



Review Article

The Effects of Korean Medicine Treatment for Meniscus Tears: A Retrospective Chart Review



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ABSTRACT

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Changes in symptoms and dysfunction related to meniscus tears following the use of Korean medicine for ≥ 4 days were studied. The medical charts of 53 cases of diagnosed meniscus tears (magnetic resonance imaging) with an admission Numeric Rating Scale (NRS) score ≥ 4 , between 2017 and 2022 were retrospectively reviewed. Treatments included acupuncture, pharmacopuncture, herbal treatment, Chuna therapy, and physiotherapy. The NRS, Western Ontario and McMaster Universities Osteoarthritis Index, and European Quality of Life 5 Dimensions were performed at admission and discharge. There were 42 females and 11 males in this study. Patients were more likely to be in their 60s (38.18%), have an unknown etiology (81.13%), and have complex tears (50.94%). After receiving a combination of alternative Korean medicine during hospitalization, the mean NRS score improved from 6.82 ± 1.19 to 3.66 ± 1.83 ($p < 0.001$), the Western Ontario and McMaster Universities Osteoarthritis Index score improved from 46.47 ± 20.99 to 37.98 ± 19.23 ($p < 0.001$), and the mean European Quality of Life Five Dimensions score improved from 0.61 ± 0.18 to 0.68 ± 0.14 ($p < 0.001$) after treatment. These results suggest that Korean medicine treatment of meniscus tears alleviated pain and improved physical function.

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Introduction

The meniscus plays an important role in knee joint mechanics by absorbing shocks and distributing the load to reduce stress on the tibia and stabilize the joint [1]. Due to the importance of these functions, meniscus tears affect the everyday lives of people and lead to an enormous economic burden on society. Meniscal tears are either acute or degenerative. Unlike acute tears which result from compressive, rotational, or shear forces applied to the knee, degenerative tears occur gradually due to normal repetitive force.

Tears are classified by their tear patterns, length, and location [2]. Horizontal and complex tears are commonly seen in elderly patients [3]. There are surgical and conservative treatment options for managing meniscus tears. Arthroscopic partial meniscectomy (APM) is performed to remove the torn meniscal fragments to relieve symptoms and its use has been increasing internationally [4]. However, there are doubts about the effectiveness of APM which have been substantiated in reports about the serious risks of this procedure [5-8]. Complications such as pyogenic arthritis, venous thromboembolism, and even deaths have been reported [5-8].

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Moreover, it has been reported that APM showed no clear benefits in the long term and showed increased risks of knee osteoarthritis [9]. Considering these factors, patients tend to prefer conservative treatments to preserve the meniscus [10]. In this retrospective review Korean medicine was used as an alternative option to APM in patients who were at risk of substantial degeneration of the meniscal tissue.

Materials and Methods

Study design

The electronic medical records (EMR) of patients who were hospitalized at Daejeon Jaseng Hospital of Korean Medicine for treatment of meniscus tears between January 1st, 2017, and January 31st, 2022 were searched. The EMR of 125 patients were retrieved from the hospital database for this retrospective chart review. Since encrypted data was used, written consent of the participants was not obtained. The study protocol was approved by the ethics committee of Daejeon Jaseng Hospital of Korean Medicine (no.: 2022-01-014).

Inclusion criteria

The inclusion criteria for this retrospective study were as follows: (1) diagnosis of meniscal tearing based on magnetic resonance imaging (MRI); (2) chief complaint of knee pain; (3) numeric rating scale score ≥ 4 at admission; and (4) hospitalization ≥ 4 days (≤ 47 days). No recruitment was required as all information was obtained from the EMR of inpatients and the patient data were anonymized.

