BMC Musculoskeletal Disorders

RESEARCH

Open Access

Effectiveness and safety of human placenta hydrolysate injection into subacromial space in patients with shoulder impingement syndrome: a single-blind, randomized trial

Du Hwan Kim[1*], Myung Woo Park[1], Hyun Iee Shin[1], Byung Chan Lee[1], Don-Kyu Kim[1], Chul-Hyun Cho[2] and Ye-Ji Kim[2]

Abstract

Background Human placental hydrolysate (hPH) contains anti-inflammatory substances. This study aimed to analyze whether injecting hPH into the subacromial space could reduce pain in patients with shoulder impingement syndrome.

Methods This single-blind, randomized controlled study enrolled 50 patients with shoulder impingement syndrome who were randomly assigned to either the hPH or placebo groups. All patients received three ultrasound-guided subacromial space injections of 4 mL hPH or normal saline every week. Outcome measurements included the Visual Analog Scale (VAS) score during daily activity, Shoulder Pain and Disability Index (SPADI), and EuroQoL 5-Dimension 5-Level (EQ-5D-5L) utility index. Patients were followed up for nine weeks after the last injection.

Results Significant differences were noted in the VAS ($p < 0.001$) during daily activity, SPADI total score ($p < 0.001$), and EQ-5D-5L utility index ($p < 0.001$) nine weeks after the last injection between the hPH group and placebo group. Significant time effects were observed for all outcome measurements (all $p < 0.001$) in the hPH group but not in the placebo group. No severe complications, such as local infections or laboratory abnormalities, were reported during this study.

Conclusions Subacromial injections showed significant improvement in pain, functional level, and quality of life in patients with shoulder impingement syndrome. Therefore, hPH can be used as an alternative treatment for shoulder impingement syndrome.

Trial registration The trial was registered on www.Clinicaltrials.gov (NCT05528705, Registration Date: 06/09/2022).

Keywords Shoulder impingement syndrome, Shoulder Pain, Human placenta hydrolysate, Inflammation, Synovitis

Background

Shoulder pain is a common symptom of musculoskeletal disorders, with a prevalence of approximately 16–26%. [1] Shoulder impingement syndrome is a common condition that causes shoulder pain and accounts for 44–65% of all shoulder pain complaints [2]. The most common causes of shoulder impingement syndrome are osteophyte abnormalities or compression of the rotator

*Correspondence:
Du Hwan Kim
ripheonix@cau.ac.kr
[1] Department of Physical Medicine and Rehabilitation, College of Medicine, Chung-Ang University, Seoul, Republic of Korea
[2] Department of Orthopedic Surgery, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Republic of Korea

cuff muscles or the subdeltoid bursa. When the arm is abducted, the humerus moves closer to the acromion process, causing impingement due to structural abnormalities based on the osteophytes of the acromion, or functional abnormalities that cause the humerus to move upward due to muscle imbalance between the deltoid and rotator cuff muscles during abduction [3]. Timely treatment of shoulder impingement syndrome is important because it can lead to rotator cuff damage and decreased motor function, resulting in a decreased quality of life. [4, 5] Representative conservative treatment options include anti-inflammatory drugs, local steroid injections, and physical therapy. [6] Conservative treatments can reduce shoulder pain and subacromial inflammation; however, they only provide temporary pain relief, and most nonsteroidal anti-inflammatory drugs (NSAIDs) have gastrointestinal and nephrogenic side effects. [2, 7]

Human placenta hydrolysate (hPH) contains essential amino acids, collagen-derived peptides, steroid hormones, growth factors, and cytokines such as hepatocyte growth factor, known to have growth-promoting, antioxidant, and anti-inflammatory properties. [8–11] It is a natural substance with significant therapeutic potential for pain treatment because it contains various biologically active substances that exert pain-reducing effects. [10, 12] hPH may inhibit inflammatory mediators of nitric oxide, tumor necrosis factor-α (TNF-*α*), inducible nitric oxide synthase, and cyclooxygenase-2 (COX-2) in vitro *study*. [12, 13] An in vivo study showed its effects such as increased pain threshold and time to pain response [14].

hPH is expected to modulate the inflammatory process in musculoskeletal disorders such as shoulder impingement syndrome. However, there is little known about the clinical effectiveness of hPH injections in patients with shoulder impingement syndrome. This study aimed to determine the effectiveness and safety of hPH injections into subacromial space in treating shoulder impingement syndrome.

Methods

For this prospective randomized controlled trial, we recruited patients who visited shoulder outpatient clinics at two tertiary medical centers in South Korea between September 2022 and October 2023. Patients who met the eligibility criteria and provided informed consent were enrolled and randomly assigned to the hPH group or the normal saline injection (placebo) group. All patients provided written informed consent. The randomization code was generated by blocked randomization. Randomization was based on concealed random allocation using sealed opaque envelopes. The investigators administering the injections were not blinded to the allocation of patients but to the outcome measurements, while the patients were blinded to their allocation. All data of the patients were stored in a separate locked placed and maintained security. This study was approved by the Institutional Review Boards of Chung-Ang University Hospital (IRB No. 2206–013–511) and Keimyung University Dongsan Hospital (IRB No. DSMC 2023–02–022) and was prospectively registered at ClinicalTrials. gov (NCT05528705, Registration Date: 06/09/2022). The data collection, analysis, and reporting in this study were in accordance with the guideline of CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Patients

