Journal of Biosciences and Medicines, 2026, 14(7), 227-241
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Fu's Subcutaneous Needling for Knee Osteoarthritis: A Randomized Controlled Trial Evaluating Clinical Efficacy and Inflammatory Mechanisms

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How to cite this paper: Ou, Z.X., Tan, S.Y., Lu, C.L., Yu, L.H., Zhou, G.J., Yang, J.E. and Jia, N. (2026) Fu's Subcutaneous Needling for Knee Osteoarthritis: A Randomized Controlled Trial Evaluating Clinical Efficacy and Inflammatory Mechanisms. *Journal of Biosciences and Medicines*, **14**, 227-241.
https://doi.org/10.4236/jbm.2026.147019

Received: June 10, 2026
Accepted: July 14, 2026
Published: July 17, 2026

Abstract

Background: Knee osteoarthritis (KOA) is a highly prevalent degenerative joint disease. Quadriceps muscle atrophy and chronic inflammation mediated by pro-inflammatory cytokines are increasingly recognized as key drivers of KOA progression. Fu's Subcutaneous Needling (FSN) is a modern acupuncture technique targeting tightened muscles, but its medium-term clinical efficacy and anti-inflammatory mechanisms remain unclear. **Objective:** To evaluate the clinical efficacy of FSN compared with intra-articular sodium hyaluronate (SH) injection and oral meloxicam (MLX) in treating KOA, and to investigate its effects on serum inflammatory mediators. **Methods:** In this parallel-group, assessor-blinded randomized controlled trial, 120 patients with Kellgren-Lawrence grade II-III KOA were randomly assigned (1:1:1) to receive FSN (n = 40, 3 sessions/week for 2 weeks), SH injection (n = 40, once/week for 5 weeks), or MLX (n = 40, 7.5 mg/day for 2 weeks). The prespecified primary endpoint was the between-group difference in VAS pain score at post-treatment (Week 2 for FSN and MLX; Week 5 for SH), with the WOMAC index at post-treatment as a coprimary endpoint. To control for multiplicity across two coprimary outcomes and four assessment time points, the significance level for primary comparisons was adjusted using Bonferroni correction (adjusted $\alpha = 0.05/8 = 0.00625$). Secondary outcomes included Lysholm knee score, range of motion (ROM), SF-12 quality-of-life score, and serum CRP, IL-1, and TNF-α. Assessments were conducted at baseline, Week 1, post-treatment, and Month 3. **Results:** All 120 randomized patients received at least one dose of

the assigned intervention and were included in the modified intention-to-treat analysis; all 120 completed the study. At post-treatment, the FSN group demonstrated significantly lower VAS scores (1.5 ± 1.6) compared with both SH (3.2 ± 1.9, $p < 0.001$) and MLX (3.0 ± 1.7, $p < 0.001$). WOMAC scores were significantly lower in the FSN group (20.7 ± 13.3) versus SH (30.9 ± 15.4, $p = 0.002$) and MLX (37.8 ± 11.2, $p < 0.001$). Improvements in Lysholm scores (72.6 ± 9.3), ROM (111.5˚ ± 10.6˚), and SF-12 (51.2 ± 12.3) were all significantly greater in the FSN group (all $p < 0.01$). At Month 3, FSN maintained superior outcomes across all measures, whereas MLX showed substantial deterioration. Serum CRP decreased by 45.1% in FSN (12.2 to 6.7 mg/L) versus 32.2% in SH and 14.6% in MLX. IL-1 decreased by 36.1% in FSN versus 25.4% in SH and 15.1% in MLX. TNF-α decreased by 38.5% in FSN versus 20.1% in SH and 15.5% in MLX. **Conclusions:** FSN therapy provides superior and sustained clinical improvement in pain, function, and quality of life for KOA patients compared with SH injection and oral MLX. The concomitant reductions in CRP, IL-1, and TNF-α are significantly correlated with clinical improvement, suggesting an association between inflammatory marker suppression and therapeutic response. Whether FSN improves KOA through restoration of periarticular muscle function remains a hypothesis that requires direct measurement in future studies.

Keywords

Fu's Subcutaneous Needling, Knee Osteoarthritis, Inflammatory Cytokines, Randomized Controlled Trial, Sodium Hyaluronate, Meloxicam

1. Introduction

Knee osteoarthritis (KOA) is a chronic degenerative joint disease affecting over 300 million people worldwide [1], with a prevalence exceeding 18% among adults over 40 years in China [2]. KOA is a leading cause of disability and is associated with elevated risks of cardiovascular events and all-cause mortality [3] [4]. As the population ages, the disease burden continues to escalate, creating an urgent need for effective therapeutic strategies.

