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Therapeutic Effects of 35 kDa Hyaluronan Injection at Trigger Points in the Treatment of Myofascial Pain Syndrome

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Abstract

Objectives: This study aimed to evaluate the prolonged therapeutic effects of a 35 kDa molecular weight hyaluronan fragment (HA35) in alleviating pain associated with myofascial pain syndrome (MPS). Hyaluronan interacts with various receptors in the human body, including CD44, LYVE-1, RHAMM, and TLR2, and is well-known for its analgesic effects when used in intra-articular or ultrasound-guided nerve trunk injections. Studies have shown that hyaluronidase cleaves high molecular weight HA to generate HA35, a low molecular weight fragment with enhanced tissue permeability, capable of binding to HA receptors on cell surfaces to produce broad-spectrum analgesic effects. **Methods**: Ten patients diagnosed with MPS were treated and assessed in this study. HA35 was administered through injection at a dosage of 100 mg daily for 15 days. Patients evaluated their MPS, overall pain levels, and treatment satisfaction using the Numerical Pain Rating Scale (NPRS), the Global Pain Scale (GPS), and the Treatment Satisfaction Questionnaire for Medication (TSQM 1.4). Follow-up evaluations were performed three months post-treatment to assess the duration of therapeutic effects. **Results**: Significant improvements were observed in NPRS, GPS, and TSQM scores both during and after the treatment period ($P < 0.0001$). The analgesic effect of HA35 was maintained throughout the three-month follow-up period. **Conclusions**: HA35 provides effective and sustained relief from pain associated with MPS, demonstrating a prolonged therapeutic benefit.

Keywords

35 kDa Hyaluronan Fragment, HA35, Pain, Myofascial Pain Syndrome, Myofascial Trigger Points

1. Introduction

Myofascial pain syndrome (MPS) commonly occurs in individuals with various repetitive strain injuries [1] [2]. Epidemiological studies show that MPS is a widespread issue, with prevalence rates ranging from 30% to 85% among those with musculoskeletal disorders [3]. Clinically, MPS is marked by soft tissue pain and involvement of skeletal muscles, presenting as tender nodules and taut muscle bands known as myofascial trigger points (MTrPs) [4]-[8]. MTrPs are hyperirritable spots in the muscles that can trigger pain. These points are often associated with palpable nodules and tight muscle bands; applying pressure to these areas can worsen pain, cause local muscle twitching, and lead to referred pain [7] [8]. Diagnostic criteria for MPS vary and are frequently updated. In China, diagnosis requires meeting five primary criteria and at least one secondary criterion, while in the United States, meeting four criteria is usually sufficient [9]. These variations in criteria can sometimes lead to misdiagnosis or underdiagnosis [3] [10]. Nevertheless, precise identification of trigger points is essential for effective diagnosis and treatment [9] [11]. Current treatment options for MPS include pharmacotherapy (e.g., non-steroidal anti-inflammatory drugs [NSAIDs] and muscle relaxants) [3] [12], physical therapy (such as massage, stretching, and strengthening exercises) [3], trigger point injections, dry needling, and cognitive behavioral therapy (CBT) [13]-[19]. Despite the standardization of pain management approaches, existing treatments have notable limitations. NSAIDs, muscle relaxants, and antidepressants can have side effects affecting the gastrointestinal, hepatic, and renal systems [3] [20] [21]. Additionally, long and often ineffective treatments, along with high costs, can place substantial economic and time burdens on patients. Emerging therapies, like stem cell therapy, face challenges due to limited clinical evidence, high costs, technical complexities, and potential risks [22].