Exclusion criteria

The exclusion criteria included patients who had knee pain that developed after a car accident, those diagnosed with certain serious diseases (malignant tumors, autoimmune diseases, fractures, and infection), those who had a history of knee surgery, and those whose complete survey records were not available. Among 125 patients in the EMR who had confirmed meniscus tears using MRI findings, 33 patients' chief complaint was not concerning the knee joint, 2 patients had a numeric rating scale (NRS) score less than 4, 20 were hospitalized for less than 4 days, 7 patients had surgery prior to admission, and 10 patients did not complete the questionnaire at discharge. There were 53 patients in total who met the inclusion criteria for this study (Fig. 1).

Treatments

Treatments included acupuncture, pharmacopuncture, herbal therapy, Chuna therapy, and physiotherapies such as medicinal steaming therapy, manual therapy, and extracorporeal shock wave therapy. Adverse events were monitored and assessed.

Acupuncture

Disposable sterile stainless-steel needles (0.25 × 40 mm, 0.20 × 30 mm) were used for acupuncture treatment (Dong-bang Medical Equipment Manufacturer, Boryung, Korea). Acupuncture was administered twice a day by a Korean medicine doctor to a depth of

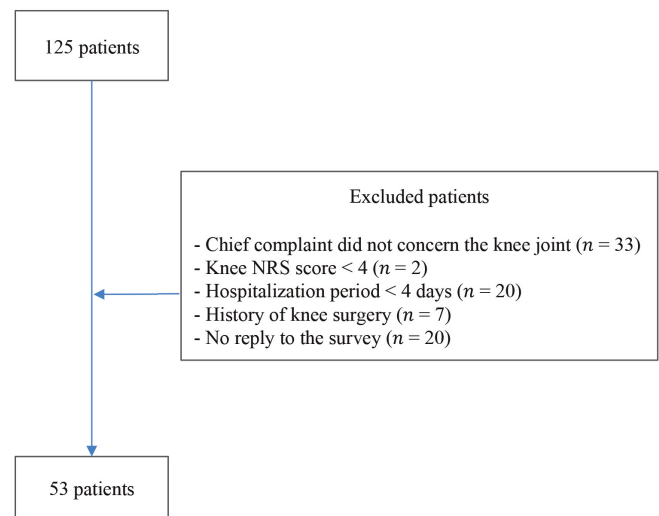


Fig. 1. Flow diagram of patients included in the study. NRS, numeric rating scale.

0.5–2.5 cm and the needle was retained for 10–15 minutes with 2–8 Hz of electricity passing through (STN-330 Stratek, Anyang, Korea). The acupoints selected were ST34, ST35, ST36, GB33, GB34, GB39, SP10, EX-LE4, EX-LE5, and the Ashi points (Table 1).

Pharmacopuncture

Considering the patient's symptoms and intensity of pain, Hwangryunhaedok, Shinbaro, bee venom, or Jahageo pharmacopuncture (Jaseng Wonoe Tangjunwon, Namyangju, Korea) was injected at ST35, SP10, EX-LE4, and EX-LE5. Disposable, single-use, 29-gauge, 12.7 mm needles on a 1 cc syringe (Sungshim Medical, Bucheon, Korea) filled with 0.2–0.5 mL of refrigerated pharmacopuncture solution was injected into the acupoints to a depth of 0.5–1.0 cm. The pharmacopuncture treatment was performed by a Korean medicine doctor once a day.

Herbal medicine

The number of herbal medications administered varied from 1 to 3 depending on the patient's condition. Herbal medicines were orally taken 3 times a day, 30 minutes after a meal.

Chuna

Chuna therapy was administered once a day by Korean medicine doctors during the hospitalization period. Knee joint mobilization and myofascial release techniques were performed.

Physiotherapy

Medicinal steaming therapy, manual therapy, or extracorporeal shock therapy were applied depending on the patient's condition.

Evaluation indexes

The NRS, Western Ontario and McMaster Universities Osteoarthritis (WOMAC), and European Quality of Life Five Dimensions (EQ-5D) scores were assessed before treatment at

Table 1. Details of Interventions Using the STRICTA 2010 Checklist.