The pathogenesis of KOA has traditionally been attributed to progressive articular cartilage degradation [5]. However, accumulating evidence indicates that KOA involves pathological changes across all periarticular structures, with quadriceps muscle atrophy and weakness playing a critical role [6] [7]. Quadriceps dysfunction may precede radiographic KOA changes, suggesting that muscle impairment is not merely a consequence but potentially an initiating factor in KOA pathogenesis [8]. The link between muscle atrophy and KOA is increasingly understood through chronic systemic inflammation. Aging is associated with progressive elevation of circulating pro-inflammatory cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) [9]. These cytokines promote muscle protein degradation via the ubiquitin-proteasome system (UPS), upregulating the muscle-

specific E3 ubiquitin ligases MuRF1 and atrogin-1 [10] [11]. TNF-α and IL-1 also activate the nuclear factor-kappa B (NF-κB) pathway, which amplifies muscle proteolysis and contributes to articular cartilage destruction [12] [13]. C-reactive protein (CRP), a systemic inflammatory marker, is consistently elevated in KOA and correlates with disease severity [9]. Inflammatory mediators, muscle wasting, and osteoarthritis thus form a self-reinforcing vicious cycle.

Fu's Subcutaneous Needling (FSN), developed by Professor Fu Zhonghua, is a modern acupuncture technique based on the principle of "pathological muscle"—skeletal muscle in a state of pathological tension, atrophy, or dysfunction [14] [15]. FSN involves insertion of a specialized needle into the subcutaneous loose connective tissue overlying the affected muscle, followed by a fan-shaped sweeping manipulation with concurrent resisted active movement (reperfusion approach). According to FSN theory, the pathological muscle undergoes ischemic and metabolic disturbances causing functional impairment, which is the root cause of KOA symptoms [16]. By mechanically releasing tightened fascia and improving local circulation, FSN is hypothesized to restore muscle function and inhibit inflammatory mediator production.

Previous studies have reported favorable short-term outcomes of FSN for KOA. Liu *et al.* [17] found FSN superior to conventional acupuncture in reducing pain after one week. Chiu *et al.* [18] demonstrated that FSN effectively reduced soft tissue pain in a randomized trial. A recent systematic review by Zhao *et al.* [19] confirmed FSN significantly improves pain and physical function, though the authors noted substantial heterogeneity and a lack of medium-term follow-up data. However, the existing literature has notable limitations: (1) most studies report only short-term outcomes; (2) many trials lack rigorous methodology including standardized inclusion/exclusion criteria; (3) the majority are case series without well-designed control groups; and (4) no study has systematically investigated the molecular mechanisms underlying FSN's therapeutic effects in KOA.

To address these gaps, we conducted a three-arm, parallel-group, assessor-blinded randomized controlled trial comparing FSN with two established treatments: intra-articular sodium hyaluronate (SH) injection, a viscosupplementation agent [20], and oral meloxicam (MLX), a selective COX-2 inhibitor [21]. We hypothesized that FSN would demonstrate superior clinical efficacy and be associated with reductions in the circulating inflammatory markers CRP, IL-1, and TNF-α.

2. Methods

2.1. Study Design

This was a prospective, three-arm, parallel-group, assessor-blinded randomized controlled trial conducted at the Department of Rehabilitation Medicine, Gaoming District People's Hospital of Foshan. The protocol was designed in accordance with the SPIRIT statement and CONSORT guidelines. The study was approved by the Ethics Committee of Gaoming District People's Hospital of Foshan and conducted in accordance with the Declaration of Helsinki. Written informed con-

sent was obtained from all participants. The trial was prospectively registered in the Chinese Clinical Trial Registry.

2.2. Participants

2.2.1. Diagnostic Criteria

KOA was diagnosed according to the Chinese Orthopaedic Association guidelines (2018 edition) [2]: (1) recurrent knee pain within the past month; plus at least one of: (2) radiographic evidence of joint space narrowing, subchondral bone sclerosis, cystic changes, or osteophyte formation; (3) age ≥ 50 years; (4) morning stiffness ≤ 30 minutes; (5) crepitus on active joint movement. Radiographic severity was classified using the Kellgren-Lawrence (K-L) grading system.

2.2.2. Inclusion and Exclusion Criteria

Inclusion criteria: (1) met the KOA diagnostic criteria; (2) age 50 - 70 years; (3) K-L grade II or III; (4) no pharmacological or physical therapy for KOA within one month prior to enrollment.