Recent research highlights the growing evidence supporting the use of hyaluronan (HA) and its fragments in managing pain, including inflammatory pain such as shoulder and neck pain, neuropathic pain from herpes zoster, chronic wound pain, cancer pain, and pain from bone metastases [23]-[25]. Specifically, the 35 kDa low molecular weight hyaluronan fragment (HA35), obtained through the enzymatic cleavage of high molecular weight HA with recombinant human sperm or bovine testicular hyaluronidase, has shown considerable promise [26] [27]. Clinical studies by Xu have demonstrated that a single local injection of HA35 into the nerve trunk significantly reduces inflammation-related shoulder and neck pain [23]. Additionally, research suggests that HA35 may alleviate pain by inhibiting TRPV1 ion channel activation and blocking Ca2+ influx [28] [29]. A study involving 98 patients with MPS indicated that the condition most commonly affects the back, followed by the neck and shoulder, with a typical duration of less than one year [9]. Based on these findings, we have designed a proof-of-concept clinical study to evaluate the therapeutic efficacy of HA35 trigger point injections for MPS-related pain. This study aims to assess the effects of a 15-day HA35 injection regimen in patients with back pain from MPS and to explore the

feasibility of using trigger points as diagnostic markers for MPS through follow-up observations extending up to three months.

2. Materials and Methods

2.1. Study Design and Participants

This study was a prospective, single-center, single-arm, open-label clinical trial conducted from May 2023 to September 2024. It was approved by the Ethics Committee of Meltes MED Orthoplastic Hospital (Approval Number: MMOH20230502) and adhered to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines. Informed consent was obtained from all participants, and the study was registered with the ClinicalTrials.gov database (NCT06444035), organized by the National Institutes of Health (NIH).

Participants were recruited from Meltes MED Orthoplastic Hospital, either seeking treatment or referred for severe pain lasting three months or longer. The inclusion criteria were: individuals aged 18-65 years, either male or female; primary complaint of back pain; presence of taut muscle bands with severe point tenderness upon palpation; pain exacerbated by cold weather or fatigue; limited range of motion in back extension; patient-reported pain of 3 or higher on the Numerical Rating Scale (NRS) (where 0 denotes no pain and 10 represents the worst imaginable pain); and a satisfactory mental status allowing for independent pain assessment and treatment cooperation, with signed written consent.

Exclusion criteria included: history of severe trauma with permanent musculoskeletal dysfunction; specific spinal disorders such as rheumatoid arthritis, ankylosing spondylitis, or osteoporosis; diagnosed psychiatric disorders; refusal to provide written consent; pregnant or breastfeeding women, or those of childbearing potential; and current or recent participation (within the past 30 days) in experimental treatments or device trials.

2.2. Study Treatment

Before the trial commenced, the attending physician thoroughly explained the study procedures to the participants. This research involves administering HA35 injection. The samples used in the study were sourced from NAKHIA IMPEX, a pharmaceutical company based in Ulaanbaatar, Mongolia. The recombinant human hyaluronidase PH20 [19] [20] is employed to cleave high-molecular-weight HA (from Bloomage Biotech) into the 35 kDa fragment, referred to as HA35 (B-HA injection, Registration Number L20200708MP07707; Ministry of Health), which is utilized for treating pain-related conditions.

2.3. Study Procedure

Participants received subcutaneous injections of HA35 solution (100 mg/5mL/day) at the designated pain points and surrounding areas on the back for 15 consecutive days. During the treatment period, participants were permitted to continue taking oral pain medications, and comparisons were made between pre- and post-treat-

ment dosages and intervals to assess the efficacy of the injections. Participants were required to self-report their pain levels daily throughout the injection period. The Numerical Rating Scale (NRS) was employed at various time points after treatment to compare pain relief effects with baseline values. Additionally, follow-up assessments were conducted via telephone and in-person visits every four weeks post-treatment, using the Global Pain Scale (GPS) [30] [31] to evaluate overall pain relief. Patient satisfaction with the treatment was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM 1.4) [32]-[34].

