Prospective Randomized Trial Comparing the Efficacy of Single 6-ml Injection of Hylan G-F 20 and Hyaluronic Acid for Primary Knee Arthritis: A Preliminary Study

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Objective: *To compare the efficacy of single 6-ml intraarticular injection between hylan G-F 20 and hyaluronic acid (HA) for knee osteoarthritis*

Material and Method: *Thirty-two patients with primary knee arthritis, who were randomly received single intraarticular injection of 6-ml hylan G-F 20 (Synvisc®) or HA (Hyalgan®), were prospectively evaluated for clinical outcomes at a minimum 26-week follow-up. The parameters, including visual analog scale (VAS) during walking, the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index and Short-Form 36 (SF-36) questionnaires, were evaluated at pre-injection, then at 1 week, 4 weeks, 8 weeks, 12 weeks and 26 weeks, post-injection.*

Results: *There were 15 patients in both groups who were available for final follow-up with no statistical differences in demographic data, VAS during walking, WOMAC score and SF-36 score at pre-injection. There was no adverse event related to viscosupplementation using in is better than of both agents. At 26-week follow-up, patients in both groups had significantly improved VAS during walking ($p < 0.01$), WOMAC score ($p < 0.01$) and SF-36 ($p < 0.05$) with no statistical differences between groups. However, the cost of hylan G-F 20 was much more expensive than that of HA (534 USD vs. 252 USD).*

Conclusion: *A single intraarticular injection of both hylan G-F 20 and HA for primary knee arthritis had no adverse event related to 6-ml volume. At 26-week follow-up of the present preliminary study, both groups had similarly improved clinical outcomes post-injection. Further study in larger population is required. As the cost of hylan G-F 20 was 2 times higher than HA, a single 6-ml intraarticular injection of HA (Hyalgan) provided better cost-effectiveness than hylan G-F 20 (Synvisc).*

Keywords: *Efficacy, Osteoarthritis, Knee, Viscosupplement, Hyaluronic acid, Hylan*

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Osteoarthritis (OA) is the most common bone and joint disease in the elderly[1]. The disease is characterized by degeneration of articular cartilage, subchondral bone, synovium and synovial fluid[2]. Osteoarthritis of the knee, a major weight bearing joint, gradually affects daily activities including progressive pain and functional disability. In symptomatic OA of the knee, weight reduction, muscle strengthening, avoid increasing knee joint stress positions, proper rehabilitation and pain medication are common methods of conservative treatment[3]. Recently, viscosupplementation[4], an intra-articular injection of artificial joint fluid in order to restore rheological properties affecting lubrication and shock absorption, has introduced as an alternative conservative treatment. The therapeutic efficacy and safety of viscosupplement injection has been documented in the literatures[5-8], although viscosupplement agents are developed from different substrates resulting in different molecular weight, pharmaceutical property and regimen of treatment.

While reduction of the number of intraarticular injection may result in improved patient's compliance and reduced adverse events[9], the standard injection protocol is still recommended for most viscosupplement agents which is once a week for 3-5 consecutive weeks[10-13]. Several studies reported comparative efficacy of various viscosupplement agents or compared the same agent with different administrative regimen[14-18]. Recently, Chevalier et al[19] reported on outcomes of single 6-ml intra-articular injection of the hylan G-F 20 in patients with knee osteoarthritis, which was safe and effective in terms of pain relief and functional improvement. Based on clinical effects of

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different mechanical properties of viscosupplement agents, some studies[14,15] reported that the hylan G-F 20, which has high molecular weight and high elastoviscous property, provided significantly greater pain-relieving effects than that of the hyaluronic acid (HA), which has lower molecular weight and less elastoviscous property.

To our knowledge, there has been no comparative study on a single intraarticular injection of 2 different molecular weight viscosupplement agents. The authors hypothesized that no difference in clinical efficacy between high- and low- molecular weight viscosupplement agents.

The purpose of the present study was to compare the clinical efficacy of a single 6-ml intraarticular injection of high molecular weight viscosupplement agent (hylan G-F 20; 6,000,000 Daltons) and low molecular weight viscosupplement agent (HA; 500,000-730,000 Daltons) for primary osteoarthritis of the knee.