Exclusion criteria: (1) prior knee surgery; (2) knee pain secondary to fracture, infection, tumor, rheumatoid arthritis, or gout; (3) severe joint destruction with ligament or capsular deficiency; (4) obvious deformity or neurovascular disease of the affected limb; (5) severe hepatic, renal, cardiovascular, or psychiatric disorders; (6) known allergy to study medications; (7) poor anticipated compliance.

2.3. Randomization and Blinding

Eligible participants were randomly assigned (1:1:1) to FSN, SH, or MLX groups. Randomization sequence was generated using SPSS 26.0 (IBM Corp.) by an independent statistician. Allocation was concealed in sealed opaque envelopes. Outcome assessors and data analysts were blinded. Treating clinicians were not blinded but were not involved in outcome assessment. All assessments and treatments were conducted in separate rooms.

2.4. Interventions

2.4.1. FSN Group

Participants received treatment 3 times/week (every other day) for 2 weeks (6 sessions). Disposable FSN needles (medium size; Nanjing Paifu Medical Technology Co., Ltd., Nanjing, China) were used. The clinician identified pathological muscles (tense or rigid) in the thigh compartments, tibialis anterior, popliteus, and peroneal muscles. The needling point was selected ~4 cm distal to the pathological muscle. After iodophor disinfection, the needle was inserted subcutaneously. A fan-shaped sweeping manipulation (~200 movements over ~2 min) was performed while the patient executed resisted active movement of the target muscle (~10 s contraction followed by relaxation). Key resisted movements included: knee extension (quadriceps), hip flexion (sartorius), hip adduction (medial thigh), knee flexion (biceps femoris and popliteus), and foot dorsiflexion (tibialis anterior). The soft cannula remained in place for 5 hours.

2.4.2. SH Group

Participants received one intra-articular injection of 25 mg sodium hyaluronate (Hyalgan®; Fidia Farmaceutici S.p.A., Italy) per week for 5 consecutive weeks, administered via the lateral patellofemoral approach.

2.4.3. MLX Group

Participants received 7.5 mg oral meloxicam (Mobic®; Boehringer Ingelheim, Germany) once daily after breakfast for 2 weeks. Gastric protection (omeprazole 20 mg once daily) was provided at the discretion of the treating physician for participants with risk factors for gastrointestinal adverse events; the number of participants receiving gastric protection was recorded. Rescue analgesics (oral acetaminophen up to 2 g/day) were permitted in all three groups, with dose and frequency documented at each assessment visit. Any use of exercise therapy, physiotherapy, or other co-interventions directed at the knee during the treatment and follow-up periods was prohibited and was monitored via patient diaries. No participant in any group received additional co-interventions during the study period.

2.5. Outcome Measures

All outcomes were assessed at baseline (T0), Week 1 (T1), post-treatment (T2), and Month 3 (T3). As the treatment durations differed across groups (FSN and MLX: 2 weeks; SH: 5 weeks), "post-treatment" refers to Week 2 for the FSN and MLX groups and Week 5 for the SH group. Despite this difference in absolute calendar timing, the post-treatment time point was defined prospectively as the primary comparison time point because it captures each intervention at the completion of its full intended course, thereby reflecting the maximal treatment effect specific to each modality and enabling a clinically meaningful direct between-group comparison.

2.5.1. Primary Outcomes

Pain intensity was measured using the Visual Analog Scale (VAS, 0 - 10). Osteoarthritis severity was assessed using the WOMAC index (0 - 96, higher = worse).

2.5.2. Secondary Outcomes

Knee function was evaluated using the Lysholm Knee Scoring Scale (0 - 100, higher = better). Range of motion (ROM) was assessed with a goniometer. Quality of life was assessed using the SF-12 Physical Component Summary (PCS, 0 - 100).

2.5.3. Inflammatory Markers

Venous blood samples were collected at each time point. Serum CRP was measured by immunoturbidimetry (Beckman Coulter AU5800). IL-1 and TNF-α were measured using commercial ELISA kits (R&D Systems, Minneapolis, MN, USA).

2.6. Sample Size and Statistical Analysis

With $\alpha = 0.05$, power = 0.80, and anticipated effect size of 0.5 for VAS, the mini-

mum required sample was 30 per group. Accounting for a 25% dropout rate, 40 participants per group were enrolled (N = 120).