2.4. Outcome Measures

2.4.1. Primary Outcome Measure

Pain Assessment: The Numerical Pain Rating Scale (NPRS) is widely used in clinical settings to evaluate pain intensity, employing an 11-point scale ranging from 0 (no pain) to 10 (worst imaginable pain) to quantify pain severity [35] [36]. Investigators will assess back pain before and after treatment from three dimensions: current pain, average pain, and maximum pain. This assessment will be conducted using the following questions: "How intense is your pain right now?" (current pain), "How intense has your average pain been today?" (average pain), and "What was the worst pain you experienced today?" (maximum pain).

2.4.2. Secondary Outcome Measures

Overall Pain Assessment During and After Injection Treatment: The GPS, developed by Gentile *et al*. in 2011, is a multidimensional tool designed to evaluate pain over the past week. It encompasses four dimensions: pain, feelings, clinical outcomes, and activities [30] [31]. The GPS was validated using Classical Test Theory (CTT) and Item Response Theory (IRT) and comprises 20 items, each rated on a 0 - 10 scale. The total score is obtained by summing the item scores and dividing by 2, with higher scores reflecting greater pain intensity and impact.

Treatment Satisfaction Survey: The TSQM 1.4, developed by Atkinson *et al*. in 2004, assesses patient satisfaction with medication over the preceding 2 to 3 weeks or since the last dose [32]-[34]. It includes four subscales with a total of 14 questions: Effectiveness (Questions 1 - 3), Side Effects (Questions 4 - 8), Convenience (Questions 9 - 11), and Global Satisfaction (Questions 12 - 14). Each subscale is scored on a 0 - 100 scale, with higher scores indicating greater satisfaction.

2.5. Safety and Adverse Events

The safety of HA35 will be evaluated by comparing laboratory results from patients before and after treatment. Any adverse effects observed by investigators or reported by patients during the treatment, such as redness, itching, or pain at the injection site, will be documented.

2.6. Statistical Analysis

Statistical analyses were conducted using GraphPad Prism software (Version 9.3.1, San Diego, CA, USA). Quantitative data are presented as mean ± standard

deviation (SD). Comparisons between two groups were performed using a paired Student's t-test [27]. A p-value > 0.05 was considered not statistically significant (denoted as "ns"); $p < 0.05$ was deemed statistically significant (denoted as "*"); $p < 0.01$ indicated more significant results (denoted as "**"); and $p < 0.0001$ was regarded as highly significant (denoted as "****") [27]. Effect sizes (ES) were calculated to assess clinical significance, defined as the mean change from baseline divided by the standard deviation of the change. Clinical significance was categorized according to Cohen's ES thresholds: ES < 0.2, negligible; ES ≥ 0.2 to <0.5, small; ES ≥ 0.5 to <0.8, moderate; and ES > 0.8, large [37].

3. Results

3.1. Patient Demographics and Baseline Characteristics

A total of 12 patients diagnosed with back MPS accompanied by trigger points were initially enrolled in this study. However, 2 patients chose not to participate, resulting in 10 patients who completed the 15-day injection regimen and the subsequent 3-month follow-up according to the informed consent protocol. All 10 patients were included in the final data analysis (see Figure 1). The demographic characteristics of the participants are summarized in Table 1. The cohort consisted of 6 females and 4 males, with an average age of 52 years and a mean BMI of 24.90. Employment included 3 individuals in clerical positions, 5 in manual labor, and 2 as athletes. The average duration of pain among the participants was 4 months, with a range from 1 month to 1 year.

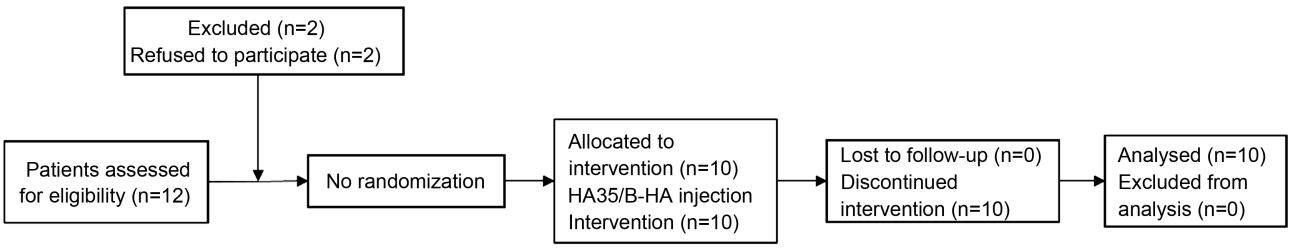

Figure 1. Flow-chart.