Patients were included in the study if they (1) had shoulder pain that required an examination due to a suspected rotator cuff lesion or injury; (2) had at least three of the five tests (Hawkins, Neer, painful arc between 60 and 120°of abduction, empty can, and resistance external rotation) that were positive [15, 16]; (3) had significant pain on a visual analog scale (VAS) of 30 mm or more during activity; and (4) had shoulder pain for more than three months. Patients were excluded from the study if they (1) had definite partial or full-thickness tears of the rotator cuff on ultrasonography, (2) had other shoulder conditions such as frozen shoulder, rheumatoid arthritis, and osteoarthritis, (3) had received medication or injections related to shoulder pain, (4) had a history of shoulder surgery, (5) were pregnant, and (6) had psychiatric disorders.

All patients who met the inclusion criteria underwent plain radiography and ultrasonography to rule out other mimicking conditions, such as osteoarthritis, rotator cuff tear or calcific tendinitis, rotator interval, or inferior capsular thickening.

Procedure

Subacromial space injections were performed under ultrasonographic guidance by two shoulder specialists with over 15 years of experience in the field. The randomized groups received a total of three injections of 4 mL hPH or normal saline injections, once a week for the first three weeks. During the procedure, patients were placed on a bed with their palms on their buttocks. The investigator identified the subacromial space between the deltoid and supraspinatus muscles using ultrasonography, and 4 mL of hPH or normal saline were injected into the subacromial space from the lateral to the medial side as a bolus injection.

All patients were instructed on behavioral modifications, such as avoidance of overhead activities and a home-based exercise program to enhance scapular stabilization, emphasizing scapular downward rotation and flexibility of the glenohumeral and scapulothoracic joints,

from a single physical therapist and were allowed to perform home-based exercises at least once a day. Stretching exercise includes 3 times repetitions of corner stretch, cross body horizontal adduction stretch, and sleeper stretch holding 30 s. Stabilization and strengthening exercise consist of 2 sets of 15 repetitions of scapular retraction with standing, isometric adduction, internal rotation and external rotation exercise, diagonal and scaption exercise with resistance band, and scapular protractions with lying down. The patients were informed to refrain from receiving acupuncture or additional treatment from other hospitals.

Human placenta hydrolysate (hPH, Laennec®)

hPH is a stock solution prepared by extracting and hydrolyzing the placenta. Laennec® is an hPH type manufactured by Green Cross Wellbeing Co., Ltd. (Seoul, South Korea). Briefly, hPH was prepared by hydrolyzing the placenta with HCl and pepsin. The final product was in liquid form and stored in 2 mL ampules, which contained many peptides with molecular weights between 100 Da and 2 000 Da and a high content of amino acids.

Outcome measurements

Outcome measurements included the VAS score during activity, Shoulder Pain and Disability Index (SPADI), and EuroQoL 5-Dimension 5-Level (EQ-5D-5L) utility index. Outcomes were evaluated at six-time points: T0 (baseline), T1 (1 week after the first injection), T2 (1 week after the second injection), T3 (1 week after the third injection), T4 (3 weeks after the third injection), and T5 (9 weeks after the third injection). Outcome measurements were evaluated during visits, except for the evaluation at T3, which was conducted telephonically. The researchers surveyed the outcome measurements and were blinded to patient allocation.

The primary outcome was the VAS (0–100 mm) during daily activities at T5. Secondary outcomes were the total, pain, and disability (SPADI) score and EQ-5D-5L utility index. The EQ-5D-5L, developed by the European Quality of Life Group, is currently one of the most widely used questionnaires in research on health-related quality of life. The EQ-5D-5L utility index was calculated using quality weights for mobility, self-care, daily activities, pain/discomfort, and anxiety/depression scores. [17] Safety assessments included vital signs and laboratory tests such as complete blood count, and chemistry tests including albumin, uric acid, glucose, aspartate aminotransferase, alanine aminotransferase, creatinine, C-reactive protein, and urine analysis at all visits except at T3.

Statistical analysis

The sample size was calculated by referring to Dadgostar et al.. [18] The expected effect size of 0.93 was calculated based on previous reports confirming changes in the VAS. A sample size of 38 provided 80% power to detect differences between groups at a significance level of 0.05. A total of 50 people were recruited, 25 per group, considering a 20% dropout rate.

This study used an intention-to-treat statistical analysis. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA). Differences between groups were tested using a two-sample t-test or Wilcoxon rank-sum test. We planned to further analyze the differences between the two groups using analysis of covariance (ANCOVA) if the covariate was expected to influence the outcome. Paired t-test or Wilcoxon signed-rank test was used to analyze the difference in outcome measurements between two time points within the same group. A P-value of < 0.05 was considered significant.

Results

Patient flow and baseline characteristics

This study followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Fig. 1). A total of 50 patients were randomized, and three dropped out. One patient in the hPH group withdrew by the investigator's judgment owing to other injections after T3, and two patients in the placebo group gave up consent after T0. None of the enrolled patients received any additional treatment for shoulder pain during the follow-up period. Despite of randomization, the mean age of the patients in the placebo group tended to be higher than that of the hPH group. (Table 1). All patients over 60 years were allocated to the placebo group. Except for age, no significant differences were noted in the baseline demographics between the hPH and placebo groups (Table 1).

