.).

## RESULTS

### Patients

A total of 20 patients were studied of whom 19 had hemophilia A and 1 had hemophilia B. Their demographic data are listed in Table 1. The median age was  $38.2 \pm 10.1$  years



**Figure 1:** Ultrasonographic evaluation of the knee joint. P = Patella; Q = Quadriceps tendon; S = Synovial hypertrophy. (a) Probe position of the lateral, middle, and medial aspects of the anterior suprapatellar recess. (b) Longitudinal ultrasonographic scan shows hypertrophic synovium of the middle aspect of the anterior suprapatellar recess. (c) Longitudinal ultrasonographic scan shows hypertrophic synovium of the medial aspect of the anterior suprapatellar recess. (d) Longitudinal ultrasonographic scan shows Grade-3 hyperemia of suprapatellar synovitis using power Doppler (>3 flags)

(range, 15–49 years). Sixteen patients had severe hemophilia, whereas four had moderate type of hemophilia. Two patients had factor VIII inhibitors and three had HIV. The mean BMI was  $24.2 \pm 4.7$  kg/m<sup>2</sup> (range, 19.1–40.3). Twenty-six (17 left and 9 right) knee joints were treated with intraarticular viscosupplementation therapy with  $7.5 \pm 3.5$  (range, 3–13) averaged Pettersson score before injection, as shown in Table 1. Changes from baseline in the VAS, SF-36, WOMAC, ROM, hemarthrosis, hyperemia and synovial thickness to those at 1, 2, 3, and 6 months after first HA injection are shown in Table 2. All of these variables except ROM were significantly improved after HA treatment as summarized below.

### Visual analog scale of pain

A significant reduction in pain from hemophilic arthropathy of knee was observed up to 6 months ( $F = 35.32$ ,  $P < 0.01$ ),

Table 1: Demographic characteristics of 20 hemophilic patients

| Characteristic           | Average   | Range       |
|--------------------------|-----------|-------------|
| Age (y/o)                | 38.2±10.1 | 15-49       |
| Height (cm)              | 169.5±5.7 | 159.0-178.1 |
| Body weight (kg)         | 69.7±13.4 | 47.7-113.6  |
| BMI (kg/m <sup>2</sup> ) | 24.2±4.7  | 19.1-40.3   |
| Severity                 |           |             |
| A, severe                | 15        |             |
| A, moderate              | 4         |             |
| B, severe                | 1         |             |
| HIV                      | 3         |             |
| Inhibitor                | 2         |             |
| Injected knee            | 26        |             |
| Right/left               | 9/17      |             |
| Pettersson score         | 7.5±3.5   | 3-13        |

BMI=Body mass index

Table 2: Outcome measures of 26 injected knees at baseline and 6-month follow-up

|                            | Baseline | 1 month     | 2 months    | 3 months    | 6 months    | RM-ANOVA             |
|----------------------------|----------|-------------|-------------|-------------|-------------|----------------------|
| VAS                        | 5.7±0.2  | 2.7±0.2***  | 1.8±0.3***  | 2.5±0.3***  | 3.2±0.5***  | $F=35.32$ , $P<0.01$ |
| SF-36                      | 48.8±3.3 | 58.8±3.4*** | 63.2±3.3*** | 64.8±2.7*** | 60.6±3.1*** | $F=17.12$ , $P<0.01$ |
| WOMAC                      | 38.1±3.6 | 22.3±2.6*** | 21.3±2.4*** | 24.8±2.7**  | 26.0±2.6**  | $F=13.79$ , $P<0.01$ |
| ROM (degree)               | 91.0±5.1 | 91.5±5.2    | 92.5±5.3    | 92.7±5.3    | 92.7±5.6    | $P=0.23$             |
| Hemarthrosis               | 0.9±0.2  | 0.2±0.1***  | 0.1±0.1***  | 0.1±0.1***  | 0.3±0.1***  | $F=16.73$ , $P<0.01$ |
| Hyperemia (score)          | 1.4±0.2  | 1.0±0.2**   | 0.8±0.2**   | 0.9±0.2**   | 1.1±0.2     | $F=4.09$ , $P<0.05$  |
| Thickness of synovium (mm) | 6.0±0.6  | 5.9±0.6     | 5.6±0.6**   | 5.7±0.6**   | 5.9±0.6     | $F=7.18$ , $P<0.05$  |