Material and Method

The present study design was a prospective randomized clinical trial to compare the clinical efficacy of a single 6-ml injection of hylan G-F 20 (Synvisc®, Genzyme, Ridgefield, New Jersey, USA), which is a high molecular weight viscosupplement agent and HA (Hyalgan®, Fidia, Abano Terme, Italy) which is a low molecular weight viscosupplement agent for treatment of osteoarthritis of the knee. The single 6-ml intraarticular regimen has been reported as an alternative method of injection for hylan G-F20[19], however, this regimen has not ever been reported or approved for the HA. Thus, the authors intended to perform the present study as a pilot-trial.

From September 2010 to June 2011, 32 patients who had primary osteoarthritis of the knee and came to orthopaedic clinic at our institution were recruited. Inclusion criteria were primary osteoarthritis of the knee according to the American College of Rheumatology criteria[20], $\geq$ 45 years of age, having pain on walking with $\geq$ 3 of 10 visual analogue scale (VAS), having $\geq$ grade II of radiologic grading of Kellgren-Lawrence criteria[21]. The exclusion criteria included prior intra articular injection within 1 year, intention to take pain medication after the injection, history of allergy to avian products, and refuse to sign the consent form.

After a 2-week washed out period, patients were allocated into 2 groups by closed envelope selection. Patient in group I received the hylan G-F 20 and group II received the HA. The intraarticular injection was blindly performed by a senior surgeon (AT) using a supero-lateral approach without any anesthetic agent. Following the injection, no pain medication was prescribed.

Clinical assessments were blindly evaluated by an independent observer (TD) using the VAS during walking, the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index[22,23] and the Short-Form 36 (SF-36) questionnaires[24]. Evaluations were performed at patient's first visit as a baseline and then at 1 week, 4 weeks, 8 weeks, 12 weeks and 26 weeks after injection.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego California USA). Descriptive statistics were expressed by mean and standard deviation. The Student t-test and the Chi-square test were used to compare quantitative and qualitative data in both groups. Statistically significance was considered when the p-value was < 0.05.

Results

During follow-up, there were one patient in the hylan G-F 20 group and one patient in the HA group were loss for complete evaluation. Thus, there were 30 patients available for the final follow-up (Fig. 1). There were no statistical differences in patient's demographic data between two groups. The majority of patients in both groups were classified as grade III based on Kellgren-Lawrence grading for severity of osteoarthritis (Table 1). There were no adverse events related to intraarticular injection of both agents in the present study.

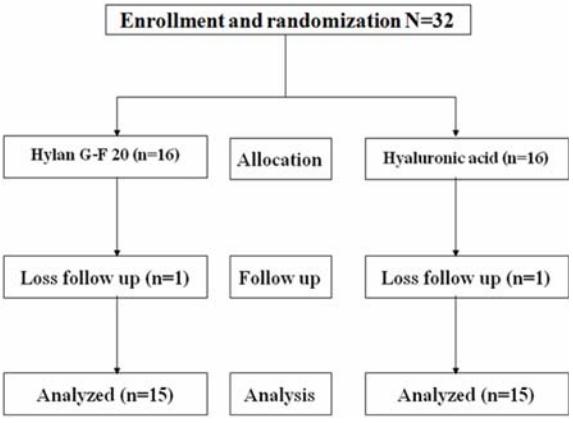

Fig. 1 Flow diagram of the study

Table 1. Demographic data of the studied patients

Parameters	Group I hylan G-F 20 (n = 15)	Group II hyaluronic acid (n = 15)	p-value
Female N (%)	12 (80)	12 (80)	1.0
Male N (%)	3 (20)	3 (20)	
Age (year) mean (SD)	65.1 (9.6)	67 (9.5)	0.59
Weight (kg) mean (SD)	67.3 (14.7)	63.3 (8.2)	0.36
Height (cm) mean (SD)	159 (6.8)	158 (8.5)	0.74
BMI (kg/m^2) mean (SD)	26.6 (5.7)	25.4 (2.5)	0.46
Kellgren-Lawrence grade N (%)			
Grade II	2 (13.3)	1 (6.7)	
Grade III	10 (66.7)	10 (66.7)	
Grade IV	3 (20.0)	4 (26.7)	

