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Original Article

Effect of denervation on knee joint function and pain in patients with knee osteoarthritis and cartilage injuries

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Abstract: Objective: To investigate the effect of denervation on knee joint function and pain in patients with knee osteoarthritis and cartilage injuries. Methods: In total, 93 patients with knee osteoarthritis and cartilage injuries hospitalized from January 2018 to January 2019 were involved in this study and divided randomly into a control group (n=46) and an observation group (n=47). The control group was treated with arthroscopic debridement while the observation group received denervation on top of arthroscopic debridement. The therapeutic effects before and after treatment were statistically evaluated between the two groups. Clinical manifestations including knee joint function, pain in knee joints, levels of IL-1β, TNF-α and FGF-21 in serum and synovial fluid, and complications were observed. Results: The observation group showed an overall response rate of 87.23%, significantly higher than 69.56% of the control group ($P < 0.05$). After operation, both groups had increased scores of knee joint function, and hip joint function was significantly higher in the observation group at 1, 3 and 6 months after operation ($P < 0.05$); the pain scores decreased in both groups and the observation group was significantly lower at 1, 3 and 6 months after operation ($P < 0.05$). Serum IL-1β and TNF-α as well as the levels of IL-1β, TNF-α and FGF-21 in the synovial fluid decreased in the two groups and were significantly lower in the observation group at 1 month after operation ($P < 0.05$); there was no significant difference in the incidence of complications between the two groups ($P > 0.05$). Conclusion: Denervation is of high application value in improving the knee joint function, alleviating postoperative pain, and reducing the levels of IL-1β, TNF-α, and FGF-21 in patients with knee osteoarthritis and cartilage injuries.

Keywords: Knee osteoarthritis, cartilage injury, denervation, knee joint function, pain, synovial fluid

Introduction

Knee osteoarthritis is a degenerative joint disease in which joint pain and dysfunction are caused by destruction of cartilage tissue and degradation or absence of the cartilage extracellular matrix. Among adults 60 years of age or older, its prevalence is approximately 49% [1]. Knee osteoarthritis patients often in combination with cartilage injury used to receive drug therapies and arthroscopic debridement. However, long-term medication brings them a variety of adverse reactions and produces little effect on correcting deformity and repairing cartilage except for relieving pain [2]. Although arthroscopic debridement alone can remove osteophytes from the articular cavity, repair meniscal injuries, remove loose debris, correct knee deformities, and improve the knee joint function; it fails to relieve the residual pain, going against the recovery of knee joint function [3]. Patients with knee osteoarthritis experience pain mainly in the articular capsule and the lower extremity of the femur. To block the pain gives patients less postoperative pain and promotes the recovery of knee joint function. Previous studies have shown that denervation treatment may significantly alleviate pain caused by knee osteoarthritis, lumbar zygapophyseal joint pain, and intractable knee pain after total knee replacement [4-6]. In this study, to observe the clinical value of denervation treatment, knee osteoarthritis patients with cartilage injury underwent the treatment and were compared with those who did not.

Material and methods

General materials

In total, 93 patients with knee osteoarthritis and cartilage injury admitted in our hospital from January 2018 to January 2019 were enrolled in the study and divided into a control group (n=46) and an observation group (n=47) in line with a random number table. Inclusion criteria: (1) patients diagnosed with osteoarthritis with cartilage injury; (2) between 18 and 75 years old; (3) with unilateral joint diseases and injuries; and (4) showing compliance, were included after signing the informed consent form. Exclusion criteria: (1) knee osteoarthritis patients with malignant tumor; (2) with serious diabetes, hypertension and other medical system diseases; (3) with surgical contraindications; (4) who are allergy sufferers; (5) with acute and chronic infectious diseases; (6) with malalignment; (7) with a history of knee joint wounds, deformity of knee joint, joint space narrowing, inflammatory arthritis, gout, bone tuberculosis, multiple osteophytes, osteomyelitis, and neurovascular injury; or (8) a history of mental illness, were excluded. Prior to this study, the protocol was approved by the Ethics Committee of our hospital, and a family member of the patient provided written informed consent.