Outcome measurements

VAS score

A significant difference was noted in the VAS scores at T1 ($p = 0.002$), T2 ($p < 0.001$), T3 ($p < 0.001$), T4 ($p = 0.002$), and T5 ($p < 0.0001$) between the hPH and placebo groups using ANCOVA. A significant improvement was noted in the VAS score from T0 to T5 in the hPH group ($p < 0.001$). However, there was no significant difference between T0 and T5 in the placebo group ($p = 0.155$) (Fig. 2 and Table 2).

SPADI score (total, pain, and disability)

Significant differences in the total SPADI scores at T1 ($p = 0.034$), T2 ($p = 0.004$), T3 ($p < 0.001$), T4 ($p < 0.001$),

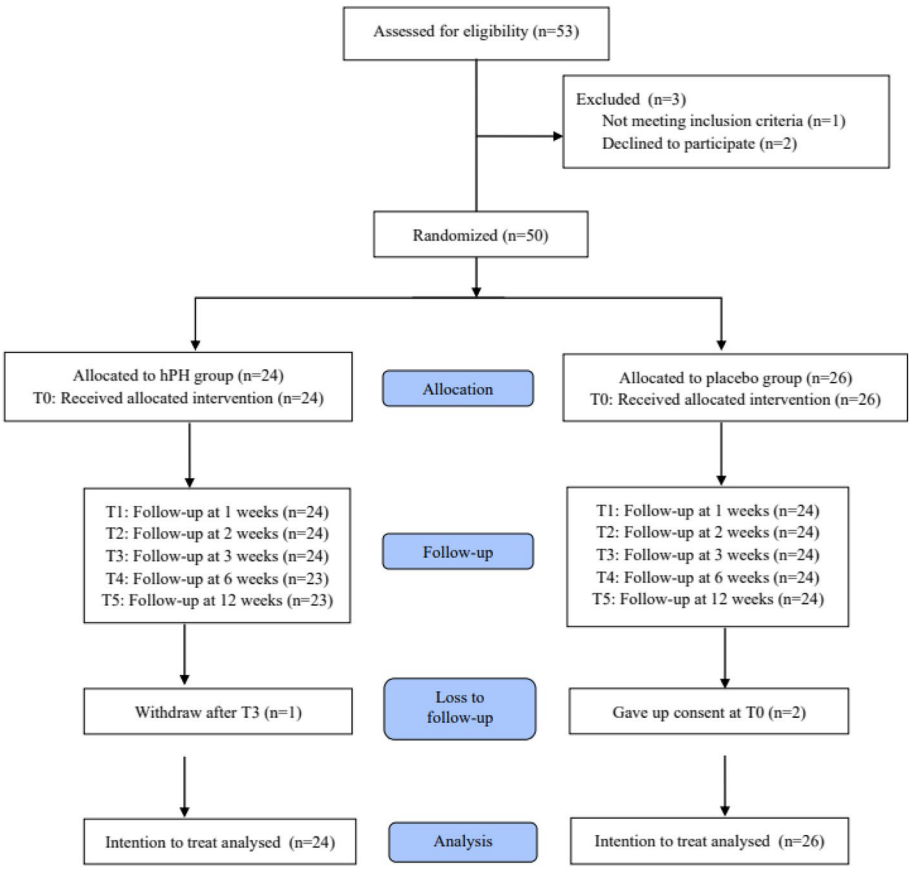

Fig. 1 Diagram of the analysis group

Table 1 Baseline demographics and clinical characteristics

	hPH group ($n=24$)	placebo group ($n=26$)
Age	41.3 ± 10.2	47.5 ± 11.7
Age, n		
20–40	11	8
40–60	13	14
60 +		4
Sex, Male/Female	16/8	13/13
Diabetes Mellitus, n	0	1
Hyperlipidemia, n	1	3
Site, Right/Left	10/14	10/16
VAS(mm)	50.1 ± 13.1	56.5 ± 15.6
SPADI total score	42.6 ± 20.4	43.0 ± 19.6
SPADI pain score	52.5 ± 20.7	51.7 ± 19.4
SPADI disability score	28.9 ± 18.8	33.9 ± 21.2
EQ-5D-5L utility index	0.80 ± 0.08	0.82 ± 0.05

Values are presented as the mean ± standard deviation

hPH, Human placenta hydrolysate, *VAS* Visual Analog Scale during activity, *SPADI* Shoulder Pain and Disability Index, *EQ-5D-5L* EuroQoL 5-Dimension 5-Level

and T5 ($p<0.001$) between the hPH group and placebo group using ANCOVA. There was a significant improvement in the total SPADI score from T0 to T5 in the hPH group ($p<0.001$); however, there was no significant difference between T0 and T5 in the placebo group ($p=0.304$) (Fig. 2 and Table 2).

A significant difference was noted in the SPADI pain scores at T1 ($p=0.038$), T2 ($p=0.003$), T3 ($p<0.001$), T4 ($p<0.001$), and T5 ($p<0.001$) between the hPH and placebo groups using ANCOVA. A significant improvement was noted in the SPADI pain score from T0 to T5 in the hPH group ($p<0.001$). However, no significant differences were noted between T0 and T5 in the placebo group ($p=0.161$) (Fig. 2 and Table 2).

