Efficacy and safety of hylan G-F 20 injection in treatment of knee osteoarthritis in Chinese patients: results of a prospective, multicentre, longitudinal study

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**Objective:** To study the efficacy and safety of single intra-articular injection of 6-mL hylan G-F 20 in Chinese patients with symptomatic knee osteoarthritis.

**Design:** Prospective case series.

**Setting:** Six government hospitals in Hong Kong.

**Patients:** Patients with primary knee osteoarthritis were recruited from six government hospitals from 1 October 2010 to 31 May 2012. All patients received 6-mL intra-articular injection of hylan G-F 20.

**Main outcome measures:** Pain visual analogue scale, functional visual analogue scale, and 5-point Likert scale on change of pain and function were assessed. Adverse events were checked. Radiographs were taken pre-injection and at 3 months and 1 year.

**Results:** A total of 110 knees of 95 patients with primary knee osteoarthritis were treated. The mean age of the patients was 62 (standard deviation, 9.8) years. All patients completed 1 year of follow-up. The mean pain visual analogue scale, functional visual analogue scale, and Likert value for pain and function showed statistically significant improvements at 6 weeks, 3 months, 6 months, and 1 year compared with the pre-injection values. No significant correlations were found between changes in visual analogue scale and age, body mass index, pre-injection radiological osteoarthritis severity, serum erythrocyte sedimentation rate, or C-reactive protein. Serial radiographs did not show any changes in the radiological severity of knee osteoarthritis. Overall, 16.4% of the patients experienced mild and self-limiting adverse events.

**Conclusion:** Hylan G-F 20 is a safe and effective therapy to relieve pain and improve function for up to 1 year in Chinese patients with knee osteoarthritis.

**New knowledge added by this study**

• This study demonstrated that hylan G-F 20 is effective and safe to treat knee osteoarthritis in Chinese patients. Past studies were only conducted in Caucasian or mixed populations.

**Implications for clinical practice or policy**

• Viscosupplementation could be a valid option for managing patients with chronic and symptomatic knee osteoarthritis. Single injection preparation is safe and effective. Injection can be performed in an out-patient setting.

**Introduction**

Osteoarthritis (OA) is a progressive degenerative joint disease initiated by multiple aetiological factors. When clinically evident, OA is characterised by joint pain, tenderness, stiffness, crepitus, effusion, and variable degrees of inflammation without systemic effects. Knee OA is a leading musculoskeletal cause of disability in elderly people around the world, and affects both Caucasian and Chinese populations. The burden of disease dramatically impacts health care costs. A local study found that, excluding joint replacement, the direct costs of
注射 hylan G-F 20 治療華籍患者膝關節骨性關節炎的效果和安全性：前瞻性、縱向多中心研究

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研究目的為探討膝關節骨性關節炎華籍患者在關節內注射 hylan G-F 20 后的效果和安全性。

注射 hylan G-F 20 中的 G-F 20 是一個平均分子量為 6000 万道尔顿的透明质酸。hylan G-F 20 用于北美洲和欧洲治疗疼痛。

Hylan G-F 20 是一种不溶性的透明质酸钠的商业产品。Hylan G-F 20 用于北美和欧洲的疼痛治疗。

研究目的：研究 Hylan G-F 20 在治疗膝关节骨性关节炎华籍患者中的效果和安全性。

研究方法：前瞻性、多中心研究。

研究对象：2010 年 10 月 1 日至 2012 年 5 月 31 日期间曾到六间公立医院的原发性膝关节骨性关节炎患者，按照以下标准进行分类：

- 患者年齡 62 岁（标准差 9.8 岁）。
- 患者完成一年随访。
- 注射前比较，患者在注射后第六週、三個月、六個月和一年的疼痛視覺模擬評分、功能性視覺模擬評分和 CRP 水平。

主要结果：注射 hylan G-F 20 后，疼痛視覺模擬評分、功能性視覺模擬評分，及膝关节内注射 hylan G-F 20。患者出现轻微和自限性不良事件。

结果：研究对对象为 95 名（110 例）原发性膝关节骨性关节炎患者，他们平均年龄 62 岁（标准差 9.8 岁）。所有患者均完成一年随访。

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pain and functional limitations were charted using a 5-point Likert scale. Standard radiographs of the knee were repeated at 3 months and 1 year to detect any changes in radiological severity.