Significant difference compared to baseline \*\* $P<0.01$ , \*\*\* $P<0.001$ . A significant difference was found in VAS score, SF-36, thickness of synovium, and WOMAC between baseline and from one to six months of follow-up. Score expressed as mean±SE. Hemarthrosis=Number of knee bleeds in last one month; Thickness of synovium=Average synovial thickness in lateral, middle, and medial aspects of suprapatellar pouch; Hyperemia=Average score of power Doppler assessment in lateral, middle, and medial suprapatellar recess synovium; ROM=Range of motion; SF-36=Short form-36; VAS=Visual analog scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; RM ANOVA=Repeated measures analysis of variance

with the maximal benefit being noted at 2 months after HA injection [Figure 2].

### Short Form 36

The SF-36 score was significantly increased for 6 months after HA viscosupplementation ( $F = 17.12$ ,  $P < 0.01$ ), and this score reached the highest level at 3 months after treatment [Figure 3].

### Western Ontario and McMaster Universities Osteoarthritis Index

WOMAC score was significantly improved for 6 months after HA viscosupplementation injection ( $F = 13.79$ ,  $P < 0.01$ ), and which was the lowest at the second month of follow-up [Figure 4].

### Synovium

HA viscosupplementation significantly reduced the thickness of suprapatellar synovium ( $F = 7.18$ ,  $P < 0.05$ ) and

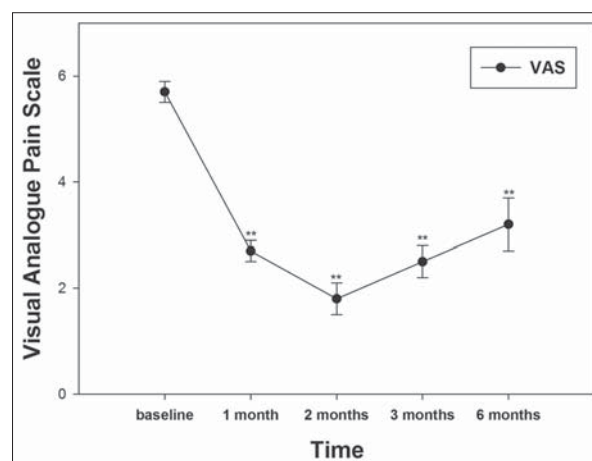
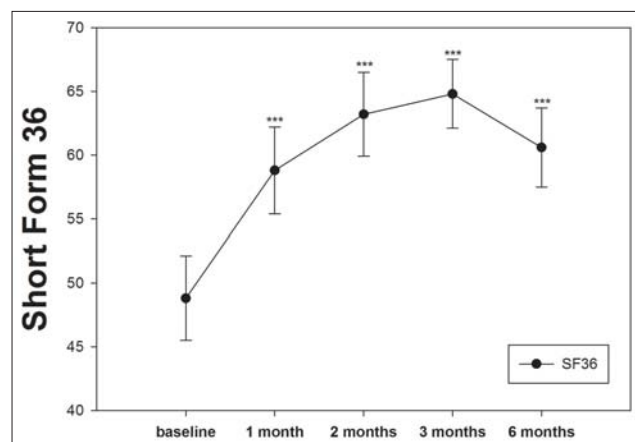


Figure 2: Mean pain score with standard error over 6 months follow-up





**Figure 3:** Mean Short Form 36 score with standard error over 6 months' follow-up

those reduction was obviously at the 2 months and 3 months, as shown in Table 2. Moreover, a significant improvement in synovial hyperemia was also achieved ( $F = 4.09$ ,  $P < 0.05$ ), as shown in Table 2.

### Hemarthrosis

The average number of monthly joint bleeds was decreased after HA treatment ( $F = 16.73$ ,  $P < 0.01$ ), as listed in Table 2. There was no bleeding in 10 knee joints (38.5%) for 6 months after HA treatment.