Table 1. Basic characteristics of participants with back pain.

Characteristic	N = 10	Percentage %
Gender		
Male	4	40%
Female	6	60%
Age, Mean ± SD	52.70 ± 8.19	-
BMI, Mean ± SD	24.90 ± 2.07	-
Occupation		
Manual Laborers	5	50%

Continued

Office Workers	3	30%
Athlete	2	20%
Pain duration		
1 - 3 months	3	30%
3 - 6 months	6	60%
7 - 12months	1	10%
More than 12 months	0	0%
Average pain time, Mean ± SD	4.30 ± 3.20	-
Causes of MPS		
Invasion of Wind-Cold	0	0%
Chronic Strain	5	50%
Muscle and Fascia Damage or Trauma	2	20%
Prolonged Poor Posture	3	30%
Previous Treatment Methods		
Physical Therapy Only, e.g., Acupuncture	4	40%
Medication Only, e.g., Anti-inflammatory and Analgesics	10	100%
Surgery Only	0	0%
Combined Treatment	5	50%

3.2. Primary Outcome Measures

Back Myofascial Pain Scores

Table 2 presents the NPRS scores for the 10 patients before treatment, during the injection period (at days 1, 3, 5, and 15), and after completing the injections (at days 30, 60, and 90). The patients rated both their current pain and the most severe pain experienced each day. The results, as illustrated in Figure 2, show a significant reduction in pain scores post-treatment ($P < 0.0001$). After just one day of injection therapy, current pain and strongest pain decreased by 50% and 40%, respectively. By the end of the 15 injections, pain relief exceeded 80%, with the scores dropping from a baseline of 6.9 ± 1.8 to 1.1 ± 1.0 (Mean ± SD, $P < 0.0001$). Follow-up scores revealed that patients maintained low pain levels over 30, 60, and 90 days (NPRS30days = 0.8 ± 1.1, NPRS60days = 0.5 ± 0.7, NPRS90days = 0.6 ± 0.8), with some participants reporting complete pain resolution (NPRS = 0).

3.3. Secondary Outcome Measures

3.3.1. Global Pain Assessment during and after Injection Treatment

Table 3 shows the GPS scores, indicating significant changes across the four dimensions of pain, feeling, clinical outcomes, and activity before and after treat-

ment ($P < 0.0001$). After 15 injections, the overall score decreased by approximately 80%, mirroring the trend observed in the primary outcome measures. Post-injection scores continued to decline, stabilizing around a mean of 2.2 at 60 days. The basic pain and the impact of pain on daily life had essentially disappeared.

Table 2. NPRS scores before and after the treatment.

NPRS pain	After treatment (days)	Patient									
		One	Two	Three	Four	Five	Six	Seven	Eight	Nine	Ten
Current pain	0	6	7	8	6	7	9	10	4	5	7
	1	4	5	6	3	5	4	5	1	2	3
	3	2	4	5	2	2	4	3	1	2	3
	5	1	3	3	1	2	3	2	0	1	2
	15	0	1	1	1	1	2	3	0	0	2
	30	0	0	2	0	0	2	3	0	0	1
	60	0	0	1	0	0	1	2	0	0	1
	90	0	0	1	0	0	2	2	0	0	1
Strongest pain	0	8	9	8	6	8	9	10	5	5	8
	1	4	5	6	4	5	5	6	2	3	4
	3	3	5	5	3	3	4	3	3	2	4
	5	2	3	4	2	2	3	2	0	2	3
	15	1	1	1	1	1	2	3	1	1	2
	30	1	1	2	0	1	2	3	0	0	2
	60	1	1	2	0	1	1	2	0	0	1
	90	0	0	2	0	0	2	3	0	0	1