The change in pain and functional VAS scores before and after injection during each visit was compared using paired t test. Using correlation tests, we tried to find out the predictive factors (including age, sex, BMI, pre-injection KL grade, pre-injection pain VAS, ESR, and CRP) of favourable treatment response. All analyses were performed using the Statistical Package for the Social Sciences (Windows version 20.0; SPSS Inc, Chicago [IL], US). Statistical significance was assumed if the P value was <0.05.

Results

A total of 110 knees of 95 patients (31 men and 64 women) were recruited from six government hospitals in Hong Kong from 1 October 2010 to 31 May 2012. There were 59 left knees and 51 right knees. All patients completed 1 year of follow-up. The mean (± standard deviation) age of the patients was 62.0 ± 9.8 (range, 33-86) years. The mean BMI was 27.7 ± 4.6 kg/m² (range, 18.3-46.8 kg/m²). The mean ESR was 23.35 ± 14.00 mm/h (range, 2.00-66.00 mm/h) and the mean CRP level was 1.3 ± 1.7 mg/L (range, 0.1-7.1 mg/L). The youngest patient in the study was 33 years old. His BMI was 25.9 kg/m². X-rays of his right knee showed KL grade 1 OA in the patellofemoral compartment and KL grade 2 OA in the tibiofemoral compartment. He denied any previous injury to his knee.

The mean pain and functional VAS scores are shown in Figures 1 and 2, respectively. There were statistically significant improvements in pain and functional VAS scores after injection at every follow-up visit when compared with the pre-injection scores (paired t test, P<0.0001 for all). Significant differences were also found between the pain and functional VAS scores at 1 year and at 6 weeks (P<0.001 and P<0.01, respectively), 3 months (P<0.003 and P<0.01, respectively), and 6 months (P<0.01 for both). The score differences between 6 weeks, 3 months, and 6 months were not significant.

Likert values were coded as 1 to 5 with 3 being no change and 1 being much reduced. A sign test against a median of 3 and an alternate hypothesis that the sample median was less than 3 was used. Significant reductions in pain and functional limitations were found at 6 weeks (P<0.001 for both), 3 months (P<0.001 for both), 6 months (P<0.001 for both), and 1 year (P<0.03 for both). The proportion of patients feeling reduced or much reduced pain was 74% at 6 weeks, 75% at 3 months, 62% at 6 months, and 49% at 1 year. The proportion of patients feeling no change in pain level (when compared with pre-injection level) was 23% at 6 weeks, 22% at 3 months, 33% at 6 months, and 43% at 1 year.

Mean 58.4 41.0 41.7 42.4 48.0
Standard deviation 17.6 18.9 21.0 23.5 20.6
Range 20.0-96.0 0-90.0 0-90.0 0-90.0 0-85.0