### Safety

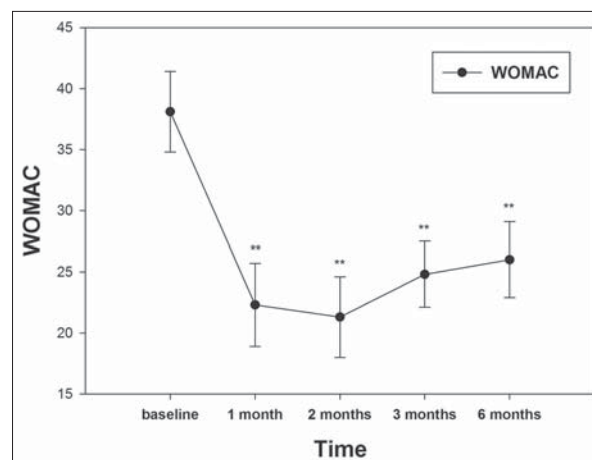
In this study, all patients completed the 3 consecutively weekly intra-articular HA injections with good tolerance. Most adverse events were minor and transient and occurred at the injection site. Postinjection soreness occurred in two patients, and injection site ecchymosis was noted in three patients.

There was no HA injection-related joint bleeding, infection, or acute inflammation.

### DISCUSSION

To the best of our knowledge, the present study is the first research to evaluate synovial thickness and hyperemia by the use of USG as therapeutic measurements in patients with hemophilic arthropathy after intra-articular HA injection. The result demonstrates that the efficacy and safety of intra-articular HA injection including pain relief, subsided synovitis, increase quality of life, enhance knee joint function, and reduced joint bleeding events at least 6 months after the first injection.

Hemophilic arthropathy is a multifactorial event and there is evidence that iron may play a major role with release of cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis



**Figure 4:** Mean Western Ontario and McMaster Universities Osteoarthritis Index score with standard error over 6 months' follow-up

factor-alpha (TNF- $\alpha$ ) leading to chronic proliferative synovitis, hypervascularity, cartilage damage, and bone destruction.<sup>22</sup> Comer *et al.* reported that HA suppressed production of TNF- $\alpha$ <sup>23</sup> and Takahashi *et al.* found HA reduced expression of IL-1.<sup>24</sup> Such evidence suggested that intra-articular HA may inhibit these inflammatory cytokines, then beneficial in the treatment of haemophilic arthropathy with synovitis.

Fernández-Palazzi *et al.* were the pioneers in using intra-articular HA injection for hemophilic patients since 1994 and reported its good efficacy and safety in treating haemophilic arthropathy in 2002.<sup>8</sup> Wallny *et al.* reported that 14 of 20 hemophilia patients had improvement in knee pain, World Federation of Hemophilia score, and walking distance after 5 consecutive weekly intra-articular injections without obvious change of MRI between baseline and 3 months after first injection of HA. Moreover, all patients had no major complications at 2 years of follow-up.<sup>9</sup> Recently, Carulli *et al.* reported 27 hemophilic patients with a mean 7-year follow-up who had excellent results regarding pain relief and functional improvement in knees following treatment with HA injection, particularly at 6 months follow-up.<sup>10</sup> Our study supports these previous claims of a benefit of intra-articular HA injection in patients with hemophilic arthropathy during 6 months of follow-up especially at the 2–3-month time points after treatment. Furthermore, we first identified the significant decrease of synovium thickness and synovial hyperemia after intra-articular HA injection. Table 3 illustrates the comparison between our study and other three published from studies.