Item	Details
Acupuncture rationale	1a) Acupoints were selected based on traditional Korean medicine meridian theory to treat knee pain. 1b) Acupuncture was performed for pain relief and cartilage protection properties. 1c) Participants underwent individualized acupuncture treatments according to their symptoms. The method varied considering the extent of pain and concomitant musculoskeletal pains.
Acupuncture details	2a) There were 6-12 needles were used per acupuncture session. 2b) The most frequently used acupoints were ST34, ST35, ST36, GB33, GB34, GB39, SP10, EX-LE4, EX-LE5, and the Ashi points. 2c) The depth of the inserted needles was between 0.5 cm and 2.5 cm. 2d) To affirm the needles had been placed properly a muscle twitch response was sought. 2e) Electrical stimulation was applied using a low-frequency electro stimulator (STN-330 Stratek, Anyang, Korea). 2f) Needles were retained for 10-15 minutes. 2g) 0.25 × 40 mm, 0.20 × 30 mm disposable stainless-steel needles were used (Dong-bang Medical Equipment Manufacturer, Boryung, Korea).
Treatment regimen	3a) All participants received acupuncture treatment twice a day during hospitalization. The number of sessions varied from 8 to 96. 3b) Acupuncture was administered for 10-15 minutes at each session.
Components of other treatment	4a) Pharmacopuncture, based on the meridian theory, was performed once a day. Shinbaro, bee venom, Hwanryunhaedok, and Jahageo were used. Herbal treatments were taken 3 times a day for their anti-inflammatory, antioxidant, and anabolic potentials. Chuna therapy was performed once a day to balance orthopedic structures, improve joint functions, and reduce pain. Physiotherapy including medicinal steaming therapy, manual therapy, or ESWT was applied depending on the patient's condition. 4b) Participants were provided explanations about their diagnosis and treatments.
Practitioners' background	5) There were 12 Korean medicine doctors with 2-15 years of clinical experience who provided treatments in the treatment room.
Control or comparator intervention	6a) This study was not relevant because there was no control group. 6b) This study was not relevant because there was no control group.

admission and after treatment prior to discharge. These measures were taken by the Korean medicine doctors who provided the treatments.

NRS

The NRS is a unidimensional measure to show the intensity of a patient's knee pain. The respondent rates his/her pain (0 to 10) where 0 indicates no pain, and 10 indicates the worst pain imaginable [11]. NRS scores were recorded at baseline and after completion of the treatment to determine the extent of pain relief.

WOMAC

The WOMAC index is a self-administered questionnaire to measure the patient's knee pain and consists of 24 items divided into 3 subscales: pain, stiffness, and physical function. Each subscale is composed of 5, 2, and 7 items, respectively. The test questions are scored on a 5-point scale, each score corresponding to the amount of pain: None (0), Mild (1), Moderate (2), Severe (3), and Extreme (4), or on 2 types of visual analog scales. The WOMAC has been used to assess activities of daily living and functional mobility for patients with knee/hip osteoarthritis [12].

EQ-5D-5L

The EQ-5D-5L is an instrument to measure the state of a patient's health in terms of 5 dimensions: mobility, self-care, usual activities, pain, and anxiety/depression. These 5 dimensions are scored on a 5-point Likert scale: (1) no problems, (2) slight problems, (3) moderate problems, (4) severe problems, and (5) extreme problems. In this study, the Korean version of EQ-5D-5L was used to monitor changes in self-reported health status through treatment [13].

Data analysis method

All data were secured from a computerized database and were inputted into Excel. Statistical analysis was processed using SPSS Version 28.0.1.0 for Windows (SPSS Inc., Chicago, IL, USA). Distributed data were shown as the mean ± SD values. To compare differences of NRS, WOMAC, and EQ-5D index scores before and after treatment, a paired *t* test was used for parametric data. If the *p* value was < 0.05, the treatment effects were considered to be significant.

