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Effect of Intra-Articular Cartipro® Injection on Pain in Patients with Knee Osteoarthritis: A Retrospective Chart Review

Lee Kwang-Hyuk*, Si-Nae Park

Regenerative Medicine Research Center, Dalim Tissen Co., LTD., 383-93, Yonnam-dong, Mapo-gu, Seoul, Korea

***Corresponding author:**

Lee Kwang-Hyuk,
Regenerative Medicine Research Center, Dalim Tissen Co., LTD., 383-93, Yonnam-dong, Mapo-gu, Seoul, Korea

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Atelocollagen; Chart review; Knee osteoarthritis; Pain

1. Abstract

1.1. Background:

Research on the long-term safety and efficacy of atelocollagen re-administration in alleviating pain in patients with knee osteoarthritis (OA) is lacking in Korea.

1.2. Objective:

To evaluate the clinical safety and efficacy of CartiPRO® re-administration in alleviating knee pain in patients with knee OA and various knee cartilage defects.

1.3. Methods:

This retrospective chart review assessed the therapeutic effects of CartiPRO® in 91 patients with knee OA. For safety assessment, the incidence of adverse events (AEs) and complications occurring within 26 weeks after CartiPRO® re-administration was examined. For efficacy evaluation, the percentage of patients who experienced relief from knee OA pain at least 30 days after CartiPRO® re-administration was calculated on the basis of the clinical research physician's comprehensive assessment. After CartiPRO® re-administration, the clinical research physician assessed efficacy as "effective," "somewhat effective," or "not effective." "Effective" and "somewhat effective" were considered effective, whereas "not effective" was considered ineffective.

1.4. Results:

The frequency and percentage of effective and ineffective results were as follows. Re-administration was "effective" in 96.70% of patients (88/91) and "ineffective" in 3.30% (3/91). In the safety set, the incidence of AEs was 38.46% (35/91, 44 cases). There were no cases of medical drug-related AEs that could conclusively be deemed unrelated to the medical drug, unexpected AEs/medical drug-related AEs, and serious adverse events.

1.5. Conclusions:

No specific issues affecting the safety and efficacy of CartiPRO® were found. Long-term use of CartiPRO®, including re-administration, is safe and effective in alleviating knee pain in patients with knee OA and various knee cartilage defects.

2. Introduction

Osteoarthritis (OA) is a condition marked by pathological changes in the entire joint, including the synovium and subchondral bone, triggered by excessive usage or physical injury of the joint or due to increased catabolic activity in cartilage cells leading to cartilage degradation [1]. It is the most common chronic disease with a prevalence rate ranging from 5–30% in South Korea, and its prevalence tends to increase with advancing age [2,3]. The ongoing population aging and increasing obesity prevalence have led to a consistent increase in the incidence of OA. According to the Korea National Health and Nutrition Examination Survey, 10.7% of Korean adults were affected as of 2008 [4]. Since the average age of diagnosis for knee OA is 55 years and patients typically live with this condition for approximately 30 years, this is a considerably impactful disease [5-9]. In addition, knee OA can lead to decreased range of motion, which is often accompanied by creaking or popping sounds and muscle weakness. Common symptoms include knee locking, swelling, and instability. Such impairments are