Methods

The control group was treated only with arthroscopic debridement: patients were placed in the standard supine position and treated with epidural anesthesia to apply a pneumatic tourniquet to the upper third of the affected limb. An arthroscopic approach via the anterolateral patellar position was performed to observe the injury of cartilage, bone and meniscus, during which the articular cavity was continuously flushed. Then, the meniscus cartilage fragments and patellar osteophytes were removed. Osteophytes were also removed from the intermalleolar fossa and tibial protrusion. In the case of diffuse articular cartilage abnormalities, it is necessary to clean up the loose, split or fibrotic articular surface. Next was to repair the damaged cartilage, clean the hyperplastic tissue and burr on the surface, and remove the calcification. If the subchondral bone is exposed due to a cartilage injury, the vertical wall surrounding the cartilage injury will be repaired with a curette to remove the ossified tissue. If joint loosening is significantly worsened or pain increases, the meniscus can be totally removed. In the event of tension of the lateral patellar retinaculum, the patella should be released properly according to the compression that it experiences and should be pushed inward for 1 cm until normal movement. The affected limb was subjected to elastic compression, with regular functional exercise.

The observation group received both denervation and arthroscopic debridement: after arthroscopic debridement, radiofrequency ablation was performed around the patella to denervate under the microscope while the femur, including the attachment of the articular capsule and the lateral and medial malleolus, was cauterized about 5-10 cm with an electric knife. Subsequently the articular cavity was cleared before the incision was sutured to complete the surgery.

Evaluation criteria

Comparison of clinical efficacy: Efficacy evaluation at 6 months postoperatively [7]: complete response: knee joint pain basically disappeared with Lysholm score ≥ 95 points; partial response: there is pain and slight swelling in the knee joint during continuous exercise, with Lysholm score between 85 and 94 points; slight response: people feel uncomfortable in knee joint during daily activities, and take nonsteroidal anti-inflammatory drugs, with Lysholm score between 64 and 84 points; and no response: no significant improvement is found in clinical symptoms, with knee pain at night and limited knee mobility (Lysholm score ≤ 65 points). Overall response rate = (number of cases with complete response + number of cases with partial response)/total number of cases in each group × 100%.

Comparison of score of knee function: Hospital for Special Surgery (HSS) Knee questionnaire was used before operation, 1, 3 and 6 months after operation for evaluation of knee joint function, from the perspectives of pain (30 points), function (22 points), range of motion (18 points), muscle strength (10 points), flexion deformity (10 points), and stability (10 points); to derive a total score. The higher the score, the better the knee function.

Table 1. Comparison of clinical data

	n	Sex (male/female)	Age (years)	Lesion location (case)		Average duration (years)	Kellgren Lawrence grades	
				Left knee	Right knee		Grade II	Grade III
Observation group	47	29/18	55.91±8.74	34	13	3.25±1.06	30	17
Control group	46	26/20	55.36±8.29	35	11	3.31±1.14	28	18
χ^2/t		0.258	0.311	0.170		0.263	0.087	
P		0.611	0.756	0.680		0.793	0.768	

Table 2. Comparison of operative efficacy [*n* (%)]

	n	Complete response	Partial response	Slight response	No response	Overall response rate
Observation group	47	25 (53.19)	16 (34.04)	4 (8.51)	2 (4.26)	41 (87.23)
Control group	46	19 (41.30)	13 (28.26)	11 (23.91)	3 (6.52)	32 (69.56)
χ^2						4.299
P						0.038

Comparison of score of pain degree: Pain score; 0-10. 0 points means no pain, and 10 means severe pain and inability to move. The higher score indicates the more obvious pain.

Comparison of IL-1β, TNF-α, and FGF-21: Levels of IL-1β, TNF-α, and FGF-21 were measured before and 6 months after operation. Three ml venous blood from all patients was extracted on an empty stomach, and centrifuged at 3000 r/min for 10 min to seperate the supernatant. The enzyme-linked immunosorbent assay was used to measure the levels of IL-1β (with kits from R & D, United States), TNF-α (CUSABIO from Wuhan Huamei Biotech Co., Ltd) and FGF-21 (kits from abeam, the United States) in the supernatant with Rayto Rt 2100c Microplate Reader Elisa from Rayto, China.