A significant difference was noted in the SPADI disability scores at T1 ($p<0.001$), T2 ($p<0.001$), T3 ($p<0.001$), T4 ($p<0.001$), and T5 ($p<0.001$) between the hPH and placebo groups using ANCOVA. A significant improvement was noted in the SPADI disability score from T0 to T5 in the hPH group ($p<0.001$). However, no significant differences were noted between T0 and T5 in the placebo group ($p=0.342$) (Fig. 2 and Table 2).

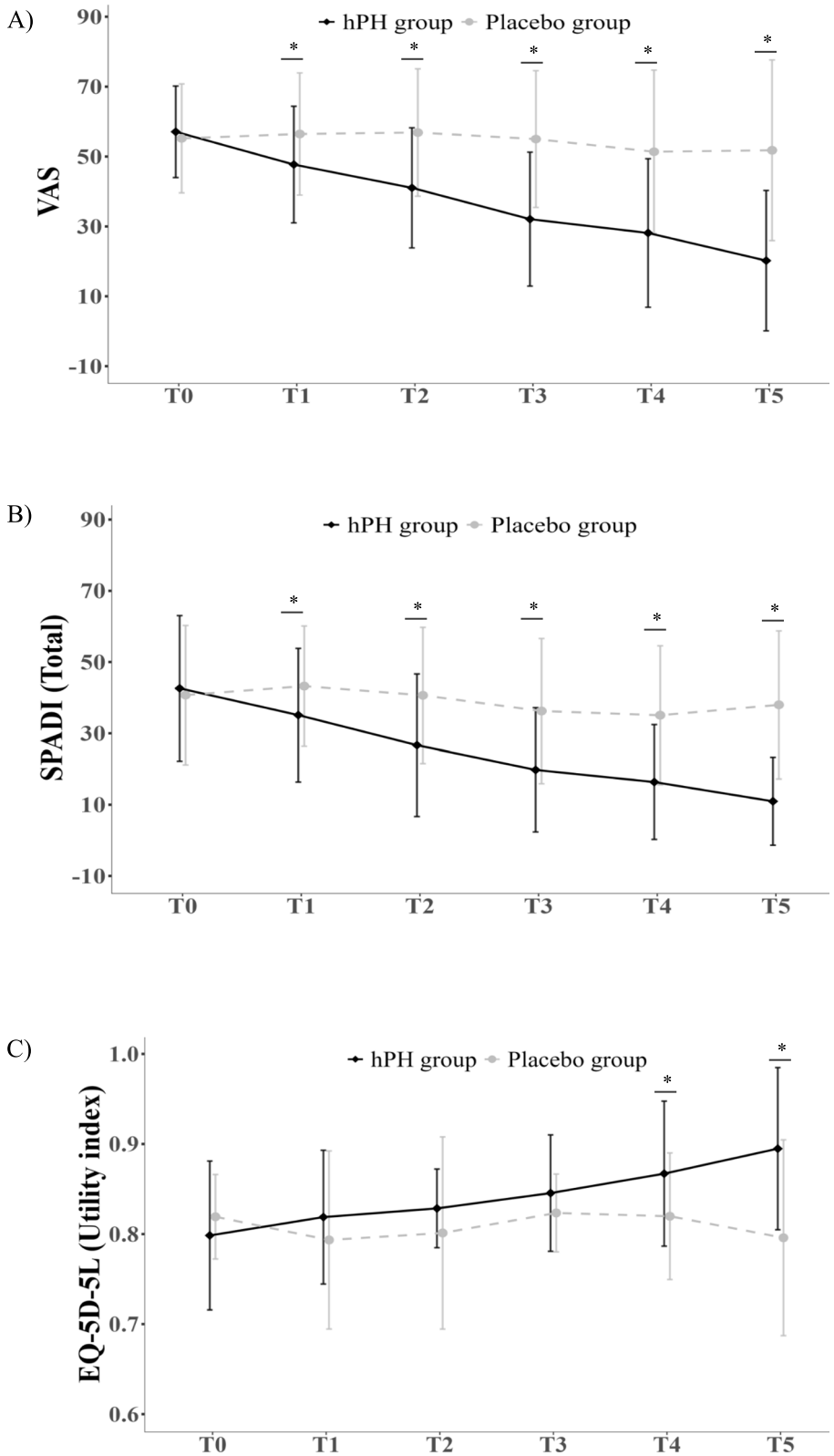

Fig. 2 Outcome measurements of VAS (**A**), SPADI total score (**B**), and EQ-5D-5L utility index (**C**) * Statistically significant differences between the hPH and placebo groups using ANCOVA hPH, Human placenta hydrolysate; VAS, Visual Analog Scale during activity; SPADI, Shoulder Pain and Disability Index; EQ-5D-5L, EuroQoL 5-Dimension 5-Level