closely related to pain and typically hinder one's activities of daily living, including household chores, walking, standing, and climbing stairs, thus degrading one's quality of life [11]. Because the profound impact on quality of life, study findings substantiating the safety and long-term pain relief effect would be highly valuable. Knee OA not only alters joint morphology and disrupts normal gait but also imposes limitations on one's activities of daily living and hinders one's physical activity. Consequently, it increases one's risks for hypertension, obesity, and cardiovascular diseases, perpetuating the vicious cycle of health deterioration. Data from the Health Insurance Review and Assessment Service indicate that knee OA was among the top five reasons for hospital and outpatient visits among individuals aged 65 years and older in 2013, with knee joint replacement surgeries nearly doubling from 23,789 in 2004 to 41,598 in 2006 (Ministry of Health and Welfare, 2011). The conventional treatment protocol for knee OA prioritizes extensive use of conservative therapies before considering surgical options, aiming to maintain the integrity of the natural joint for as long as possible. Surgical interventions are considered when pharmacological treatments fail to control pain adequately, when there is substantial functional decline that impairs one's activities of daily living and in the absence of medical contraindications [12]. Korean Knee Society Subcommittee on Osteoarthritis Guidelines, 2010). The pharmacological management of knee OA primarily involves symptomatic treatments, but there are only a limited number of suitable analgesics, immunosuppressants, and antidepressants. Compared with systemic administration, intra-articular drug delivery offers several benefits, such as fewer side effects, quicker onset of action, and infrequent dosing (once up to every 6 months), that promotes good adherence. Nevertheless, the scope of intra-articular treatments for managing knee OA over the past two decades has been restricted to a few non-validated alternative therapy modalities, including analgesics, glucocorticoids, hyaluronic acid, duloxetine, opioids, topical non-steroidal anti-inflammatory drugs, and capsaicin [13,14]. However, no existing treatments can reverse the progression of knee OA; thus, treatment is focused on alleviating pain and enhancing functionality [15,16]. The disease progression of OA involves a chronic inflammatory response. This process involves exposure of cartilage cells in the joint space, alterations in the osmotic pressure of the joint cartilage, and the gradual migration of proteoglycans disrupting the natural healing processes [17,18]. Pro-inflammatory cytokines, e.g., tumor necrosis factor-β, interleukin (IL)-6, IL-1α, and IL-1β, are released, activating cartilage-degrading enzymes, e.g., a disintegrin and a metalloprotease with thrombospondin motifs and matrix metalloproteases [19]. Consequently, these enzymes induce the degradation of the extracellular matrix (ECM), including collagen [20]. Therefore, the administration of exogenous collagen has been explored as a potential adjunct or alternative therapy for OA [21,22]. Collagen is a major component of connective tissue and a key structural protein of the human body that constitutes approximately 45–75% of the dry weight in ligaments, tendons, and cartilage. Collagen fibers are a crucial component of the ECM that supports most tissues and plays an essential role in maintaining cellular structures [23]. Researchers have hypothesized that intra-articular injections of atelocollagen could alleviate joint pain by replenishing collagen in the cartilage defect areas in patients with knee pain due to OA or other cartilage defects. Accordingly, numerous collagen-based intra-articular injections have been developed and clinically tested, producing significant results. Studies with up to 6–12 months of follow-up after administration have documented effective pain relief as measured by scales such as Western Ontario and McMaster Universities Arthritis Index and visual analog scale. Table 1 presents the current status of clinical trials involving various collagen-based intra-articular injections for knee OA [24]. As shown in Table 1, the first collagen-based tissue filler for patients with knee pain received manufacturing approval from the Korean Ministry of Food and Drug Safety (MFDS) in 2013 on the basis of significant clinical data from Korea and abroad. In 2022, Darim Tisen Co., Ltd. obtained MFDS manufacturing approval for CartiPRO® in 2022, which features the same mechanism of action as the first collagen-based tissue filler. However, research on the long-term safety and efficacy of atelocollagen re-administration in alleviating pain in patients with knee OA is lacking in Korea.

To address this gap, we conducted a retrospective study to compare the safety and pain relief efficacy of CartiPRO® re-administration in patients with knee OA by administering the product in accordance with the approval details in real clinical settings at five primary and secondary care facilities. Herein, we report the insights gained from this study.

Table 1: Summary of clinical trials of intra-articular injection using collagen.