Results

Baseline characteristics

There was a total of 53 patients included in this study, consisting of 11 males (20.75%) and 42 females (79.25%). The mean age of the participants was 63.07 ± 8.64 years. More than half of the patients were in their 60s (56.60%), followed by 10 in their 70s (18.87%), 9 in their 50s (16.98%), and 4 in their 40s (7.55%). The reason for the meniscus tear was unknown in 43 cases (81.13%), 6 cases (11.32%) were associated with overwork or excessive exercise, and the other 4 cases (7.55%) involved a trauma/fall. There were 9 patients who were hospitalized for 4-7 days (16.98%), 17 patients for 8-14 days (32.08%), 10 patients for 15-21 days (18.87%), 8 for 22-28 days (15.09%), 2 for 29-35 days (3.77%), 4 for 36-42 days (7.55%), and the rest 3 for 42-49 days (5.66%). The mean hospitalization period was 18.02 ± 11.77 days (range, 4-47 days). There were 39 cases (73.58%) of a tear in the medial meniscus, 7 cases (13.21%) of a tear in the lateral meniscus, and a tear in both the medial and lateral menisci were seen in 7 cases (13.21%). The most common

Table 2. Baseline Characteristics.

		N	%
Gender	Male	11	79.25
	Female	42	20.75
Age (y)	40-49	4	7.55
	50-59	9	16.98
	60-69	30	56.6
	70-79	10	18.87
Causes	Reason unknown	43	81.13
	Overwork/ excessive exercise	6	11.32
	Trauma/ fall	4	7.55
Period of hospitalization (d)	4-7	9	16.98
	8-14	17	32.08
	15-21	10	18.87
	22-28	8	15.09
	29-35	2	3.77
	36-42	4	7.55
	42-49	3	5.66
Tear location	Medial	39	73.58
	Lateral	7	13.21
	Both	7	13.21
Tear pattern	Complex	27	50.94
	Horizontal	17	32.08
	Radial	4	7.55
	Longitudinal	2	3.77
	Flap	2	3.77
Concomitant	Joint effusion	31	58.49
	Osteoarthritis	48	90.57
	Cyst	15	28.3
	Bursitis	19	35.85
	Bone Marrow Edema	26	49.06
	Anterior cruciate ligament tear	11	20.75
Medical history	Hypertension	19	35.85
	Hyperlipidemia	14	26.42
	Diabetes mellitus	8	15.09
	Cardiovascular disease	2	3.77
	Respiratory disease	2	3.77
	Gastrointestinal disease	2	3.77

tear pattern was complex, which was observed in 27 cases (50.94%), followed by horizontal in 17 cases (32.08%), radial in 4 cases (7.55%), longitudinal in 2 cases (3.77%), and flap in 2 cases (3.77%; Table 2).

The meniscus tears were categorized based upon MRI findings. Concomitant joint effusion was observed in 31 cases (58.49%), osteoarthritis in 48 cases (90.57%), cysts in 15 cases (28.30%), bursitis in 19 cases (35.85%), bone marrow edema in 26 cases (49.06%), and a torn anterior cruciate ligament in 11 cases (20.75%; Table 4)

The data of the patients' past medical history was collated. There were 19 patients who had hypertension (35.85%), 14 had hyperlipidemia (26.42%), 8 had diabetes mellitus (15.09%), 2 had cardiovascular disease (3.77%), 2 had respiratory disease (3.77%), and 2 had gastrointestinal disease (3.77%; Table 2).

Treatments

Distribution of pharmacopuncture therapy

Shinbaro was used the most frequently and was injected into 40 patients (75.47%). Bee venom was used in 7 patients (13.21%), and both Hwanryunhaedok and Jahageo were used in 1 patient (1.89%), respectively (Table 3).