Table 2 Changes in the VAS, SPADI (total, pain, and disability), and EQ-5D-5L utility index after hPH or normal saline injections

	group	T0	T1	T2	T3	T4	T5	*P*-value [c](T0 vs T5)
VAS	hPH group ($n=24$)	57.1 ± 13.1	47.7 ± 16.7	41.0 ± 17.2	32.1 ± 19.2	28.1 ± 21.3	20.2 ± 20.1	< 0.001 *
	placebo group ($n=26$)	55.2 ± 15.6	56.5 ± 17.5	56.9 ± 18.2	55.0 ± 19.6	51.4 ± 23.4	51.8 ± 25.9	0.155
	P-value[a] (hPH vs placebo)	0.646	0.123	0.003 *	< 0.001 *	0.002 *	< 0.001 *	
	P-value [b] (hPH vs placebo)		0.002*	< 0.001 *	< 0.001 *	< 0.001 *	< 0.001 *	
	effect size (Cohen's d, [95% CI])	0.131 [−0.439, 0.701]	−0.512 [−1.103, 0.078]	−0.894 [−1.503, −0.284]	−1.184 [−1.813, −0.554]	−1.041 [−1.660, −0.422]	−1.365 [−2.010, −0.719]	
	effect size (Cohen's f, [95% CI])		0.456 [0.147, 0.761]	0.648 [0.324, 0.966]	0.759 [0.425, 1.087]	0.672 [0.346, 0.992]	0.933 [0.579, 1.279]	
SPADI (total)	hPH group ($n=24$)	42.6 ± 20.4	35.1 ± 18.7	26.7 ± 20.0	19.8 ± 17.4	16.4 ± 16.1	11.0 ± 12.3	< 0.001 *
	placebo group ($n=26$)	40.7 ± 19.6	43.2 ± 16.9	40.6 ± 19.1	36.3 ± 20.4	35.1 ± 19.5	38.0 ± 20.8	0.304
	P-value[a] (hPH vs placebo)	0.738	0.121	0.015 *	0.003 *	< 0.001 *	< 0.001 *	
	P-value[b] (hPH vs placebo)		0.034 *	0.004 *	< 0.001 *	< 0.001 *	< 0.001 *	
	effect size (Cohen's d, [95% CI])	0.095 [−0.474, 0.665]	−0.457 [−1.045, 0.132]	−0.715 [−1.314, −0.116]	−0.869 [−1.477, −0.261]	−1.046 [−1.666, −0.427]	−1.582 [−2.248, −0.916]	
	effect size (Cohen's f, [95% CI])		0.384 [0.075, 0.685]	0.504 [0.191, 0.811]	0.558 [0.242, 0.870]	0.632 [0.310, 0.949]	0.921 [0.569, 1.266]	
SPADI (pain)	hPH group ($n=24$)	52.5 ± 20.7	45.0 ± 21.1	34.8 ± 23.1	25.8 ± 19.7	22.1 ± 18.7	15.3 ± 16.6	< 0.001 *
	placebo group ($n=26$)	51.7 ± 19.4	53.0 ± 16.8	50.2 ± 20.3	43.9 ± 20.0	43.3 ± 21.0	47.1 ± 22.9	0.161
	P-value[a] (hPH vs placebo)	0.887	0.153	0.020 *	0.002 *	0.001 *	< 0.001 *	
	P-value[b] (hPH vs placebo)		0.038 *	0.003 *	< 0.001 *	< 0.001 *	< 0.001 *	
	effect size (Cohen's d, [95% CI])	0.040 [−0.529, 0.610]	−0.419 [−1.006, 0.168]	−0.705 [−1.304, −0.106]	−0.910 [−1.521, −0.300]	−1.068 [−1.689, −0.447]	−1.592 [−2.259, −0.925]	
	effect size (Cohen's f, [95% CI])		0.384 [0.075, 0.685]	0.504 [0.191, 0.811]	0.558 [0.241, 0.870]	0.632 [0.309, 0.949]	0.921 [0.569, 1.2661]	
SPADI (disability)	hPH group ($n=24$)	36.4 ± 21.7	28.9 ± 18.8	21.6 ± 19.4	16.0 ± 17.0	12.8 ± 15.4	8.3 ± 10.7	< 0.001 *
	placebo group ($n=26$)	33.9 ± 21.2	37.2 ± 18.1	34.7 ± 19.6	31.5 ± 21.2	29.9 ± 20.1	32.3 ± 21.0	0.342
	P-value[a] (hPH vs placebo)	0.677	0.129	0.011 *	0.003 *	< 0.001 *	< 0.001 *	
	P-value[b] (hPH vs placebo)		< 0.001 *	< 0.001 *	< 0.001 *	< 0.001 *	< 0.001 *	
	effect size (Cohen's d, [95% CI])	0.119 [−0.451, 0.688]	−0.446 [−1.034, 0.142]	−0.673 [−1.271, −0.076]	−0.805 [−1.409, −0.200]	−0.952 [−1.565, −0.339]	−1.440 [−2.092, −0.7881]	
	effect size (Cohen's f, [95% CI])		0.521 [0.207, 0.8301]	0.573 [0.255, 0.885]	0.592 [0.272, 0.905]	0.625 [0.303, 0.942]	0.888 [0.540, 1.229]	

Table 2 (continued)

	group	T0	T1	T2	T3	T4	T5	*P*-value [c](T0 vs T5)
EQ-5D-5L (Utility index)	hPH group ($n=24$)	0.80 ± 0.08	0.82 ± 0.07	0.83 ± 0.04	0.85 ± 0.06	0.87 ± 0.08	0.89 ± 0.09	< 0.001 *
	placebo group ($n=26$)	0.82 ± 0.05	0.79 ± 0.10	0.80 ± 0.11	0.82 ± 0.04	0.82 ± 0.07	0.80 ± 0.11	0.304
	P-value[a] (hPH vs placebo)	0.700	0.501	0.737	0.137	0.073	0.001 *	
	P-value[b] (hPH vs placebo)		0.053	0.099	0.054	0.021 *	< 0.001 *	
	effect size (Cohen's d, [95% CI])	−0.313 [−0.885, 0.260]	0.290 [−0.294, 0.874]	0.335 [−0.250, 0.920]	0.401 [−0.186, 0.988]	0.626 [0.031, 1.221]	0.991 [0.375, 1.607]	
	effect size (Cohen's f, [95% CI])		0.191 [0.000, 0.485]	0.190 [0.000, 0.484]	0.230 [0.000, 0.525]	0.329 [0.000, 0.627]	0.548 [0.232, 0.859]	