Statistical analyses were performed using SPSS 22.0. Continuous variables are presented as mean ± SD. The primary analysis was conducted on a modified intention-to-treat (mITT) population. For the two coprimary outcomes (VAS pain and WOMAC index) assessed at four time points, the significance level was adjusted using Bonferroni correction to control the family-wise error rate (adjusted $\alpha = 0.05/8 = 0.00625$ for primary comparisons at post-treatment). Group comparisons at each time point used one-way ANOVA with Tukey's HSD post-hoc test. Secondary outcomes were compared without further multiplicity adjustment and are considered exploratory. Pearson correlation coefficients examined associations between changes in inflammatory markers and clinical outcomes. All tests were two-tailed.

2.7. Quality Control

All personnel underwent standardized training. Treatment was performed by certified clinicians with >3 years of FSN experience. Outcome assessments were conducted by trained evaluators blinded to group allocation.

3. Results

3.1. Participant Characteristics

Of 156 patients screened, 120 met inclusion criteria and were randomized: 40 per group. The primary analysis was conducted on a modified intention-to-treat (mITT) basis, defined as all randomized participants who received at least one dose of the assigned intervention and provided at least one post-baseline assessment. All 120 participants met these criteria and were included in the mITT analysis. All 120 completed the study with no dropouts. Adherence to the assigned intervention was 100% (40/40) in the FSN group (all 6 sessions completed), 100% (40/40) in the SH group (all 5 injections received), and 95% (38/40) in the MLX group (at least 12 of 14 daily doses taken). Baseline characteristics were well balanced across groups (Table 1). Mean age was 61.8 ± 5.9 years, and 71.7% were female.

Table 1. Baseline demographic and clinical characteristics.

Characteristic	FSN (n = 40)	SH (n = 40)	MLX (n = 40)	p-value
Age (years)	62.1 ± 5.8	61.5 ± 6.2	61.8 ± 5.7	0.892
Female, n (%)	29 (72.5)	28 (70.0)	29 (72.5)	0.961
BMI (kg/m^2)	26.4 ± 3.6	26.7 ± 3.4	26.2 ± 3.7	0.815
K-L Grade II/III	22/18	23/17	21/19	0.903
Disease duration (yr)	4.2 ± 3.1	3.9 ± 2.8	4.1 ± 3.3	0.887
VAS (0 - 10)	6.3 ± 1.0	6.6 ± 0.9	6.4 ± 0.8	0.352
WOMAC (0 - 96)	46.4 ± 9.1	47.4 ± 11.7	49.0 ± 9.2	0.518

Continued

Lysholm (0 - 100)	54.4 ± 8.2	56.2 ± 8.4	54.9 ± 7.3	0.590
ROM (degrees)	96.7 ± 9.2	96.4 ± 10.3	93.8 ± 9.3	0.319
SF-12 PCS	38.7 ± 10.0	36.0 ± 7.7	37.4 ± 8.2	0.372
CRP (mg/L)	12.2 ± 3.5	12.1 ± 3.9	13.0 ± 4.2	0.512
IL-1 (pg/mL)	18.3 ± 6.4	18.9 ± 4.8	19.2 ± 5.2	0.758
TNF-α (pg/mL)	35.1 ± 9.4	35.8 ± 9.9	37.4 ± 8.8	0.520

Note: Values are mean ± SD or n (%). FSN, Fu's Subcutaneous Needling; SH, sodium hyaluronate; MLX, meloxicam; BMI, body mass index; K-L, Kellgren-Lawrence.

3.2. Primary Outcomes

3.2.1. Pain (VAS)

All three groups showed significant reductions in VAS from baseline to post-treatment (all $p < 0.001$; Table 2). At post-treatment, the FSN group achieved significantly lower VAS (1.5 ± 1.6) compared with both SH (3.2 ± 1.9; $p < 0.001$) and MLX (3.0 ± 1.7; $p < 0.001$). At Month 3, FSN maintained significantly lower VAS (1.9 ± 2.0) versus SH (4.0 ± 1.9; $p < 0.001$) and MLX (4.3 ± 1.9; $p < 0.001$). The MLX group showed a pronounced rebound after treatment cessation.

3.2.2. WOMAC Index

WOMAC scores improved significantly in all groups (Table 2). At post-treatment, FSN showed significantly lower WOMAC (20.7 ± 13.3) versus SH (30.9 ± 15.4; $p = 0.002$) and MLX (37.8 ± 11.2; $p < 0.001$). At Month 3, FSN maintained improvement (24.3 ± 15.5), while MLX approached baseline levels (40.8 ± 15.4; $p < 0.001$ vs. FSN).

Table 2. Clinical outcomes by group and time point.