Comparison of IL-1β, TNF-α and FGF-21 levels in synovial fluid: Levels of IL-1β, TNF-α and FGF-21 in the synovial fluid were measured before and 6 months after operation. Two ml of synovial fluid was extracted by joint puncture and centrifuged at 3000 r/min for 10 min to remove the supernatant. The measurement was made with the same reagents by the same method as above.

Comparison of complications between the two groups: Complications were observed in both groups.

Statistical analysis

SPSS 19.0 software helped complete the statistical analysis. The measurement data were expressed as $\bar{x} \pm s$ and compared with the *t*-test while the count data were expressed as a percentage and compared with χ^2 test. The results were considered statistically significant at $P < 0.05$.

Results

Data comparison

The two groups were comparable and showed no significant difference in gender, age, course of knee osteoarthritis, disease location and Kellgren Lawrence grades (P > 0.05) (**Table 1**).

Denervation produced significantly higher clinical efficacy

The overall response rate of the observation group was 87.23%, higher than that of the control group (69.56%), which showed a statistically significant difference (P < 0.05). It suggested that the application of denervation after arthroscopic debridement could produce significantly higher clinical efficacy (**Table 2**).

Denervation significantly increased scores in the HSS Knee questionnaire

After operation, HSS Knee questionnaire scores of both groups increased with time and the observation group had higher scores at 1, 3 and 6 months after the operation in terms of hip joint function (P < 0.05). It suggested that the combination of denervation with arthroscopic debridement could significantly increase scores of the HSS Knee questionnaire, and pro-

Table 3. Comparison of HSS Knee questionnaire score ($\bar{x}\pm s$, points)

Group	*n*	Before operation	1 month after operation	3 months after operation	6 months after operation
Observation group	47	50.84±7.29	80.92±4.07	84.13±3.72	87.31±2.88
Control group	46	51.26±7.65	76.43±5.64	80.26±3.39	84.80±2.96
T		0.271	4.410	5.241	4.415
P		0.787	0.000	0.000	0.000

Table 4. Comparison of pain score ($\bar{x}\pm s$, points)

Group	*n*	Before operation	1 month after operation	3 months after operation	6 months after operation
Observation group	47	6.61±1.34	4.22±1.15	3.28±1.12	2.39±1.01
Control group	46	6.75±1.29	5.28±1.07	4.32±1.18	3.64±1.16
T		0.513	4.600	4.360	5.546
P		0.609	0.000	0.000	0.000

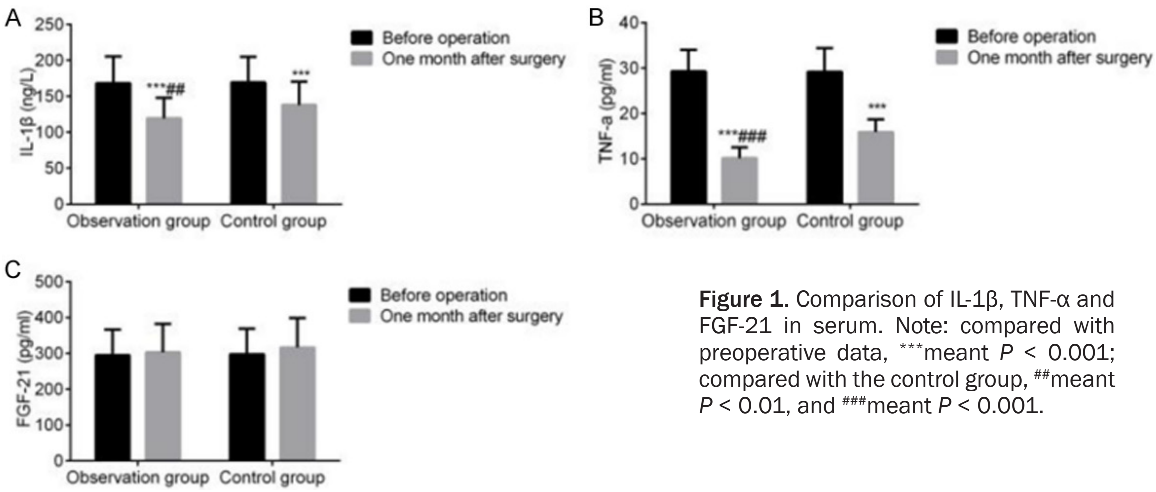


Figure 1. Comparison of IL-1β, TNF-α and FGF-21 in serum. Note: compared with preoperative data, ***meant $P < 0.001$; compared with the control group, ##meant $P < 0.01$, and ###meant $P < 0.001$.

duce a better effect than arthroscopic debridement alone (**Table 3**).