Mean 59.3 42.9 42.3 42.1 48.0
Standard deviation 17.5 21.1 19.7 21.4 20.1
Range 20.0-100.0 0-90.0 0-85.0 0-80.0 0-85.0
In a 26-week RCT, hylan G-F 20 single-injection formulation resulted in significant improvements in WOMAC pain score, observer-reported disease status, and patient-reported health status score.12 Our study is the first in Chinese patients to investigate the efficacy and safety of hylan G-F 20. The results show that the single 6-mL intra-articular injection could significantly improve pain and function in patients with primary knee OA. The beneficial effect could be sustained for up to 6 months. The VAS scores increased again by the 1-year follow-up visit, but the values were still significantly lower than the pre-injection levels. The 5-point Likert scale also revealed that about 75% of patients had reduced pain at 3 months, 62% at 6 months, and the percentage remained decreased at 50% at the 1-year follow-up visit. A total of 16.4% of patients experienced mild and self-limiting local adverse reactions. No pseudo-septic reaction or severe acute inflammatory reaction was reported.13 The interview was conducted by telephone at 2 weeks after injection, and was partly carried out by research assistants or nurses. Some patients might have confused ‘additional/new pain over the injection site’ with ‘pre-existing OA pain’, which led to the higher self-reported adverse event incidence. There are reports on HA causing adverse reactions; the most common of which is an inflammatory reaction or flare at the injection site characterised by injection site pain and swelling.15-16 Hypersensitivity reactions to HA or avian proteins are listed as contra-indications for use of many of the HA products. Many of the inflammatory responses appear to be due to the molecular structure of the HA, as naturally derived hyaluronic sources appear to be better tolerated than highly cross-linked hyaluronan.13,17,18 Leopold et al19 demonstrated increased frequency of acute local reaction to hylan G-F 20 in patients receiving more than one course of treatment. Recently a murine model study showed a single injection of hylan G-F 20 led to less inflammation and lower antibody reaction when compared with a three-shot series of injections. In our study, the 6-mL single injection preparation was used. This approach offers another advantage over a multiple-injection regimen as it reduces the number of consultations, therefore saves money and manpower in government hospitals with limited health care resources.

The serial knee radiographs in our study did not show any changes (either progression or regression) of the radiological severity of OA after hylan G-F 20 injection. To date, there is no concrete evidence in the literature to support the disease-modifying effect of HA injection. The radiographic KL grading system may not be sensitive enough to detect minor changes in the articular cartilage. We also did not have a control group for comparison. In a magnetic
resonance imaging–based RCT on articular cartilage volume change after four courses of hylan G-F 20 injection at 6-month intervals, the authors claimed that there was less cartilage loss in the treatment group at 24 months (2.7% over the medial tibial plateau and 2.6% over the lateral tibial plateau).20 Whether these differences are clinically significant is doubtful, however. We could not find any specific factors predicting good clinical response in our patients. This could be due to the relatively small sample size and the heterogeneity of our patients. The pre-injection parameters we investigated may not be sufficiently sensitive to survive the analysis.

There are a few limitations to this study. The pain and functional VAS scores were used because we believe they are patient-reported outcome measures, which would better reflect the clinical efficacy from the patients’ perspectives. The VAS scores are also easy to use, especially in the setting of a multicentre study. We did not include parameters such as knee range of motion, walking tolerance, or other knee scores as they were not the primary objectives of our study. It is well known that the placebo effect may account for 30% of the perceived benefits of medical treatment.21 We could not ascertain how much of the pain relief and functional improvement were attributable to the true therapeutic effects of hylan G-F 20 in view of the nature of our study design. A prospective, blinded, RCT may be able to eliminate the potential confounding factors and information bias. Changes in other treatment modalities during the follow-up period were not compared because of the potential complexity. It is difficult to standardise conservative treatment in terms of oral medication and exercise therapy, simply because patients with advanced knee OA may need stronger analgesics. Patients would also have a high non-compliance rate if we forced them to follow a single regimen. We decided to let all patients carry on with their usual conservative management and asked them if there were any changes in the pain and functional VAS scores during each follow-up after the viscosupplement injection.

**Conclusion**

This prospective, multicentre study showed that single intra-articular injection of 6-mL hylan G-F 20 was effective in providing statistically significant pain relief and functional improvement up to 1 year in Chinese patients with primary knee OA. Although adverse events were not uncommon, all of them were mild and self-limiting. Viscosupplementation with hylan G-F 20 could be a safe and beneficial option in managing patients with knee OA.

**Declaration**

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All patients purchased their own injection.

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**References**

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