USG examination, which is convenient, inexpensive, and readily available, has been primarily recommended for the diagnosis of inflammatory arthritis<sup>25,26</sup> and arthropathy involving the synovial fluid, synovium, and articular cartilage.<sup>27</sup> With advancements in USG technique, such as

Table 3: Comparison of HA interventions and outcomes in our study with other major previously reported studies

| Reference                                           | HA                   | Treatment times | Patients number | Outcome                                                             | Side effect                            | Follow-up period |
|-----------------------------------------------------|----------------------|-----------------|-----------------|---------------------------------------------------------------------|----------------------------------------|------------------|
| Fernández-Palazzi <i>et al.</i> , 2002 <sup>8</sup> | Synvisc              | 3 times         | 17              | Improvement of pain and                                             | No mention                             | 1-15 months      |
| Wallny <i>et al.</i> , 2000 <sup>9</sup>            | Hyalart              | 5 times         | 20              | Improvement in pain (VAS), WFH score and walking distance           | No mention                             | Up to 31 months  |
| Carulli <i>et al.</i> , 2013 <sup>10</sup>          | Hyalgan<br>Hyalubrix | Varies          | 27              | Improvement in pain (VAS), WFH score and quality of life (SF-36)    | No side effect                         | From 2-8 years   |
| This study                                          | Hyalgan              | 3 times         | 20              | Improvement in pain (VAS), WOMAC score, SF-36 and reduced synovitis | Injection site ecchymosis and soreness | 6 months         |

SF-36=Short form-36; HA=Hyaluronic acid; WFH=World federation of hemophilia; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; VAS=Visual analog scale

Power Doppler, it appears that this modality can provide more detailed assessment of vascularity and disease activity.<sup>12,13,28</sup> Doppler sonography has been shown to provide USG measure of synovial vascularity in hemophilic joints that is very comparable to dynamic contrast-enhanced MRI.<sup>13</sup> Finally, systematic protocols for USG image acquisition<sup>14</sup> as well as USG scale for evaluation of hemophilic joints,<sup>18,29</sup> have been developed, which should enable a more standardized clinical application on a broader scale in the near future. In this study, synovial thickness and hyperemia of knee joints were measured by USG and a statistically significant reduction in both with this treatment was demonstrated. This may be related to anti-inflammatory effects of HA. We also found reduced frequency of joint bleeds after HA injection. Supplementation of HA by increasing joint lubrication and decreasing joint shearing force<sup>30,31</sup> may reduce the friction of synovium and frequency of hemarthrosis, and may even block the vicious cycle of hemarthrosis-synovitis-hemarthrosis.

With regard to safety of HA injection, three cases of injection sites ecchymoses were noted in our study when a 23 G injection needle was used. After changing to a 25G needle, however, there were no such events. No serious adverse effect was noted in this study. Both Fernández-Palazzi *et al.* and Wallny *et al.* reported no major complications in their studies although Athanassiou-Metaxa *et al.* reported an 8-year-old boy who received intra-articular HA knee injection but had the treatment interruption due to hemarthrosis.<sup>32</sup> There was no treatment interruption due to hemarthrosis in our study.

There are some limitations to this study. The main limitation was the small samples size and absence of a control group. Although a larger series with randomized controlled trial may help further verify the efficacy of intra-articular HA injection for hemophilic arthropathy of knee, the hemophilia is an uncommon condition and injection of saline as placebo into

the knee joint of a hemophilia patient would not be ethically justifiable. Moreover, treatment bias can hardly explain the significant 6-months effect and decreased synovium thickness and hyperemia which were subjectively measured by USG in patients with recalcitrant hemophilic arthropathy. The limitation of the lack of control group in our study could be ignored mostly. Finally, we did not investigate the long-term effect beyond the 6<sup>th</sup> months. Nevertheless, the significant difference in all measurements except ROM compared with baseline until the 6<sup>th</sup> months [Table 2] imply that the therapeutic effect may extend beyond the follow-up period examined in this study.

## CONCLUSIONS

This study has shown that three consecutive weekly intra-articular HA (Hyalgan) injections were safe and effective in treating recalcitrant hemophilic arthropathy of knee with synovitis for a period of up to 6 months and can improve quality of life, pain, synovium thickness, and knee function in such patients. HA viscosupplementation therapy could, therefore, be an option in case of failure of factor prophylaxis therapy and as an alternative to certain other joint directed therapies such as radiosynovectomy. Finally, it may also serve as a temporizing measure before arthroscopic synovectomy and total knee arthroplasty.

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### Conflicts of interest

There are no conflicts of interest.

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