Authors	Type of collagen used	KL grade	Groups	Intervention	Timing of the clinical assessment	Outcomes	Adverse effect
Furuzawa-Carballeda et al.	Type-I polymerized collagen	Not measured	Collagen (n = 27) vs. placebo (n = 26)	12 injections (weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24)	Baseline, 6 months, 12 months	↓ Lequesne Index ↓ WOMAC ↓ VAS ↓ NSAID use ↑ Likert score	Injection site pain lasting <24 h (2/27, collagen group) and cases of aseptic acute arthritis
Furuzawa-Carballeda et al.	Type-I polymerized collagen	III–IV	Collagen (n = 10) vs. placebo (n = 9) after arthroscopic lavage	6 injections (1 after arthroscopic lavage then 1 per week for 5 weeks after surgery)	Baseline, 3 months, 6 months	↓ Lequesne Index ↓ WOMAC ↓ VAS ↓ NSAID use ↑ Likert score ↑ evaluation of drug efficacy	Injection site pain lasting <24 h
Martin et al.	Type-I polymerized collagen	II–III	Collagen (n = 32) vs. HA (n = 32)	5 injections (1 per week for 5 consecutive weeks)	Baseline, 3 months, 6 months	↓ Lequesne Index ↓ VAS ↓ Pain killer consumption ↑ SF-36 questionnaire	Moderate post-injection reaction (1/32, collagen group)
Lee et al.	Type-I atelocollagen	I–III	Collagen (n = 101) vs. placebo (n = 99)	1 injection	Baseline, 1 month, 3 months, 6 months	↓ VAS ↓ WOMAC ↑ SF-36 questionnaire	11/101, of which 55% knee pain
Borja-Flores et al.	Type-I polymerized collagen	II–III	Collagen (n = 309)	6 injections (1 per week for 6 consecutive weeks)	Baseline, 6–11 months, 12–35 months, 36–48 months, 49–60 months	↓ VAS ↓ WOMAC ↑ functional disability ↑ time of surgical referral of TKA	Injection site pain <24 h in all patients
De Luca et al.	Type-1 hydrolyzed collagen	I–IV	Collagen (n = 20)	3 injections (weeks 1, 15, and 45)	Baseline, 15 days, 1 month, 6 months	↓ Lequesne Index ↓ WOMAC ↓ VAS	None
Volpi et al.	Type-1 hydrolyzed collagen	I–IV	Collagen (n = 70)	3 injections (weeks 1, 15, and 45)	Baseline, 15 days, 1 month, 6 months	↓ Lequesne Index ↓ WOMAC ↓ VAS	None

Abbreviations: KL: Kellgren-Lawrence grade; vs: versus; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: Visual Analog Scale; TKA: Total Knee Arthroplasty; SF-36: 36-Item Short Form Survey; NSAID: Non-Steroidal Anti-Inflammatory Drug.

2. Methods

2.1: Ethics Statement

Informed consent was not obtained from patients as this was a retrospective, non-interventional study conducted in accordance with Korean law and institutional review board regulations at each institution.

2.2: Patients

A total of 91 patients who had been diagnosed with knee OA (radiologically assessed as Kellgren–Lawrence [KL] grades I, II, and III), had undergone the first treatment for at least 6 months, and had medical record data available for at least 1 month after re-administration of CartiPRO® at five facilities from May 2023 to September 2023 were included in this retrospective study. The inclusion criteria did not specify a specific side for affected knee, but patients who received injections on different sides between the first and second administrations were excluded. In accordance with the approval details, adults aged 19 years and older were enrolled, and patients who received the product for purposes other than knee OA, contraindicated patients (e.g., pregnant women), and others deemed inappropriate for data collection by the principal investigator were excluded.

2.3: Methods

Using the electronic medical record (EMR) system, we collected and retrospectively analyzed data from patients radiologically diagnosed with mild to moderate knee OA (KL grades I, II, and III).

2.4: Study Variables

The data collected included patient information (initials, age, sex, date of birth, weight, and height), medical history (other diseases, alcohol consumption, and smoking status), imaging data (e.g., magnetic resonance imaging and radiography findings where applicable), quantitative joint condition data (KL grade), clinical assessments (by the clinical study physician; rated as "effective," "somewhat effective," or "ineffective"), additional medication history (use of analgesic within 28 days before and after re-administration), adverse events (AEs) occurring within 26 weeks of re-administration of CartiPRO®, and concomitant medication history (medications concomitantly administered with CartiPRO® obtained from medical records or other collected data).

2.5: Clinical assessment and Safety Evaluation

2.5.1: Clinical Assessment: The clinical assessment was performed by the principal investigator at each facility, and effectiveness was rated as effective, somewhat effective, or not effective on the basis of the degree of pain relief determined by palpation, the patient questionnaire in the EMR, and imaging data. Pain relief was determined on the basis of the clinical research physician's assessment of patient reports of pain and subsequent medication use. A lack of pain complaints after re-administration was defined as "effective," and a decrease in pain severity and reduced need for additional pain medication was defined as "somewhat effective." Continued pain or the need for more pain medication was defined as "not effective." After re-administration of CartiPRO®, the clinical research physician assessed efficacy as "effective," "somewhat effective," or "not effective." "Effective" and "somewhat effective" were deemed as effective, whereas "not effective" was deemed as ineffective.