Outcome/Time point	FSN (n = 40)	SH (n = 40)	MLX (n = 40)	p-value
VAS (0 - 10)				
Baseline	6.3 ± 1.0	6.6 ± 0.9	6.4 ± 0.8	0.352
Week 1	3.0 ± 1.4	5.3 ± 1.7	3.7 ± 1.5	<0.001
Post-treatment	1.5 ± 1.6	3.2 ± 1.9	3.0 ± 1.7	<0.001
Month 3	1.9 ± 2.0	4.0 ± 1.9	4.3 ± 1.9	<0.001
WOMAC (0 - 96)				
Baseline	46.4 ± 9.1	47.4 ± 11.7	49.0 ± 9.2	0.518
Week 1	30.1 ± 11.8	42.1 ± 15.4	37.2 ± 12.3	<0.001
Post-treatment	20.7 ± 13.3	30.9 ± 15.4	37.8 ± 11.2	<0.001
Month 3	24.3 ± 15.5	35.5 ± 16.7	40.8 ± 15.4	<0.001
Lysholm (0 - 100)				
Baseline	54.4 ± 8.2	56.2 ± 8.4	54.9 ± 7.3	0.590
Week 1	64.8 ± 10.2	59.0 ± 10.5	59.9 ± 10.3	0.034

Continued

Post-treatment	72.6 ± 9.3	69.4 ± 10.8	64.8 ± 10.8	0.003
Month 3	72.1 ± 12.7	66.7 ± 10.8	62.0 ± 12.4	<0.001
ROM (degrees)				
Baseline	96.7 ± 9.2	96.4 ± 10.3	93.8 ± 9.3	0.319
Week 1	105.0 ± 11.2	100.7 ± 11.7	98.0 ± 11.2	0.026
Post-treatment	111.5 ± 10.6	107.2 ± 13.7	99.8 ± 12.2	<0.001
Month 3	108.7 ± 11.4	106.9 ± 11.9	96.9 ± 11.4	<0.001
SF-12 PCS (0 - 100)				
Baseline	38.7 ± 10.0	36.0 ± 7.7	37.4 ± 8.2	0.372
Week 1	44.9 ± 10.3	38.4 ± 8.5	43.4 ± 9.6	0.008
Post-treatment	51.2 ± 12.3	45.0 ± 10.7	43.9 ± 9.8	0.013
Month 3	51.0 ± 11.3	44.2 ± 10.2	38.1 ± 10.1	<0.001

Note: Values are mean ± SD.

3.3. Secondary Clinical Outcomes

Lysholm scores improved most substantially in the FSN group (Table 2). At post-treatment, FSN achieved 72.6 ± 9.3, significantly higher than SH (69.4 ± 10.8; $p = 0.048$) and MLX (64.8 ± 10.8; $p < 0.001$). At Month 3, FSN remained at 72.1 ± 12.7 versus 66.7 ± 10.8 (SH) and 62.0 ± 12.4 (MLX).

Knee ROM improved from 96.7˚ ± 9.2˚ to 111.5˚ ± 10.6˚ at post-treatment in FSN (mean increase: +14.8˚), significantly exceeding MLX (99.8˚ ± 12.2˚; $p < 0.001$). At Month 3, FSN maintained 108.7˚ ± 11.4˚ versus 96.9° ± 11.4° in MLX ($p < 0.001$).

SF-12 PCS improved most in FSN, rising from 38.7 ± 10.0 to 51.2 ± 12.3 at post-treatment. While MLX showed comparable early improvement at Week 1 (43.4 ± 9.6), it declined to 38.1 ± 10.1 by Month 3, near baseline. FSN remained at 51.0 ± 11.3 ($p < 0.001$ vs. MLX).

3.4. Inflammatory Markers

Baseline serum levels of CRP, IL-1, and TNF-α were comparable across groups (Table 3, Figure 1). FSN exhibited significant and sustained reductions in all three markers. In contrast, MLX showed only transient suppression with rebound to near-baseline by Month 3.

Table 3. Inflammatory marker levels by group and time point.