Distribution of herbal medicine

Gwanjul-go was prescribed to 37 patients (69.81%) and was the

most common herbal medicine taken, followed by Chungpajun-shinbang No. 2 (56.6%), Mabalgwanjeol-tang (37.74%), and Cheongshinbaro-hwan (35.85%; Table 4).

Assessments

Before treatment, the total mean of the NRS, WOMAC, and EQ-5D-5L scores was 6.82 ± 1.19, 46.47 ± 20.99, and 0.61 ± 0.18, respectively. After treatment, the scores significantly improved to 3.66 ± 1.83, 37.98 ± 19.23, and 0.68 ± 0.14 (*p* < 0.001), respectively (Table 5).

Table 3. Distribution of Pharmacopuncture Therapy.

Pharmacopuncture therapy	N	%
Shinbaro	40	75.47
Bee venom	7	13.21
Hwangryunhaedok	1	1.89
Jahageo	1	1.89
None	4	7.55

Table 4. Distribution and Composition of Herbal Medicine.

Prescription	Composition of medicinal herbs	N	%
Gwanjul-go	Poria cocos (Schw.) Wolf 1.634g Ginseng Radix Alba 0.817g Achyranthes bidentata Bl. 0.204g Asini Gelatinum 0.102g Rehmanniae Radix 3.268g Cervi Cornus Colla 0.34g Mel 1.634g	37	69.81
Chungpajun-shinbang No. 2	Acanthopanax Cortex 7.5 g, Eucommiae Cortex 7.5 g, Saposhnikovia Radix 7.5 g, Achyranthes bidentata Bl. 7.5 g, Cibotii Rhizoma 7.5 g, Atractylodis Rhizoma Alba 3.75 g, Amomi Fructus 3.75 g, Geranii Herba 3.75 g, Zin giberis Rhizoma 1.875 g, Scolopendra morsitans L 0.375 g, Glycyrrhizae Radix 2g	30	56.6
Mabalgwanjeol-tang	Lasiosphaera Seu Calvatia 12g, Achyranthis Radix 8g, Ginseng Radix 8g, Glycyrrhizae Radix 4g, Osterici Radix 4g, Testudinis Plastrum 4g, Angelicae Pubescentis Radix 4g, Hordei Fructus Germinatus 4g, Saposhnikoviae Radix 4g, Amomi Fructus 4g, Astragali Radix 4g, Aconiti Tuber 2.8g	20	37.74
Cheongshinbaro-hwan	Rehmanniae Radix 0.208g, Mel 0.104g, Pachyma hoelen rumpius 0.052g, Gingseng Radix 0.026g, Glue of Cervi Parvum Cornu and Cervi Cornu 0.022g, Atractylodis Rhizoma alba 0.017g, Achyranthis Radix 0.013g, Cibotii Rhizoma-Eucommiae Cortex-Cibotii Rhizoma, Gallbladder of Bos taurus L. 0.009g, Gelatinum 0.006g, Achyranthis Radix-Ledebourieliae Radix-Acanthopanax Cortex-Scolopendra 0.004g, Cheongshinbaro-hwan dried extract 0.5g	19	35.85

Table 5. The Total mean of NRS, WOMAC, EQ-5D Scores Before and After Treatment.

	N	Total mean of scores		Difference of mean	p
		Before	After		
NRS	53	6.28 ± 1.19	3.66 ± 1.83	2.62	< 0.001*
WOMAC	53	46.47 ± 20.99	37.98 ± 19.23	8.43	< 0.001*
EQ-5D	53	0.61 ± 0.18	0.68 ± 0.14	-0.07	< 0.001*

Data are presented as mean ± SD.

* Statistical significance was evaluated by using the paired sample t test.

EQ-5D-5L, 5-level EuroQol- 5 Dimensions; NRS, numeric rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Adverse effects

Adverse events were monitored and there were no reports of adverse effects that interfered with treatment.