2.5.2: Safety Evaluation: EMR data regarding AEs occurring within 26 weeks following re-administration of CartiPRO® were retrospectively reviewed, and results are presented as percentages.

2.5.3: Other Evaluations: In addition to the clinical assessment, changes in the KL grades after CartiPRO® re-administration (as determined radiologically) were analyzed.

2.5. 6: Statistical Analysis

The sample size was not calculated, but we planned to collect the medical records of approximately 100 patients. The results of the clinical safety and efficacy evaluations are presented herein. The incidence of all AEs, incidence of AEs related to the study product, and 95% confidence intervals are presented. Differences in AE incidence by patient background and treatment factors were analyzed using the chi-square test. The percentages of each rating assigned by the clinical research physician were calculated. If data were available, changes in the radiological data and KL grade after administration of the product were analyzed using the chi-square test. Statistical analysis was performed using SAS software (SAS Institute).

3. Results

3.1: Demographic and Clinical Characteristics

A total of 91 patients who met the study criteria were enrolled. Patients' mean age was 74.03 ± 10.07 years, with 64.83% (59/91) aged 70 years and older, 26.37% (24/91) aged 60–69 years, and 6.59% (6/91) aged 50–59 years. Overall, 82.42% (75/91) of patients were older adults aged 65 years and older. Patients' mean height, weight, and body mass index were 159.92 ± 7.35 cm, 63.02 ± 8.30 kg, and 24.58 ± 2.19 kg/m^2, respectively. Among all patients, 8.79% (8/91) had a smoking history, while 7.69% (7/91) had an alcohol consumption history (Table 2).

Table 2: Patients' demographic and general characteristics.

		Safety set n = 91
Sex	Male	5 (5.49%)
	Female	85 (93.41%)
	UK	1(1.10%)
Age (years)	n	91
	Mean ± SD	74.03 ± 10.07
	Median (Min, Max)	75 (42, 95)
Age group (years)	19–29	0 (0.00%)
	30–39	0 (0.00%)
	40–49	2 (2.20%)
	50–59	6 (6.59%)
	60–69	24 (26.37%)
	≥70	59 (64.84%)
Older adult	<65	16 (17.58%)
	≥65	75 (82.42%)
Height (cm)	n	20
	Mean ± SD	159.92 ± 7.35
	Median (Min, Max)	159.50 (138.00, 170.00)
Body weight (kg)	n	20
	Mean ± SD	63.02 ± 8.30
	Median (Min, Max)	62.50 (50.00, 82.00)
BMI (kg/m^2)	n	20
	Mean ± SD	24.58 ± 2.19
	Median (Min, Max)	24.61 (20.83, 29.30)
Smoking history	Yes	0 (0.00%)
	No	8 (8.79%)
	NA	83 (91.21)
Alcohol consumption history	Yes	1 (1.10%)
	No	7 (7.69%)
	NA	82 (90.11%)

Abbreviations: UK: Unknown; NA: Not Applicable; SD: Standard Deviation; Min: Minimum; Max: Maximum; BMI: Body Mass Index

3.2 : Medical history

Overall, 79.12% of patients (72/91) had a documented medical history. The medical histories of the patients were categorized using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), as System Organ Class (SOC) and Preferred Term (PT). According to the SOC classification, the most common medical history was "Musculoskeletal and connective tissue disorders" (61.54%; 56/91), followed by "Metabolism and nutrition disorders" (27.47%; 25/91), and both "Gastrointestinal disorders" and "Vascular disorders" (23.08%; 21/91 each). According to PT classification, "Osteoporosis" was as the most common condition (50.55%; 46/91) followed by "Hyperlipidemia" (26.37%; 24/91) and "Chronic gastritis," "Spinal osteoarthritis," and "Hypertension" (21.98%; 20/91 each) (Table 3).

Table 3: Patients' medical history.