N: number

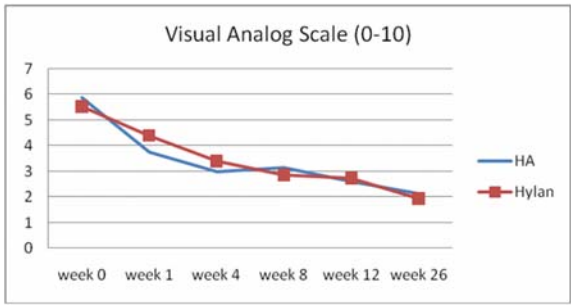

Fig. 2 Comparing the mean of visual analog scale (VAS) during walking between 2 groups

The VAS during walking

The baseline VAS during walking of both groups were similar (5.53 $\pm$ 1.9 vs. 5.86 $\pm$ 1.8, p = 0.6). Both hylan G-F 20 and HA groups had similarly decreasing in VAS during waking in relation to the follow-up time, with a mean change of at 26-week follow-up of 3.60 $\pm$ 1.6 points, p < 0.01 and 3.73 $\pm$ 2.2 points, p < 0.01, respectively). However, there were no statistical differences in the improvement of VAS during walking between 2 groups at 26 weeks post injection (p = 0.85) (Fig. 2).

The WOMAC score

At baseline, there were no differences in the WOMAC pain, stiffness and function subscales between the hylan G-F 20 and the HA groups (p = 0.9, 1.0 and 0.7, respectively). At 26-week follow-up, both groups had significant improvement in all WOMAC subscales comparing to scores at baseline (p < 0.01 in both groups) with no statistical differences in all WOMAC subscales (p = 0.7, 0.3 and 0.6, respectively) (Fig. 3).

The SF-36

The baseline SF-36 including the mental component summary scores (MCS) and the physical component summary (PCS) scores of both groups were similar (p = 0.6 and 0.6 respectively). At 26-week follow-up, although the hylan G-F 20 and the HA groups had no significant improvement in MCS score (p = 0.11 and p = 0.38, respectively), both groups had significant improvement in PCS scores of SF-36 from the baseline (p < 0.01 and p = 0.03, respectively). Additionally, the overall SF-36 scores of both groups at the final follow-up were not statistically different (p = 0.4) (Fig. 4).

Discussion

Viscosupplement has been documented as an effective mean of conservative treatment for osteoarthritis of the knee[3-5]. However, various administrative protocols are different according to molecular weights and precursors of different agents. Although studies[14,15] comparing the efficacy of hylan G-F 20 and HA using a standard treatment protocol showed superior clinical results of hylan G-F 20 over the HA, a recent meta-analysis[16] stated that there was lack of a superior effectiveness of the hylan G-F 20 over the HA with an increased risk of local adverse events with the hylan G-F 20 group. This meta-analysis emphasized the previous review[5] that was inclusive whether which agents or administrative protocol was the best choice of viscosupplementation.