Discussion

The meniscus, intra-articular fibrocartilage located between the femoral condyle and the tibial plateau, plays a critical role in knee mechanics by absorbing shocks and protecting the cartilage. Meniscus injuries are the most common orthopedic diagnosis of the knee joint, resulting in clinical symptoms such as pain, swelling, locking, and stiffness [14]. The meniscus can be torn from acute trauma or chronic repetitive stresses, and various tear patterns can appear in different locations [15].

Tear patterns and locations of meniscus tears were classified in this study according to standardized terminology validated by the International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine [16]. Tear patterns are described as: longitudinal, horizontal, radial, flap, or complex by using radiology findings. Longitudinal tears, also known as vertical tears, develop parallel to the circular curve of the meniscus tissue. This tear pattern is associated with twisting injuries, where the meniscus separates into the outer and inner parts. A horizontal tear appears as a horizontal line, parallel to the tibial plateau. Horizontal tears are commonly degenerative in origin and have the highest incidence of association with parameniscal or intrameniscal cyst formation. A radial tear is oriented perpendicular to the tibial plateau extending across the circumferential axis of the meniscus. A flap tear, either vertical or horizontal, commonly comprises a displaced flap fragment that can get caught within the joint. A complex tear indicates a combination of 2 or more tear patterns. Tear locations were divided into 3 different zones: anterior, middle, and posterior, each covering approximately 1/3 of the meniscus. For convenience, these locations were presented not by how far the tear extended into the meniscus, but how far the tear was located from front to back.

The treatments for these tears include a partial meniscectomy, meniscal repair, or conservative management. Tear patterns, the extent of the tear, patient characteristics, chronicity, and associated ACL injury are taken into consideration when determining the appropriate method of treatment to manage the tear [17]. In most cases, degenerative horizontal tears are usually given the recommendation for conservative treatment to delay cartilage loss by minimizing overload. Other tear patterns such as unstable tears, displaced flaps, and complex tears are often given the recommendation for surgical management [18]. However, resecting meniscal tissue is not a guaranteed success, with a beneficial long-term effect yet to be proven. This current study reviews 53 cases of meniscus injury (11 men, 42 women) treated with Korean medicine. Over half of these patients were in their 60s and had unknown causes except for 4 cases who had certain causes. This finding suggests most cases were caused by chronic strain since the patients were aged ≥ 40 years.

Damage to the medial meniscus (39 patients, 73.58%) was more common than damage to the lateral meniscus (7 patients, 13.21%), and the remaining 7 (13.21%) patients had damage to both

menisci. The most common tear pattern was a complex pattern, followed by a horizontal pattern. Our study suggests that meniscus tears affect the medial meniscus more often and are likely to be a complex pattern of tear in the age groups included. Regarding the concomitant, previous findings suggest that meniscus injuries commonly occur in conjunction with knee osteoarthritis [19,20]. Similarly, this current study showed a high prevalence of osteoarthritis (90.57%). Degenerative meniscal damage may signal early osteoarthritic disease.

Anterior cruciate ligament disruption was observed in 11 cases (20.75%). The incidence has been reported to vary considerably [21,22]. Other concomitants such as joint effusion, cysts, bursitis, and bone marrow edema are related to meniscal dysfunction [23].