SOC	PT	Safety set n = 91
Medical history	Yes	72 (79.12%)
	No	19 (20.88%)
Blood and lymphatic system disorder		2 (2.20%)
	Anemia	2 (2.20%)
Cardiac disorder		4 (4.40%)
	Angina pectoris	2 (2.20%)
	Arrhythmia	1 (1.10%)
	Atrial fibrillation	1 (1.10%)
	Cardiac disorder	1 (1.10%)
Endocrine disorder		5 (5.49%)
	Hypothyroidism	5 (5.49%)
Gastrointestinal disorder		21 (23.08%)
	Chronic gastritis	20 (21.98%)
	Gastritis	1 (1.10%)
Hepatobiliary disorder		2 (2.20%)
	Hepatic steatosis	2 (2.20%)
Injury, poisoning, and procedural complication		3 (3.30%)
	Rib fracture	2 (2.20%)
	Spondylolysis	1 (1.10%)
Metabolism and nutrition disorder		25 (27.47%)
	Diabetes mellitus	10 (10.99%)
	Gout	4 (4.40%)
	Hyperlipidemia	24 (26.37%)
Musculoskeletal and connective tissue disorder		56 (61.54%)
	Back pain	1 (1.10%)
	Cervical spinal stenosis	1 (1.10%)
	Intervertebral disc disorder	2 (2.20%)
	Muscle disorder	1 (1.10%)
	Osteoporosis	46 (50.55%)
	Periarthritis	1 (1.10%)
	Rheumatoid arthritis	2 (2.20%)
	Spinal osteoarthritis	20 (21.98%)
	Spinal stenosis	4 (4.40%)
Nervous system disorder		11 (12.09%)
	Carpal tunnel syndrome	1 (1.10%)
	Cerebral infarction	1 (1.10%)
	Cognitive disorder	3 (3.30%)
	Dementia	6 (6.59%)
Psychiatric disorder		7 (7.69%)
	Anxiety disorder	3 (3.30%)
	Delusional disorder, unspecified type	1 (1.10%)
	Insomnia	3 (3.30%)
	Panic disorder	1 (1.10%)

	Sleep disorder	1 (1.10%)
Renal and urinary disorder		4 (4.40%)
	Glycosuria	1 (1.10%)
	Hematuria	3 (3.30%)
Respiratory, thoracic, and mediastinal disorder		1 (1.10%)
	Asthma	1 (1.10%)
Surgical and medical procedure		1 (1.10%)
	Bowel obstruction surgery	1 (1.10%)
Vascular disorder		21 (23.08%)
	Hypertension	20 (21.98%)
	Peripheral venous disease	2 (2.20%)
	Varicose vein	1 (1.10%)

Abbreviation: SOC: System Organ Class; PT: Preferred Term.

3.3: Concomitant Medication History

In this study, 72.53% of patients (66/91) used concomitant medications. These medications were classified according to the Anatomical Therapeutic Chemical (ATC) code level 1 (Anatomical main group) and level 2 (Therapeutic subgroup). According to the ATC code level 1 classification, medications for the "MUSCULO-SKELETAL SYSTEM" were the most frequently administered (31.87%; 29/91), followed by drugs for the "ALIMENTARY TRACT AND METABOLISM" (30.77%; 28/91), "NERVOUS SYSTEM" (18.68%; 17/91), and "CARDIOVASCULAR SYSTEM" (17.58%; 16/91) (Table 4).

Table 4: Concomitant drugs.

ATC Level 1	**ATC Level 2†**	**Safety Set N = 91**
Concomitant Medication Use History	Yes	66 (72.53%)
	No	25(27.47%)
Alimentary Tract And Metabolism		28 (30.77%)
	Antiemetics and Antinauseants	1 (1.10%)
	Bile and Liver Therapy	1 (1.10%)
	Drugs for Acid Related Disorders	20 (21.98%)
	Drugs for Functional Gastrointestinal Disorders	1 (1.10%)
	Drugs Used in Diabetes	4 (4.40%)
	Mineral Supplements	5 (5.49%)
	Vitamins	1 (1.10%)
Antiinfectives For Systemic Use		1 (1.10%)
	Antivirals For Systemic Use	1 (1.10%)
Blood And Blood Forming Organs		11 (12.09%)
	Antianemic Preparations	6 (6.59%)
	Antithrombotic Agents	7 (7.69%)
	Blood Substitutes and Perfusion Solutions	1 (1.10%)
Cardiovascular System		16 (17.58%)
	Agents Acting on the Renin-Angiotensin System	6 (6.59%)
	Calcium Channel Blockers	3 (3.30%)
	Cardiac Therapy	1 (1.10%)
	Lipid Modifying Agents	8 (8.79%)
	Peripheral Vasodilators	2 (2.20%)
	Vasoprotectives	3 (3.30%)