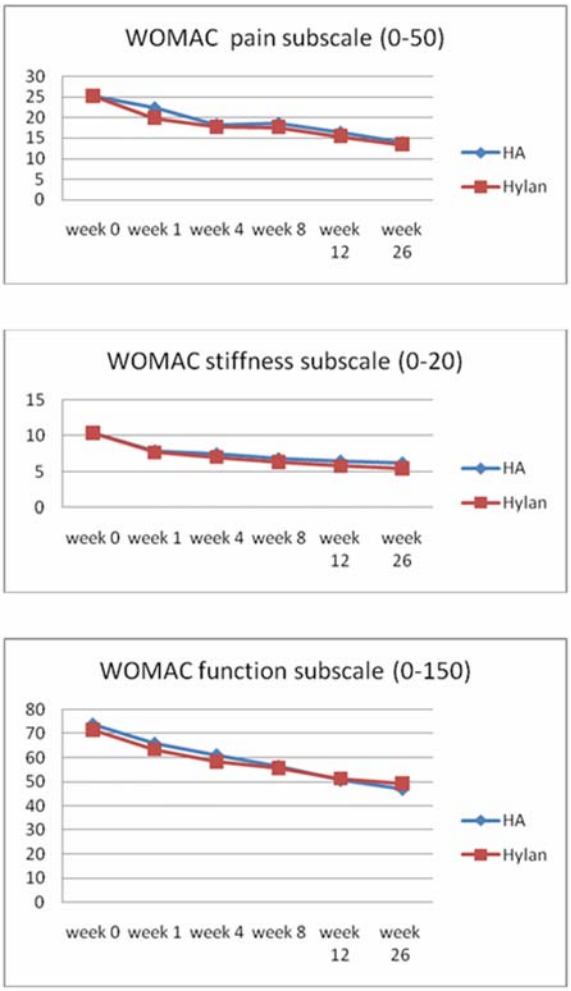

Fig. 3 Comparing the mean of WOMAC pain, stiffness, and function subscales between 2 groups

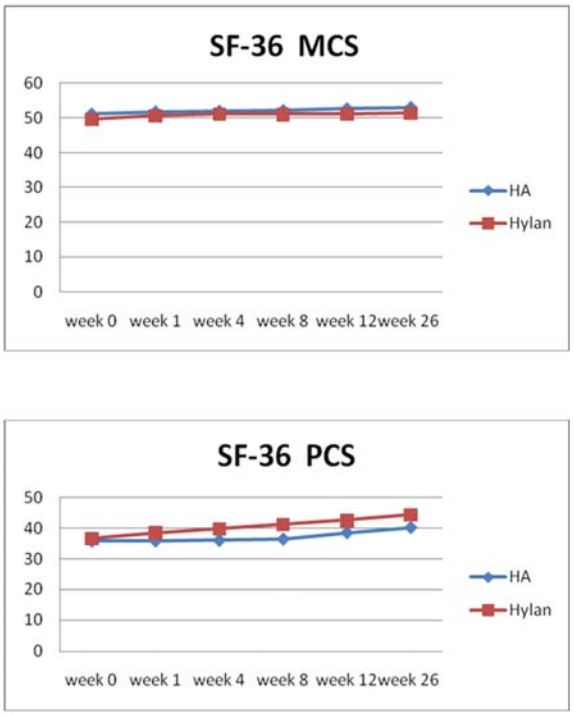

Fig. 4. Comparing the mean of SF-36 mental component summary scores (MCS) and physical component summary (PCS) scores between 2 groups

According to the study of Chevalier et al[19] a 6-ml single injection of viscosupplement had no adverse event related to the volume. This had drawn our intention to design the present study with the injection of a 6-ml dose of viscosupplement for comparative study of 2 different viscosupplement agents. Clinical outcomes of viscosupplementation based on the different molecular weight of agents with a similar injected volume demonstrated that there were significant reduced walking pain by VAS, improved the knee function assessed with WOMAC pain, stiffness and function scores, as well as the SF-36 scores, with no statistical differences between 2 groups.

Regarding the economical consideration, as one of important concerned issues related to the health care system, the cost of treatment of both viscosupplement agents in Thailand was approximately 2 times in difference. According to the selling price in public hospital system in Bangkok, the cost of 6-ml HA (Hyalgan®) was 252 US dollars, while the cost of 6-ml hylan G-F20 (Synvisc®) was 534 US dollars. This finding had high clinical impact in drug selection for treatment in developing countries, especially in Thailand, which implies that the cheaper product with same efficacy is more interesting to choose.

The limitations of the present study included small group of studied patients, short-term of follow-up and no comparison with the placebo group. As the single dose protocol for the HA has not been approved as the standard protocol, the present study was designed as a preliminary study. Following the present study, further larger patient group and longer follow-up time should be continued.