Denervation significantly alleviated postoperative pain

The pain scale of the observation group showed a decrease after operation and was lower than that of the control group at 1, 3 and 6 months post operation ($P < 0.05$). It suggested that the application of denervation with arthroscopic debridement can significantly alleviate postoperative pain, as shown in **Table 4**.

Denervation significantly improved the levels of inflammatory cytokines

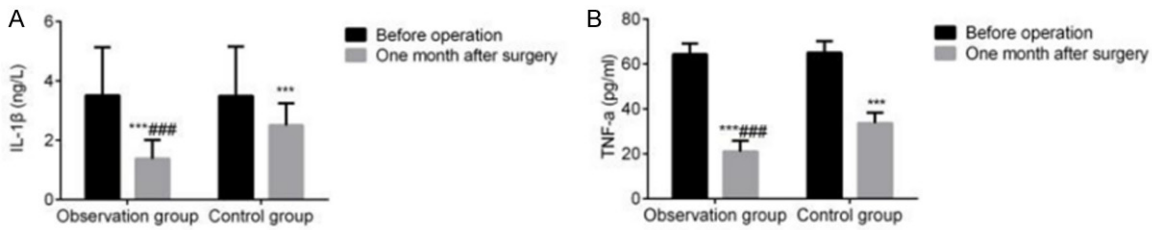
Serum IL-1β and TNF-α decreased in the two groups at 1 month after operation and the observation group showed lower levels ($P < 0.05$). There was no significant change in the level of FGF-21 in the two groups before and 1 month after operation ($P > 0.05$). This suggested that the combination therapy can significantly improve the serum levels of IL-1β, TNF-α and FGF-21 in patients (**Figure 1**).

Comparison of IL-1β, TNF-α and FGF-21

One month after operation, the two groups had levels of IL-1β, TNF-α and FGF-21 decrease in the synovial fluid, and the observation group showed significantly lower levels ($P < 0.05$). It indicated that the combination therapy can significantly improve the levels of IL-1β, TNF-α and FGF-21 in synovial fluid, as shown in **Figure 2**.

Comparison of complications

There was no significant difference in the incidence of complications between the two groups ($P > 0.05$), as shown in **Table 5**.



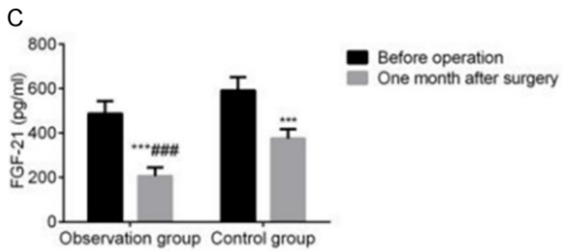


Figure 2. Comparison of IL-1β, TNF-α and FGF-21 in synovial fluid ($\bar{x}\pm s$). Note: compared with preoperative data, ***meant $P < 0.001$; compared with the control group, ##meant $P < 0.01$, and ###meant $P < 0.001$.

Table 5. Comparison of complications [n (%)]

Group	n	Wound infection	Joint swelling	Venous thrombosis of lower extremity	Incidence
Observation group	47	0 (0.00)	1 (2.13)	0 (0.00)	1 (2.13)
Control group	46	1 (2.17)	1 (2.17)	1 (2.17)	3 (6.52)
χ^2					0.284
P					0.296