Values are presented as the mean ± standard deviation

* Statistically significant difference between the hPH and placebo groups

[a] Comparison between the hPH group and placebo group using two-sample t-test or Wilcoxon's rank sum test

[b] Comparison between the hPH group and placebo group using ANCOVA

[c] Comparison between T0 and T5 using paired t-test or Wilcoxon signed rank test

hPH, Human placenta hydrolysate; VAS, Visual Analog Scale during activity; SPADI, Shoulder Pain and Disability Index; EQ-5D-5L, EuroQoL 5-Dimension 5-Level; CI, confidence interval

EQ-5D-5L utility index

A significant difference was noted in the EQ-5D-5L utility index at T4 ($p=0.021$), T5 ($p<0.001$) between the hPH and placebo groups using ANCOVA. A significant improvement was noted in the EQ-5D-5L utility index from T0 to T5 in the hPH group ($p<0.001$). However, no significant difference was noted between T0 and T5 in the placebo group ($p=0.304$) (Fig. 2 and Table 2).

Safety evaluation variables

No unexpected adverse reactions were observed, and no significant changes were noted in the vital signs or laboratory test results of the study participants (Supplementary 1).

Discussion

To our knowledge, this is the first clinical trial to prove the effectiveness and safety of hPH injections into the subacromial space for shoulder impingement syndrome. This study aimed to clarify whether subacromial injections have pain relief in patients with shoulder impingement syndrome. It demonstrated that compared to placebo injections, three serial injections of hPH into the subacromial space led to significant progressive improvement in pain and function up to 9 weeks after the last third injection.

Shoulder impingement syndrome is characterized by pain provoked by shoulder movements above the horizontal plane because the acromion can irritate the rotator cuff tendons. There is clear evidence that tendons injured by impingement produce inflammatory cytokines, such as interleukin −1beta, TNF-alpha, and tissue growth factor-β in the subacromial tissue and joint capsule. [19–23]

Our authors postulated that hPH may be a potential treatment for shoulder impingement syndrome. This is based on the background that several studies have proven that hPH has antioxidant, anti-apoptotic, and anti-inflammatory properties activities. [9, 24–26] For example, hPH treatment led to less pronounced fibrosis and a reduction in TNF-α and metalloproteinase (MMP)−9 expression in a non-alcoholic steatohepatitis-mouse model. [13, 24] Bak et al. reported that hPH inhibited hydrogen peroxide-induced cell death on muscle atrophy through myostatin gene expression. [27] However, in the field of musculoskeletal disorders, there is insufficient evidence of the anti-inflammatory effects of hPH. [25] One study suggested that hPH may modulate the inflammation in the pathogenesis of musculoskeletal disorder. [28] In that study, there was a significant in vivo reduction in MMP-2 and MMP-9 levels and radiographic severity in the hPH-treated group in a rat model of monoiodoacetate-induced osteoarthritis. [28] The authors suggested that hPH might inhibit the transition of chondrocytes to stress-induced premature senescence, thereby providing favorable conditions for cartilage regeneration. In our

study, we expected that hPH containing high levels of growth factors, anabolic cytokines, and essential amino acids might have the potential to regenerate the inflamed rotator cuff and subacromial bursa and attenuate inflammation. Our results indirectly demonstrate an anti-inflammatory effect in shoulder impingement syndrome, related to the pathophysiological inflammation of the subacromial bursa and rotator cuff triggered by mechanical factors.

This study showed relatively weak difference in the VAS and SPADI scores between the hPH and placebo groups one week after the first injection. In contrast, the differences persisted from 1 week after the second injection to 9 weeks after the last injection. This difference becomes more evident over time. This result suggested the possibility that the single dose in the first injection was insufficient or that hPH has the characteristic of having a cumulative effect through successive injections. There is no standardized hPH protocol for treating musculoskeletal disorders associated with hPH. Further research is required to determine the most effective protocols for hPH administration.

The pharmacological mechanism by which hPH regulates pain in patients with shoulder impingement syndrome remains unclear. It is speculated that hPH may be involved in a pathway different from that of NSAIDs, among other pathways that regulate pain. Most NSAIDs inhibit both COX-1 and COX-2, resulting in anti-inflammatory effects of COX-2 inhibition as well as side effects of COX-1 inhibition, such as gastric ulceration and kidney damage. [7, 29] It also inhibits the production of thromboxane A2 by platelets, leading to complications such as the inhibition of platelet aggregation and prolonged bleeding time. [30, 31] However, hPH contains amino acid complexes, collagen-derived peptides, and growth factors and is known to inhibit the expression of inflammatory cytokines such as TNF-α and COX-2 rather than COX-1. [9, 11] Although there were limitations to the short duration of follow-up in this study, there were no common side effects of NSAIDs, such as gastric discomfort and kidney injury, after hPH injections.