Marker/Time point	FSN (n = 40)	SH (n = 40)	MLX (n = 40)	p-value
CRP (mg/L)				
Baseline	12.2 ± 3.5	12.1 ± 3.9	13.0 ± 4.2	0.512
Week 1	9.5 ± 3.8	11.4 ± 4.6	10.5 ± 4.7	0.142

Continued

Post-treatment	6.7 ± 4.5	8.2 ± 4.2	11.1 ± 4.3	< 0.001
Month 3	8.1 ± 4.9	10.4 ± 5.0	11.8 ± 5.2	0.004
IL-1 (pg/mL)				
Baseline	18.3 ± 6.4	18.9 ± 4.8	19.2 ± 5.2	0.758
Week 1	15.0 ± 7.3	17.3 ± 5.0	17.9 ± 6.2	0.088
Post-treatment	11.7 ± 6.9	14.1 ± 4.6	16.3 ± 6.5	0.004
Month 3	11.7 ± 7.6	14.7 ± 6.0	18.3 ± 6.8	< 0.001
TNF-*α* (pg/mL)				
Baseline	35.1 ± 9.4	35.8 ± 9.9	37.4 ± 8.8	0.520
Week 1	28.8 ± 9.2	33.9 ± 10.9	33.0 ± 10.1	0.060
Post-treatment	21.6 ± 11.5	28.6 ± 11.9	31.6 ± 9.5	< 0.001
Month 3	23.5 ± 11.5	30.1 ± 11.7	34.2 ± 11.5	< 0.001

Note: Values are mean ± SD.

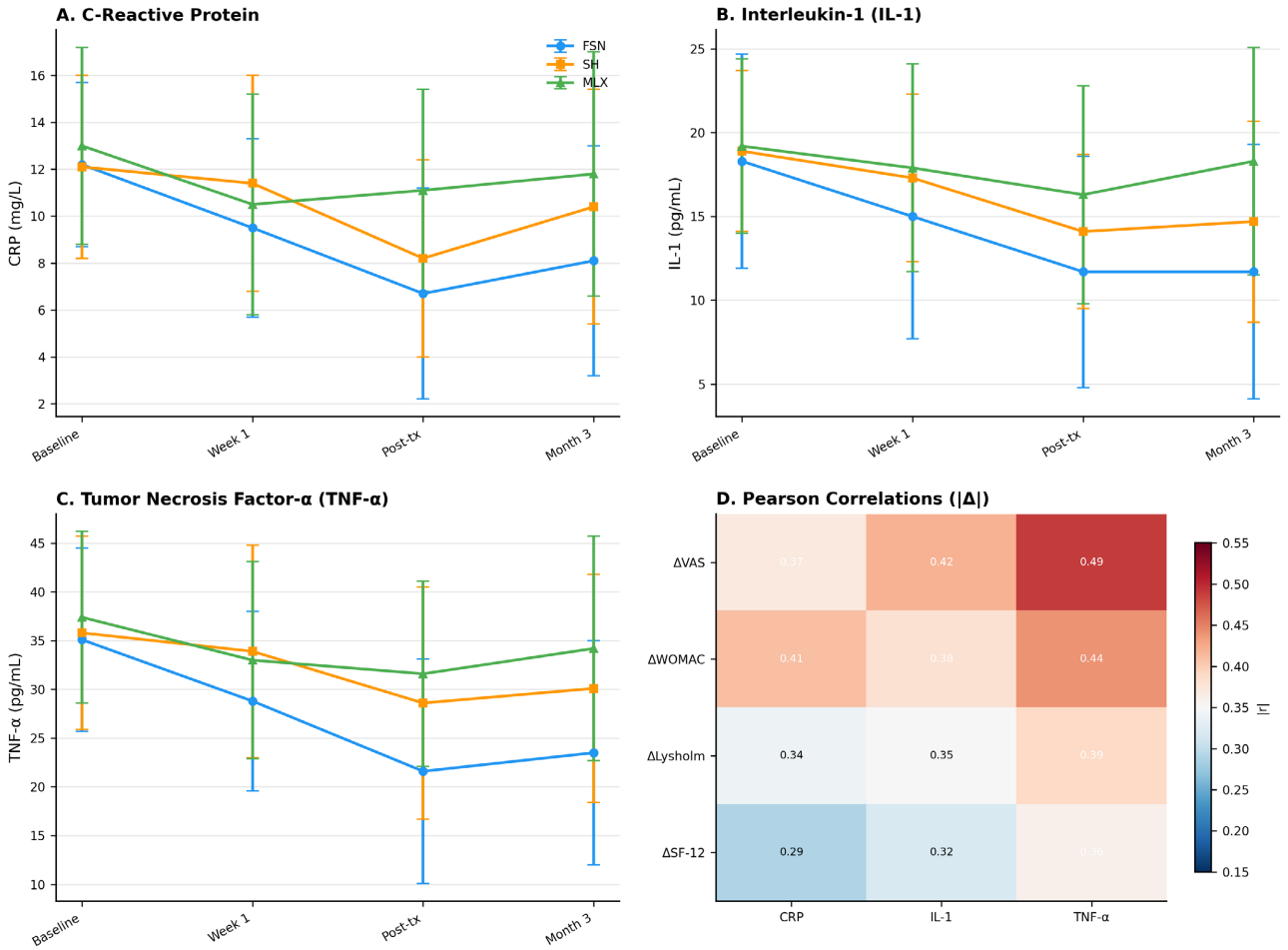

Figure 1. Serum inflammatory marker levels over time. (A) C-reactive protein (CRP), (B) Interleukin-1 (IL-1), (C) Tumor necrosis factor-alpha (TNF-*α*). (D) Pearson correlation heatmap between changes in inflammatory markers (Δ, baseline to post-treatment) and changes in clinical outcomes. Data are presented as mean ± SD.