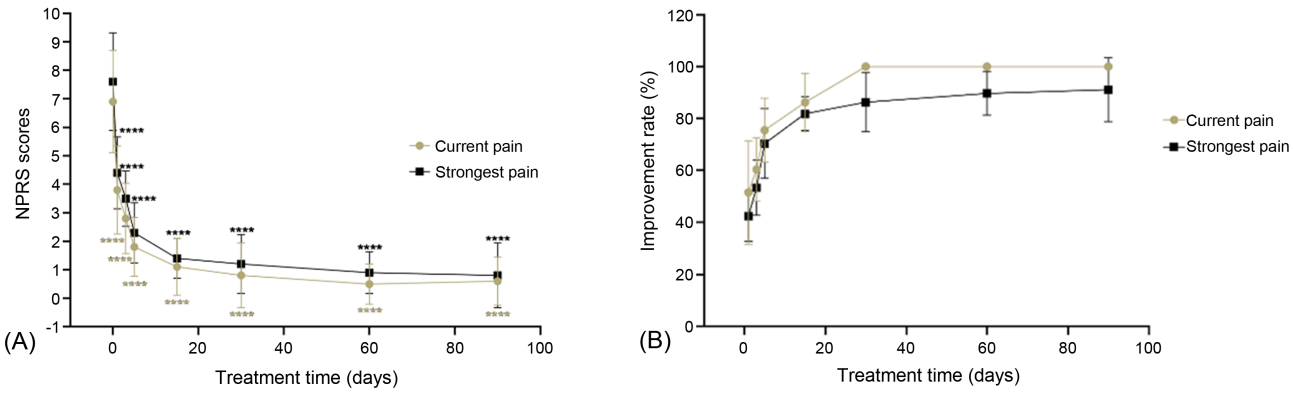

Figure 2. Average values of current pain and strongest pain before and after treatment in all patients.

Table 3. Percentage and number of patients improvement in the pain scores.

Patient	After treatment (days)				
	0	15	30	60	90
One	52.5	9.5	3.5	2.5	2.5
Two	51	8	4	2	1
Three	56	9	5	2	2
Four	53	8.5	3	1	1
Five	60	15.5	3.5	1.5	2
Six	62	14	9.5	2.5	2.5
Seven	75	19.5	13	4.5	4
Eight	51	10	2.5	2	3
Nine	50.5	11	2	2	3
Ten	51.5	9.5	4.5	2	2
Mean ± SD	56.3 ± 7.7	11.5 ± 3.7	5.1 ± 3.5	2.2 ± 0.9	2.3 ± 0.9
P-value	-	0.0001	0.0001	0.0001	0.0001

3.3.2. Satisfaction with Injection Treatment

Comparison of TSQM scores before and after HA35 injection treatment revealed high levels of treatment satisfaction among participants, as demonstrated by significant improvements in both statistical significance and effect size, as shown in **Table 4**, which provides details on the Treatment Satisfaction Questionnaire for Medication (TSQM), and in **Figure 3**, which illustrates the average TSQM scores for the four total items. As shown in **Table 4**, the TSQM1.4 item scores increased from a range of 1.3 - 3.1 to 3.8 - 6.0, corresponding to a percentage score increase from 27 - 40 to 58.1 - 81.4 (**Figure 3**). As illustrated in **Figure 3**, the highest satisfaction was reported in the areas of side effects (86.0, $P < 0.0001$, $ES > 0.8$), effectiveness (81.4, $P < 0.0001$, $ES > 0.8$), and overall satisfaction (82.9, $P < 0.0001$, $ES > 0.8$). The internal consistency of TSQM1.4 was confirmed by Cronbach's alpha coefficients above 0.76 across all subscales, indicating reliability [27].

Table 4. TSQM indicates treatment satisfaction questionnaire for medication.