Conclusion

A the follow-up of 26 weeks, the intraarticular injection of a single 6-ml hylan G-F 20 and a single 6-ml of HA in patients with primary osteoarthritis of the knee resulted in similar improved clinical outcomes, in terms of significant pain reduction of VAS during walking and WOMAC scores without adverse event. As, the HA group provided much less cost of treatment

than the hylan G-F 20, we concluded that the HA provided a better cost-effectiveness than the hylan G-F 20.

Potential conflicts of interest

None.

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การศึกษาประสิทธิภาพของการใช้สารหล่อข้อปริมาณ 6 มิลลิลิตรระหว่างไฮแลน-20 และไฮยาลูโรนิกในผู้ป่วยข้อเข่าเสื่อมปฐมภูมิ: รายงานวิจัยเบื้องต้น

ยุทธนา คณาสุข, ธีรยุทธ เดชมณีนิล, อารี ตนาวลี

วัตถุประสงค์*: เพื่อศึกษาประสิทธิภาพของการฉีดสารหล่อข้อปริมาณ 6 มิลลิลิตร ระหว่าง ไฮแลน-20 และไฮยาลูโรนิกในผู้ป่วยข้อเข่าเสื่อมปฐมภูมิ*

วัสดุและวิธีการ*: เป็นการศึกษาแบบสุ่ม โดยใช้อาสาสมัคร 32 รายที่มีโรคข้อเข่าเสื่อมปฐมภูมิ ซึ่งจะสุ่มสารหล่อข้อระหว่างไฮแลน-20 และไฮยาลูโรนิก และประเมินผลลัพธ์ที่เกิดขึ้น ได้แก่ คะแนนความปวดระหว่างเดิน, คะแนน WOMAC (Western Ontario and Mc Master Universities Osteoarthritis) และคะแนน SF-36 (Short-Form 36) ซึ่งจะประเมินผลก่อน และหลังการฉีดสารหล่อข้อ 1, 4, 8, 12 และ 26 สัปดาห์*

ผลการศึกษา*: อาสาสมัครในแต่ละกลุ่มสุทธิ 15 รายที่เข้าหลักเกณฑ์ พบว่า ก่อนฉีดสารหล่อข้อ ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างข้อมูลประชากร, คะแนนความปวดระหว่างเดิน, คะแนน WOMAC และ คะแนน SF-36 ทั้งนี้ ไม่พบอาการข้างเคียงที่เกิดจากการฉีดสารหล่อข้อทั้ง 2 กลุ่ม แต่เมื่อติดตามอาสาสมัครนี้ที่สัปดาห์ที่ 26 พบว่า มีความแตกต่างอย่างมีนัยสำคัญเมื่อเทียบกับก่อนฉีดสารหล่อข้อโดยที่ คะแนนความปวดระหว่างเดิน ($p<0.01$), คะแนน WOMAC ($p<0.01$) และ คะแนน SF-36 ($p<0.05$) ทั้งนี้ ไม่พบความแตกต่างของพารามิเตอร์ทั้งหมดระหว่างกลุ่มไฮแลน-20 และไฮยาลูโรนิก*

สรุป*: การฉีดสารหล่อข้อข้อระหว่างไฮแลน-20 และไฮยาลูโรนิกในผู้ป่วยข้อเข่าเสื่อมปฐมภูมิ ไม่มีผลข้างเคียงจากการใช้ปริมาณ 6 มิลลิลิตร และได้ผลลัพธ์ในเชิงบวกที่ 26 สัปดาห์หลังฉีดสารหล่อข้อ แต่ทั้งนี้การศึกษานี้มีอาสาสมัครไม่มาก การศึกษาที่มีจำนวนอาสาสมัครมากจะทำให้เห็นผลลัพธ์ได้ชัดเจนขึ้น อย่างไรก็ตามราคาของสารหล่อข้อ 2 ชนิดนี้ต่างกันอย่างมาก โดยที่ไฮแลน-20 มีราคาสูงกว่าไฮยาลูโรนิก ประมาณ 2.1 เท่า ในแง่เศรษฐศาสตร์การให้ยาไฮยาลูโรนิก ปริมาณ 6 มิลลิลิตรจึงน่าจะมีความคุ้มค่ากว่า*