Discussion

As knee osteoarthritis progresses, it can lead to the exposure of more bone, bone sclerosis, cartilage destruction, osteophyte, and cartilage damage. Clinically, knee osteoarthritis with cartilage injury is characterized by limited knee joint function or even loss of knee joint function. For patients with severe knee osteoarthritis, arthroscopic debridement is the main clinical treatment option. It may remove meniscal fragments, patellar osteophytes, osteophytes of intertrochanteric fossa, hyperplastic tissue and bone spurs, correct the joint varus or valgus deformities, repair cartilage, reduce entrapment, remove joint dysfunction, release lateral retinaculum, and alleviate the local abnormal mechanical properties to reduce pain and promote the recovery of knee joint function [8, 9]. Osteophytes in the intermediate zone and patellofemoral zone of knee joint have been considered as the main factors for knee pain in patients with knee osteoarthritis [10]. Arthroscopic debridement fails to completely remove joint inflammation, totally repair cartilage, while articular cartilage denudation and free nerve endings are relevant factors for knee joint pain [11]. The patella has its nerves mostly overlapped and the cauterization and denervation that it experiences have no obvious effect on the peripheral skin sensation and innervation [12]. Denervation treatment can cut down the number of nociceptive neurons, cut off afferent nerves of local chronic pains, block nerve conduction, reduce the release of neuropeptide substances, and alleviate pain after arthroscopic debridement [13]. The results herein showed that the overall response rate of the observation group was higher than that of the control group, with higher scores in HSS Knee questionnaire and pain scale, which were basically consistent with the relevant studies [14, 15]. Denervation confers several advantages to patients with knee osteoarthritis, including blocking local nerve conduction, lowering pain, providing conditions for joint functional exercise after operation to promote the recovery of knee joint function, and relieving pain-induced limited knee mobility, so as to produce better effects. As the wound gradually healed after operation, patients experienced significantly less considerable pain, and their knee joints recovered better [16].

Despite still being in a unclear pathophysiology, knee osteoarthritis has been linked to inflammatory factors in a large number of studies [17-19]. It was found that patients with knee osteoarthritis have higher levels of IL-1β and TNF-α in serum and synovial fluid by comparison with healthy people, which is in positive correlation with the Kellgren-Lawrence (K-L) grades [20]. A large number of inflammatory factors are released into the blood in the process of knee osteoarthritis and cartilage disease, making IL-1β and TNF-α abnormally over-expressed in serum and synovial fluid. IL-1β is a subtype and the main component of interleukin-1 (IL-1), produced by chondrocytes, synoviocytes, and the like. IL-1 can stimulate the production of matrix metalloproteinase 13, thus inhibiting proteoglycan synthesis of Type II collagen in cartilage matrix and accelerating its degradation. TNF-α is secreted by macrophages and less in normal human serum. However, in patients with chronic inflammatory diseases, TNF-α increases and promotes T cells to produce various inflammatory factors, thereby aggravating inflammatory responses [21]. TNF-α in synovial fluid can inhibit the production of cartilage collagen, act on fibroblasts to inhibit proteoglycan production and accelerate cartilage destruction. In addition, it stimulates the production of IL-1β and mediates joint tissue damage. As an adipokine primarily produced in hepatocytes and skeletal muscle, FGF-21 plays an important role in the nervous system, wound healing and tissue repair. It was found that patients with knee osteoarthritis had significantly higher levels of FGF-21 in the synovial fluid than the healthy controls, which was positively correlated with the K-L grades, while there was no significant difference between the two groups in the serum FGF-21 [22]. Consistent with what has been reported by related studies, the results showed that the observation group prevailed over the control group in levels of IL-1β and TNF-α in serum as well as IL-1β, TNF-α, and FGF-21 in synovial fluid [23]. It may be in that the denervation treatment can cauterize innervation in the synovium, block the reflex arc of pain, alleviate the long-term pain and the pain of bone and joint after operation, and inhibit the hyperactivity of stress response to pain. As the stress response can interact with residual inflammation, the inhibition of stress response will help reduce inflammatory responses and the release of IL-1β and TNF-α, lower destruction of joints and surrounding tissues by inflammatory factors, slow down the process of osteoarthritis, and reduce the release of FGF-21 [24, 25]. The results showed that significant differences did not exist in the incidence of complications between the two groups, suggesting that in treating patients with knee osteoarthritis and cartilage injury under arthroscopic debridement, denervation has high safety and will not increase complications.

In conclusion, denervation is of high application value in improving the knee joint function, alleviating postoperative pain, and reducing the levels of IL-1β, TNF-α, IL-1β, TNF-α, and FGF-21 in patients with knee osteoarthritis and cartilage injuries.

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Disclosure of conflict of interest

None.

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