Dermatologicals		3 (3.30%)
	Antibiotics and Chemotherapeutics for Dermatological Use	1 (1.10%)
	Antifungals for Dermatological Use	1 (1.10%)
	Corticosteroids, Dermatological Preparations	1 (1.10%)
Musculo-Skeletal System		29 (31.87%)
	Antiinflammatory and Antirheumatic Products	15 (16.48%)
	Muscle Relaxants	11 (12.09%)
	Other Drugs for Disorders of the Musculo-Skeletal System	6 (6.59%)
Nervous System		17 (18.68%)
	Analgesics	2 (2.20%)
	Anesthetics	5 (5.49%)
	Other Nervous System Drugs	2 (2.20%)
	Psychoanaleptics	6 (6.59%)
	Psycholeptics	5 (5.49%)
Respiratory System		3 (3.30%)
	Cough and Cold Preparations	2 (2.20%)
	Drugs for Obstructive Airway Diseases	1 (1.10%)
Systemic Hormonal Preparations, Excluding Sex Hormones And Insulins		8 (8.79%)
	Corticosteroids for Systemic Use	8 (8.79%)

Abbreviation: ATC: Anatomical Therapeutic Chemical.

3.4 : Clinical Asessment

Treatment with CartiPRO® was effective in 73.63% of patients (67/91), somewhat effective in 23.08% (21/91), and not effective in 3.30% (3/91). “Effective” and “somewhat effective” were categorized as effective, whereas “not effective” was categorized as ineffective. Consequently, CartiPRO® was effective in 96.70% (88/91) and ineffective in 3.30% (3/91).

3.5 : Safety evaluation and other Evaluations

3.5.1 : Other evaluations: change in the KL grade after re-administration of CartiPRO®: The mean KL grades were 2.55 ± 0.88 before re-administration and 2.55±0.79 after re-administration. The mean change from baseline was -0.03±0.38. The change in the KL grade after re-administration from the baseline was not significant (Table 5). Regarding changes in the KL grade after re-administration, 1.43% of patients had the grade changed from G3 to G2, while 2.86% had the grade changed from G2 to G1 (Table 6). None of the patients with G4 or G1 at the baseline had their grades lowered after re-administration.

Table 5: Changes in the KL grade after re-administration of CartiPRO®.

	Efficacy set n = 91			
	Before administration	**After administration[a]**	**Change (after administration–before administration)**	**p-value**
n	84	77	70	0.5310 £
Mean ± SD	2.55 ± 0.88	2.55 ± 0.79	-0.03 ± 0.38	0.7656§
Median (Min, Max)	3.00 (1.00, 4.00)	3.00 (1.00, 4.00)	0.00 (-2.00, 1.00)	

[a] Based on the latest data after administration.

£: paired t-test, §: Wilcoxon signed rank test.

Abbreviations: SD: Standard Deviation; Min: Minimum; Max: Maximum; KL: Kellgren-Lawrence.

Table 6: Changes in the KL grade after re-administration of CartiPRO®.

Before administration / After administration	G0	G1	G2	G3	G4	p-value
G0	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.9477¢
G1	0 (0.00%)	6 (8.57%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	
G2	0 (0.00%)	1 (1.43%)	20 (28.57%)	1 (1.43%)	0 (0.00%)	
G3	0 (0.00%)	1 (1.43%)	2 (2.86%)	31 (44.29%)	0 (0.00%)	
G4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (8.57%)	

3.5.2 : Safety Evaluation

Among 91 patients in the safety set, 38.46% (35/91, 44 cases) developed an AE. However, there were no cases of medical drug-related AEs, serious adverse events (SAEs), serious drug-related AEs, unexpected AEs, unexpected drug-related AEs, serious and unexpected AEs, or serious and unexpected drug-related AEs (Table 7).