At post-treatment, CRP decreased by 45.1% in FSN (12.2 to 6.7 mg/L), compared with 32.2% in SH and 14.6% in MLX. IL-1 decreased by 36.1% in FSN versus 25.4% in SH and 15.1% in MLX. TNF-α decreased by 38.5% in FSN versus 20.1% in SH and 15.5% in MLX. At Month 3, FSN-maintained CRP reduction of 33.6%, compared with 14.0% in SH and 9.2% in MLX. IL-1 reduction was 36.1% in FSN versus 22.2% in SH and 4.7% in MLX. TNF-α reduction was 33.0% in FSN versus 15.9% in SH and 8.6% in MLX.

3.5. Correlation Analysis

Pearson correlation analysis (Table 4) revealed significant correlations between changes in inflammatory markers and clinical outcomes from baseline to post-treatment. The strongest correlations were between ΔTNF-α and ΔVAS ($r = 0.49$, $p < 0.001$) and between ΔCRP and ΔWOMAC ($r = 0.41$, $p < 0.001$).

Table 4. Pearson correlations between changes in inflammatory markers and clinical outcomes (Baseline to Post-treatment).

Clinical outcome	ΔCRP	ΔIL-1	ΔTNF-α
ΔVAS	0.37**	0.42**	0.49**
ΔWOMAC	0.41**	0.38**	0.44**
ΔLysholm	−0.34**	−0.35**	−0.39**
ΔSF-12	−0.29*	−0.32*	−0.36**

Note: Δ denotes change from baseline to post-treatment. **$p < 0.05$; *$p < 0.001$.

3.6. Safety and Adverse Events

No serious adverse events were reported. In the FSN group, minor adverse events included transient local ecchymosis (n = 5, 12.5%) and mild subcutaneous hematoma (n = 3, 7.5%), all resolving spontaneously. In the SH group, transient post-injection pain (n = 6, 15.0%) and mild joint swelling (n = 2, 5.0%) were reported. In the MLX group, gastrointestinal discomfort occurred in 8 participants (20.0%). No participant withdrew due to adverse events.

4. Discussion

4.1. Principal Findings

This randomized controlled trial provides robust evidence that FSN is superior to both SH injection and oral MLX for treating KOA across multiple clinically meaningful domains over a 3-month period. FSN produced greater reductions in pain and WOMAC scores, greater improvements in knee function, joint mobility, and quality of life, with sustained benefits beyond the active treatment period. Importantly, FSN was associated with significant and sustained reductions in CRP, IL-1, and TNF-α. These cytokine changes were correlated with clinical improvements, suggesting an association between systemic inflammatory marker suppression and therapeutic response.

4.2. Clinical Efficacy of FSN

The magnitude of pain relief with FSN (VAS reduction of 4.8 points, 76.2% improvement at post-treatment) substantially exceeds the minimal clinically important difference (MCID) of 2.0 points for VAS in KOA [22]. At Month 3, FSN-maintained pain relief (VAS: 1.9) remained robust, whereas MLX showed regression (VAS: 4.3), highlighting the transient nature of COX-2 inhibition.

WOMAC results reinforce FSN's superiority. At Month 3, the FSN group maintained a 47.6% reduction from baseline, versus 25.1% for SH and 16.7% for MLX. This pattern was consistent across Lysholm, ROM, and SF-12 outcomes, demonstrating that FSN's benefits encompass functional recovery and quality-of-life improvement beyond analgesia.

4.3. Anti-Inflammatory Effects and Mechanism

A primary objective of this study was to investigate whether FSN treatment was associated with changes in systemic inflammatory mediators. Our data demonstrate that FSN is associated with significant and sustained reductions in CRP, IL-1, and TNF-α, with the magnitude of reduction exceeding that observed in both the SH and MLX groups. The MLX group, despite being a direct COX-2 inhibitor, showed only transient changes, suggesting that pharmacological COX-2 inhibition alone is not associated with sustained reductions in these circulating inflammatory markers in KOA. It is important to note that these findings are associative and do not establish a causal relationship between FSN treatment and inflammatory mediator suppression.