Our study had several limitations. First, this study did not demonstrate the long-term effects of hPH because of its short follow-up period. Second, despite randomization, there was a tendency of age differences between two groups. Because we analyzed the outcomes using the ANCOVA to control the factor of age, the effect of age difference between two groups might be negligible. Third, this study only evaluated changes in clinical outcome measurements. Further studies may be necessary to elucidate the anti-inflammatory effects using histological and radiological methods, such as immunohistochemistry and vascularity or bursa thickness on ultrasonography. Fourth, we did not survey compliance with home-based exercise and behavioral modifications, although exercise and behavioral factors can affect the outcomes. Fifth, we did not evaluate the subaromial space and the type of acromion radiographically although these factors could affect the results.

This study demonstrated the pain-relieving effect of hPH injections in patients with shoulder impingement syndrome. hPH injections have clinical implications as a safe alternative treatment for patients at high risk of side effects from oral NSAIDs and local steroid injections.

Conclusions

Subacromial injections of hPH significantly improved the pain, functional level, and quality of life in patients with shoulder impingement syndrome. No adverse effects were observed after injecting hPH into the subacromial space. Therefore, hPH may be a novel alternative treatment for shoulder impingement syndrome.

Abbreviations

hPH	Human placenta hydrolysate
VAS	Visual Analog Scale
SPADI	Shoulder Pain and Disability Index
EuroQoL 5	Dimension 5-Level (EQ-5D-5L)
NSAIDs	Nonsteroidal anti-inflammatory drugs
TNF-α	Tumor Necrosis Factor-α
COX	Cyclooxygenase
T0	Baseline
T1	One week after the first injection
T2	At one week after the second injection
T3	One week after the third injection
T4	At three weeks after the third injections
T5	At nine weeks after the third injection

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-024-08266-4.

Supplementary Material 1: Comparison of the changes of laboratory tests between baseline and follow-up.

Supplementary Material 2.

Acknowledgements

Drug for this study was supported by Green Cross WellBeing, Korea.

Authors' contributions

DH.K. designed the study. MW.P., HI.S., BC.L., C-H.C., Y-J.K., and DH.K. analyzed and interpreted the data. DH.K. drafted the manuscript. DH.K., D-K.K. and C-H.C. revised the manuscript. All the authors critically revised the manuscript for intellectual content and approved the final version. All authors agree to be accountable for the work and to ensure that any questions related to the accuracy and integrity of the paper are investigated and properly resolved.

Funding

No funding was received for this research.

Data availability

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in line with the principles of the Declaration of Helsinki and approved by the Institutional Review Board Committee of Chung-Ang University Hospital (IRB No. 2206–013-511) and Keimyung University Dongsan Hospital (IRB No. DSMC 2023–02-022). This trial has been registered at www.ClinicalTrials.gov (NCT05528705). Informed consent was obtained from all individual participants prior to recruitment in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 3 June 2024 Accepted: 27 December 2024
Published online: 03 January 2025