In terms of the MedDRA SOC, "Musculoskeletal and connective tissue disorders" were the most prevalent (12.09%; 11/91 patients, 11 cases), followed by "Nervous system disorders" (5.49%; 5/91 patients, 6 cases), "Vascular disorders" (5.49%; 5/91 patients, 5 cases), and "Infections and infestations" (4.40%; 4/91 patients, 4 cases). Concerning the MedDRA PT, "Back pain" was the most prevalent (4.40%; 4/91 patients, 4 cases), followed by "Osteoporosis" (3.30%; 3/91 patients, 3 cases) and "Anemia," "Gastritis," "Herpes virus infection," "Arthralgia," "Dizziness," "Insomnia," "Hypertension," and "Peripheral venous disease" (2.20%; 2/91 patients, 2 cases each). Regarding the incidence of AEs according to the use of analgesics, the incidences of AEs were 48.98% (24/49 patients, 29 cases) among those who used analgesics and 26.19% among those who did not use analgesics (26.19%; 11/42 patients, 15 cases).

Table 7: Incidence of AEs by type.

	Safety set n = 91		
	n (%)	95% CI	Number of cases
Adverse event	35 (38.46%)	(28.45%, 49.25%)	44
Drug-related AE[a]	0 (0.00%)	0 (0.00%)	0
SAE	0 (0.00%)	0 (0.00%)	0
Medical drug-related SAE	0 (0.00%)	0 (0.00%)	0
Unexpected AE	0 (0.00%)	0 (0.00%)	0
Unexpected drug-related AE	0 (0.00%)	0 (0.00%)	0
Serious and unexpected AE	0 (0.00%)	0 (0.00%)	0
Serious and unexpected drug-related AE	0 (0.00%)	0 (0.00%)	0

[a]All AEs excluding those that are "not related" or "likely not related" to the medical drug.
Abbreviations: AE: Adverse Event; SAE: Serious Adverse Event; CI: Confidence Interval.

4. Discussion

This study evaluated the safety and efficacy of knee OA treatment during a minimum follow-up of 7 months (6 months post-initial administration plus a minimum of 1month post-re-administration). After a minimum of 1 month following re-administration of CartiPRO®, the drug was "effective" in 96.70% of patients and "ineffective" in 3.30%, confirming its efficacy in alleviating knee pain in patients with OA and various knee cartilage defects.

Of the 91 participants evaluated for safety, 38.46% reported AEs. However, there were no cases of medical drug-related AEs that can conclusively be deemed unrelated to the medical drug, unexpected AEs/medical drug-related AEs, and SAEs. Regarding the incidence of AEs according to the use of analgesics, the incidences of AEs were 48.98% among those who used analgesics and 26.19% among those who did not use analgesics. Given that no drug-related AEs that were "related" or "probably related" to the medical drug were reported, the difference in the incidence of AEs between patients who did and did not use an analgesic is presumed to be attributed to the inclusion of AEs caused by the analgesic. Changes in the KL grades were examined for exploratory purposes. However, there were no significant changes in the KL grade

after the re-administration of CartiPRO® compared to the baseline. Given that this study retrospectively collected the degree of pain relief in patients, we could not compare the changes using imaging data (e.g., radiography) at exact time points before and after the re-administration of CartiPRO®; thus, further research is needed to investigate the effects of intra-articular injection of atelocollagen on cartilage regeneration. This study has a few limitations. First, only a small patient sample was studied, and the patient group was not compared to a control group. Future studies using a design that addresses these issues as well as prospective clinical trials are needed. Second, we did not use the widely used pain scales, such as the visual analog scale; instead, we had pain assessed by the principal investigator, which could have potentially introduced biases. Third, the safety evaluations were solely based on EMR data without any follow-up visits. Thus, the incidence of AEs after re-administration of CartiPRO® in a large population and more detail on the causal relationship with CartiPRO® need to be discussed in the future.

5. Conclusion

This study confirmed the long-term effectiveness of CartiPRO® in alleviating knee pain. The safety of CartiPRO® was also established, as evidenced by the absence of drug-related AEs, unexpected AEs, and SAEs. This study's findings suggest that intra-articular injection of CartiPRO® is a safe and effective long-term pain treatment option for patients with knee OA. The present study lays a foundation for future research on long-term pain relief using atelocollagen in patients with knee OA. Furthermore, it contributes to establishing clinical approaches by evaluating the long-term safety and efficacy of a second round of intra-articular injection of a Korean collagen filler product. Further prospective research, e.g., randomized clinical trials, should be conducted in larger study populations.

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