The correlations between inflammatory marker reductions and clinical improvements are consistent with a potential mechanistic link but do not confirm causality. As a hypothesis-generating framework, FSN's mechanical action on subcutaneous fascia and underlying pathological muscle may improve local microcirculation and tissue oxygenation, thereby reducing hypoxia-driven inflammatory signaling [23]. If such improvements occur, restoration of normal muscle function may break the pain-disuse-atrophy cycle, with a concomitant decrease in the release of damage-associated molecular patterns (DAMPs) and pro-inflammatory mediators. This could in turn attenuate systemic inflammatory burden, as reflected by the observed reductions in circulating CRP, IL-1, and TNF-α. However, periarticular muscle restoration was hypothesized but not directly measured in this trial.

The 38.5% reduction in TNF-α with FSN is particularly significant. TNF-α promotes muscle protein degradation via both the UPS pathway (MuRF1 and atrogin-1 upregulation) and NF-κB pathway [10]-[12]. These associations raise the hypothesis that FSN may simultaneously influence pathways related to muscle catabolism and joint cartilage destruction, potentially addressing the common inflammatory pathways linking muscle wasting and osteoarthritis [13]. This dual association—clinical improvement coupled with inflammatory marker reduction—is consistent with the hypothesis that FSN may exert therapeutic benefit through both

local mechanical effects and systemic biochemical modulation; however, the observational nature of the cytokine data precludes causal inference. These findings align with the broader acupuncture literature showing modulation of inflammatory pathways including NF-κB suppression [24].

4.4. Comparison with Previous Studies

Our results extend previous findings. Liu *et al.* [17] reported superior short-term pain relief with FSN. Chiu *et al.* [18] demonstrated FSN efficacy for soft tissue pain. The systematic review by Zhao *et al.* [19] confirmed FSN improves pain and function, noting the need for longer follow-up and biomarker assessment. Our study addresses these limitations with 3-month follow-up, a three-arm design with active comparators, and comprehensive inflammatory marker data providing mechanistic insight. We employed rigorous methodology including concealed allocation, assessor blinding, and standardized outcome measures.

4.5. Clinical Implications

Our findings have important clinical implications. FSN represents a promising non-pharmacological treatment that provides superior symptom relief while addressing underlying muscle dysfunction—a key disease driver not targeted by SH or MLX. The sustained benefits suggest a brief 2-week course may produce durable improvement, potentially reducing the need for ongoing pharmacotherapy and its associated risks [25]. The association with reductions in inflammatory markers suggests that FSN may have effects beyond purely symptomatic relief, though causal relationships have not been established.

4.6. Limitations

Several limitations should be acknowledged. Treating clinicians could not be blinded, though outcome assessors and analysts were blinded. The single-center design may limit generalizability; multi-center validation is needed. The 3-month follow-up, while longer than most previous FSN studies, is insufficient to assess very long-term outcomes. We measured only circulating serum markers; synovial fluid and tissue analyses would elucidate local mechanisms. Periarticular muscle restoration was hypothesized as a mediator of therapeutic benefit but was not directly measured in this trial. No sham FSN or placebo control was included. The observed associations between inflammatory markers and clinical outcomes are correlational; causal mediation analyses are needed to establish definitive pathways.

5. Conclusion

This randomized controlled trial demonstrates that Fu's Subcutaneous Needling provides superior and sustained clinical benefits for patients with knee osteoarthritis compared with intra-articular sodium hyaluronate injection and oral meloxicam over a 3-month period. FSN produced significantly greater improvements in

pain, function, joint mobility, and quality of life, with efficacy sustained beyond the active treatment period. FSN was associated with significant and persistent reductions in CRP, IL-1, and TNF-α, which correlated with clinical improvement. These cytokine findings are associative and do not establish causality. Periarticular muscle restoration was hypothesized but not directly measured in this trial. Future studies including direct muscle assessments and causal mediation analyses are warranted to clarify the mechanisms underlying FSN's clinical benefits.

Funding

Supported by Foshan Municipal Health Bureau Medical Research Project (Grant No. 20260077).

Data Availability

Data are available from the corresponding author upon reasonable request.

Acknowledgements

The authors thank all participating patients for their cooperation. We acknowledge the staff of the Department of Rehabilitation Medicine, Gaoming District People's Hospital of Foshan.

Conflicts of Interest

The authors declare no conflicts of interest.

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