TSQM1.4 items		Item means (SD)		ES(r)
		Baseline	After treatment 90 days	
Effectiveness	Prevents or treats/7	2.2 ± 0.8	5.7 ± 0.8	0.90
	Relieves symptoms/7	1.9 ± 1.0	5.4 ± 0.8	0.88
	Time to start working/7	2.0 ± 1.1	6.0 ± 0.8	0.90

Continued

Side effects	Bothersome side effects/5	1.3 ± 1.1	4.1 ± 0.7	0.83
	Interfere physical function/5	1.6 ± 1.1	4.3 ± 0.8	0.81
	Interfere mental function/5	1.4 ± 0.8	4.3 ± 0.9	0.86
	Side effect impact on satisfaction/5	1.1 ± 0.7	4.5 ± 0.7	0.92
Convenience	Easy to use/7	3.1 ± 1.0	4.2 ± 0.8	0.51
	Plan when to use/7	3.0 ± 1.2	4.2 ± 0.9	0.49
	Convenient to take/7	2.3 ± 1.3	3.8 ± 0.8	0.57
Overall satisfaction	Confident in benefits/5	2.3 ± 0.8	4.5 ± 1.1	0.75
	Good outweighs the bad/5	2.1 ± 0.9	4.2 ± 0.9	0.75
	All things into account/7	1.5 ± 0.7	5.4 ± 1.3	0.88

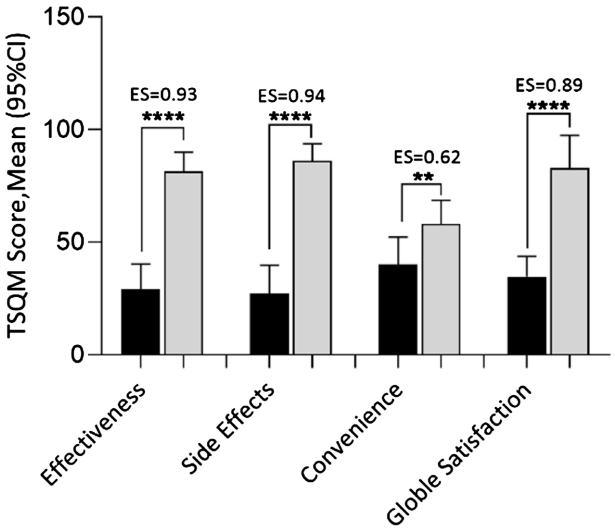

Figure 3. Average TSQM scores for the four total items.

4. Discussion

In this study, we report for the first time the efficacy of the low-molecular-weight hyaluronan fragment HA35 in treating MPS. The etiology of MPS has long been a topic of interest in the medical community. Some research suggests that the pain associated with MPS may result from the stimulation of sensory nerves by algogenic substances within an inflammatory environment, as well as from nerve compression by edematous tissues [3] [38]. Alternative theories propose that impaired blood circulation and the accumulation of metabolic by-products due to prolonged static activity may trigger referred pain and allodynia by activating peripheral nerve endings [1] [4]-[10]. Nonetheless, the majority of research has concentrated on MTrPs, which are considered the "gold standard" for diagnosing MPS. The detection of MTrPs using a three-point method is es-

sential for the clinical diagnosis and management of MPS [39]. In our study, the enrolled patients, comprising three office workers, three manual laborers, and two athletes, all demonstrated MTrPs. Their pain durations ranged from 1 month to 1 year, and they had previously received various physical therapies, including acupuncture and massage, alongside pain medication. Despite these treatments, as indicated by the TSQM results in **Table 4**, patients generally reported dissatisfaction, with baseline scores significantly below 50%. Following HA35 injection therapy, substantial pain relief was observed, as illustrated in **Figure 2** and **Table 2**. After just one injection, both current pain and maximum pain scores on the NPRS showed significant reductions, with 60% of patients experiencing more than 50% improvement in pain; however, only three patients achieved more than 50% improvement in maximum pain. By the third injection, 80% of patients reported over 50% improvement in current pain, and 70% showed similar improvement in maximum pain. After five injections, all patients experienced more than 50% improvement in both current and maximum pain. Follow-up data indicated that post-treatment pain remained stable within the low range of 0-3 on the NPRS. Some participants reported pain relief as early as 20-60 minutes post-injection, suggesting that HA35 may offer rapid analgesic effects due to its tissue permeability. Imaging studies using Life's iQID demonstrated that 125I-labeled HA35 appeared in the spleen and lymph nodes within 5 minutes of injection into the hind limb of mice [27].