References

1. Mitchell C, Adebajo A, Hay E, Carr A. Shoulder pain: diagnosis and management in primary care. BMJ. 2005;331(7525):1124–8.
2. Consigliere P, Haddo O, Levy O, Sforza G. Subacromial impingement syndrome: management challenges. Orthop Res Rev. 2018;10:83–91.
3. Garving C, Jakob S, Bauer I, Nadjar R, Brunner UH. Impingement Syndrome of the Shoulder. Dtsch Arztebl Int. 2017;114(45):765–76.
4. Greenberg DL. Evaluation and treatment of shoulder pain. Med Clin North Am. 2014;98(3):487–504.
5. Welsh TP, Yang AE, Makris UE. Musculoskeletal Pain in Older Adults: A Clinical Review. Med Clin North Am. 2020;104(5):855–72.
6. Uhl RL, Roberts TT, Papaliodis DN, Mulligan MT, Dubin AH. Management of chronic musculoskeletal pain. J Am Acad Orthop Surg. 2014;22(2):101–10.
7. Meek IL, Van de Laar MA. H EV: Non-Steroidal Anti-Inflammatory Drugs: An Overview of Cardiovascular Risks. Pharmaceuticals (Basel). 2010;3(7):2146–62.
8. Choi JY, Lee K, Lee SM, Yoo SH, Hwang SG, Choi JY, Lee SW, Hwang JS, Kim KK, Kang HC, et al. Efficacy and safety of human placental extract for alcoholic and nonalcoholic steatohepatitis: an open-label, randomized, comparative study. Biol Pharm Bull. 2014;37(12):1853–9.
9. Gwam C, Ohanele C, Hamby J, Chughtai N, Mufti Z, Ma X. Human placental extract: a potential therapeutic in treating osteoarthritis. Ann Transl Med. 2023;11(9):322.
10. Shin EH, Kim M, Hada B, Oh CT, Jang MJ, Kim JY, Han HJ, Kim DH, Choi BH, Kim BS. Effects of Human Placenta Extract (Laennec) on Ligament Healing in a Rodent Model. Biol Pharm Bull. 2019;42(12):1988–95.
11. Sur TK, Biswas TK, Ali L, Mukherjee B. Anti-inflammatory and anti-platelet aggregation activity of human placental extract. Acta Pharmacol Sin. 2003;24(2):187–92.
12. Nair B, Elmore AR. Final report on the safety assessment of human placental protein, hydrolyzed human placental protein, human placental enzymes, human placental lipids, human umbilical extract, placental protein, hydrolyzed placental protein, placental enzymes, placental lipids, and umbilical extract. Int J Toxicol. 2002;21(Suppl 1):81–91.
13. Yamauchi A, Kamiyoshi A, Koyama T, Iinuma N, Yamaguchi S, Miyazaki H, Hirano E, Kaku T, Shindo T. Placental extract ameliorates non-alcoholic steatohepatitis (NASH) by exerting protective effects on endothelial cells. Heliyon. 2017;3(9):e00416.
14. Lee KH, Kim TH, Lee WC, Kim SH, Lee SY, Lee SM. Anti-inflammatory and analgesic effects of human placenta extract. Nat Prod Res. 2011;25(11):1090–100.
15. Schydlowsky P, Szkudlarek M, Madsen OR. Comprehensive supervised heavy training program versus home training regimen in patients with subacromial impingement syndrome: a randomized trial. BMC Musculoskelet Disord. 2022;23(1):52.
16. Witten A, Mikkelsen K, Wagenblast Mayntzhusen T, Clausen MB, Thorborg K, Hölmich P, Barfod KW. Terminology and diagnostic criteria used in studies investigating patients with subacromial pain syndrome from 1972 to 2019: a scoping review. Br J Sports Med. 2023;57(13):864–71.
17. Kim SH, Ahn J, Ock M, Shin S, Park J, Luo N, Jo MW. The EQ-5D-5L valuation study in Korea. Qual Life Res. 2016;25(7):1845–52.
18. Dadgostar H, Fahimipour F, Pahlevan Sabagh A, Arasteh P, Razi M. Corticosteroids or platelet-rich plasma injections for rotator cuff tendinopathy: a randomized clinical trial study. J Orthop Surg Res. 2021;16(1):333.
19. Blaine TA, Cote MA, Proto A, Mulcahey M, Lee FY, Bigliani LU. Interleukin-1β stimulates stromal-derived factor-1α expression in human subacromial bursa. J Orthop Res. 2011;29(11):1695–9.
20. Ellis I, Schnabel LV, Berglund AK. Defining the Profile: Characterizing Cytokines in Tendon Injury to Improve Clinical Therapy. J Immunol Regen Med. 2022;16:100059.
21. Farfaras S, Roshani L, Mulder J, Mitsios N, Hallström EK, Kartus JT. Increased levels of inflammatory markers in the subscapularis tendon and joint capsule in patients with subacromial impingement. Knee Surg Sports Traumatol Arthrosc. 2021;29(7):2228–36.
22. Sakai H, Fujita K, Sakai Y, Mizuno K. Immunolocalization of cytokines and growth factors in subacromial bursa of rotator cuff tear patients. Kobe J Med Sci. 2001;47(1):25–34.
23. von Wehren L, Blanke F, Todorov A, Heisterbach P, Sailer J, Majewski M. The effect of subacromial injections of autologous conditioned plasma versus cortisone for the treatment of symptomatic partial rotator cuff tears. Knee Surg Sports Traumatol Arthrosc. 2016;24(12):3787–92.
24. Bak DH, Na J, Choi MJ, Lee BC, Oh CT, Kim JY, Han HJ, Kim MJ, Kim TH, Kim BJ. Anti-apoptotic effects of human placental hydrolysate against hepatocyte toxicity in vivo and in vitro. Int J Mol Med. 2018;42(5):2569–83.
25. McIntyre JA, Jones IA, Danilkovich A, Vangsness CT Jr. The Placenta: Applications in Orthopaedic Sports Medicine. Am J Sports Med. 2018;46(1):234–47.
26. Mochizuki H, Kada T. Antimutagenic action of mammalian placental extracts on mutations induced in Escherichia coli by UV radiation, gamma-rays and N-methyl-N'-nitro-N-nitrosoguanidine. Mutat Res. 1982;95(2–3):457–74.
27. Bak DH, Na J, Im SI, Oh CT, Kim JY, Park SK, Han HJ, Seok J, Choi SY, Ko EJ, et al. Antioxidant effect of human placenta hydrolysate against oxidative stress on muscle atrophy. J Cell Physiol. 2019;234(2):1643–58.
28. Kim JK, Kim TH, Park SW, Kim HY, Kim S, Lee S, Lee SM. Protective effects of human placenta extract on cartilage degradation in experimental osteoarthritis. Biol Pharm Bull. 2010;33(6):1004–10.
29. Wallace JL. How do NSAIDs cause ulcer disease? Baillieres Best Pract Res Clin Gastroenterol. 2000;14(1):147–59.
30. Gengo FM, Rubin L, Robson M, Rainka M, Gengo MF, Mager DE, Bates V. Effects of ibuprofen on the magnitude and duration of aspirin's inhibition of platelet aggregation: clinical consequences in stroke prophylaxis. J Clin Pharmacol. 2008;48(1):117–22.
31. Saxena A, Balaramnavar VM, Hohlfeld T, Saxena AK. Drug/drug interaction of common NSAIDs with antiplatelet effect of aspirin in human platelets. Eur J Pharmacol. 2013;721(1–3):215–24.

Publisher's Note