During hospitalization, the patients underwent a combination of Korean medicine treatments including acupuncture, pharmacopuncture, herbal treatment, and physiotherapy. Acupuncture involves the insertion of sterile needles on the skin to stimulate defined acupoints. Acupuncture has been essential in traditional Korean medicine to treat many types of health issues due to its minimal risks and beneficial effects. Acupuncture is effective at relieving chronic knee pain [24]. The mechanisms of acupuncture underlying its curative effects are not fully elucidated, but it is thought to promote pain relief and prevent further cartilage erosion [25,26]. Pharmacopuncture originated from the meridian theory, which combines acupuncture and the injection of purified herbal extracts into the acupoints. Numerous types of herbal extract are being used to manage musculoskeletal conditions [27]. In this study, Shinbaro, bee venom, Hwanryunhaedok, and Jahageo were used (Table 6). Shinbaro is extracted from a mixture of six oriental herbs which have been widely used for pharmacopuncture to treat inflammatory diseases. Shinbaro pharmacopuncture has been reported to repair nerve damage, protect cartilage, regulate inflammatory responses, and reduce pain [28,29]. Diluted bee venom [saline (10,000): bee venom [1]] was used in those patients who were not allergic to bee venom (skin test confirmed). Bee venom has been reported to have anti-inflammatory, antiapoptotic, and antiarthritic effects, and be immunoprotective [30,31]. Hwangryunhaedok is composed of 4 herbs, which has anti-inflammatory, detoxification, and pyretic effects and is used for pharmacopuncture [32]. Jahageo pharmacopuncture therapy, also known as Hominis Placenta pharmacopuncture, has been used for its anti-inflammatory, anti-oxidative, and analgesic properties [33]. Chuna therapy is a manipulating treatment using body parts or assistive devices to balance orthopedic structures, improve joint functions, and reduce pain [34]. In this study, mobilization and soft tissue release techniques were used. Herbal medicine, based on Korean medicine theory, uses medicinal plants to improve health, prevent disease, and treat illness. Herbal medicine has multiple chemical components, leading to potentiating bioactivities compared with single-component drugs. Likewise, the phytochemical compounds used in this study contains several herbs (Ledebouriellae Radix, Achyranthes bidentata, Acanthopanax Cortex, Eucommiae Cortex, Lasiosphaera Seu Calvatia) commonly used for knee pain (Table 4). These remedies have been reported to help relieve pain by acting as an anti-inflammatory, and anti-oxidant agent, and act as an anabolic potential [35].

To assess the treatment, before and after treatment NRS, WOMAC, and EQ-5D-5L scores were used. The NRS was used to assess the degree of pain, the WOMAC was used to measure stiffness, as well as physical function in addition to pain. The EQ-5D-5L was used to compare overall life improvement after the treatment. The NRS, WOMAC, and EQ-5D-5L scores all showed a significant decrease indicating improvement after treatment ($p < 0.001$) across the entire group.

This observational study aimed to summarize the changes in symptoms and dysfunctions among patients with meniscus tears after Korean medicine treatments. Previous studies include case reports of Korean medicine treatments for meniscus tears [36–38]. In this current study we included a larger sample of data for the analysis.

While the data in this study needs to be interpreted with caution, patients with meniscus tears who were treated with Korean medicine showed improvement in pain, physical functions, and quality of life. However, some limitations of this study should be addressed. Firstly, this study included only 53 inpatients and therefore results cannot be generalized. Secondly, the WOMAC score has been reported as suboptimal as a patient-reported measurement for meniscus tears [39]. Studies should be conducted to determine the best measurement for symptom improvement for meniscus tears. Thirdly, considering the observational nature of this retrospective study, it was not possible to exclude confounding factors. Lastly, patients have had the tendency to over-report efficacy when responding to the healthcare provider [40]. Thus, further research is required to provide additional evidence to determine the potential benefits and effectiveness of Korean medicine treatment of meniscus tears.

Conclusion

This study focused on observing the general characteristics, and symptomatic and functional changes of patients with meniscus tears after treatment with Korean medicine, and improvements in pain, physical functions, and quality of life were observed. The results of this study may prove helpful in designing further studies and in clinical practice.

Author Contributions

Conceptualization: PJW. Methodology: PJW. Formal investigation: PJW, JMI and HHW. Data analysis: PJW and KJE. Writing original draft: PJW. Writing – review and editing: PJW, JWJ, BJH, KSJ and BJE.

Conflicts of Interest

The authors declare that they have no competing interests.

Funding

None.

Ethical Statement

This research did not involve any human or animal experiment.

Data Availability

All relevant data are included in this manuscript.

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