Myofascial pain, if untreated, can lead to significant physical discomfort and adversely affect daily activities, social interactions, and emotional well-being [3]. Hence, accurate diagnosis and effective treatment are essential. Research on long-lived naked mole rats, which possess high concentrations of hyaluronan and its fragments, has shown they remain cancer-free throughout their lives and exhibit a reduced incidence of inflammation-related diseases [40] [41]. Preliminary clinical studies have suggested that HA35 may be effective in treating lung cancer pain, with improvements observed in patients' facial expressions, mood, and comfort following treatment. Additionally, cytological research indicates that HA35 promotes the migration of neutrophils and mononuclear cells. Combined with iQID imaging, these findings suggest that HA35 may alleviate inflammation by enhancing lymphocyte migration and lymphatic circulation [26]. In our study, the GPS scores at three different time points before and after treatment highlighted significant impacts of pain on patients' daily lives, including fear, depression, exhaustion, sleep quality, ability to work independently, overall physical sensations, shopping, and interpersonal relationships. Following 15 HA35 injections, 80% of patients demonstrated notable improvements in these areas, with no recurrence of pain during the follow-up period; rather, patients' overall conditions continued to improve. This suggests that HA35 can effectively alleviate chronic myofascial pain with lasting therapeutic benefits. The efficacy and satisfaction with HA35 treatment are further illustrated by the TSQM scores in **Figure 3**, which show high overall satisfaction with HA35 injections for chronic MPS within 90 days post-treatment. The effect sizes (ES) for

side effects, effectiveness, and overall satisfaction were close to 0.9, indicating significant correlations. Throughout the treatment and follow-up period, no adverse reactions or side effects were reported [23] [24] [42]. Moreover, patients who were using pain medications prior to treatment either reduced or discontinued their use afterward. The TSQM scores in **Figure 3** demonstrate that the side effects score reached 86.0 ($P < 0.0001$), reflecting a significant reduction in the side effects experienced by patients during previous treatments, which had been a major concern beyond achieving effective pain relief.

The primary limitation of this study is the small sample size, which may affect the generalizability of the results. However, as a proof-of-concept experiment, this study aimed to preliminarily validate the efficacy and safety of HA35 injections in treating MPS, providing a valuable reference for MPS diagnosis and pain management. The study met the expected primary and secondary outcomes.

5. Conclusion

MTrPs are the hallmark indicators for diagnosing MPS. The 35 kDa hyaluronan fragment HA35 effectively relieves back myofascial pain and provides sustained therapeutic benefits over an extended period post-treatment.

Supplementary Materials

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author Contributions

E.P. and D.T.: conceptualization; validation, investigation; formal analysis; writing—original draft; writing—review and editing; visualization. Z.M.: investigation; formal analysis; validation. X.J.: investigation; formal analysis; validation; writing—original draft; writing—review and editing. T.G.: project administration; supervision; formal analysis. M.H.: conceptualization; writing—review and editing; project administration; funding acquisition; supervision; validation; formal analysis. D.E.: conceptualization; project administration; funding acquisition; investigation; formal analysis; validation; supervision; writing—original draft; writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

The study was conducted in accordance with the Ethics Committee of Meltes MED Orthoplastic Hospital (approval number MMOH20230502).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available in the article.

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Conflicts of Interest

All other authors report no conflicts of interest or relationships relevant to the contents of this paper to disclose.

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