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Intra-articular Administration of ELHLD Peptide for the Recovery of Articular Function after Medial Patellar Luxation Corrective Surgery in Dogs

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ABSTRACT

Background: Medial patellar luxation (MPL) surgery in dogs commonly induces postoperative pain, inflammation and early joint dysfunction, which may contribute to long-term degenerative joint changes. Although NSAIDs are widely used, their limitations and adverse effects have led to increased interest in intra-articular therapies. Transforming growth factor-β1 (TGF-β1) plays a dual role in cartilage homeostasis, but its overexpression in osteoarthritis promotes cartilage degeneration via the Smad 1/5/8 pathway. The ELHLD peptide, a selective inhibitor of TGF-β1, has been developed to suppress this pathway while promoting cartilage regeneration. This study aimed to evaluate the effects of intra-articular ELHLD peptide on postoperative inflammation, pain and functional recovery following MPL surgery.

Methods: This study was conducted in 15 dogs with bilateral grade II MPL undergoing corrective surgery. The right hindlimb was assigned to the treatment group (ELHLD peptide injection) and The left hindlimb was used as an untreated control, while ELHLD peptide (100 µg/kg) was administered intra-articularly immediately after surgery. Clinical evaluations included inflammatory index, muscle circumference of the femur (MCF), radiographic muscle width of the femur (MWF), range of motion (ROM) and owner-based gait scores. Measurements were performed preoperatively and at 2, 4, 6 and 8 weeks postoperatively.

Result: At 2 weeks postoperatively, both groups showed increased inflammation and decreased joint function; however, the treated group exhibited a relatively smaller deterioration. The inflammatory index significantly decreased in the ELHLD-treated group compared to the control group at 6 and 8 weeks. Both MCF and MWF exhibited an initial decrease at 2 weeks, followed by a gradual increase. Notably, between 4 and 8 weeks, the treated group demonstrated a significantly greater recovery compared to the control group. ROM decreased by approximately 30% at 2 weeks in both groups but showed a significantly greater recovery in the treated group starting at 4 weeks, reaching near preoperative levels by 8 weeks. Gait scores also declined initially but improved progressively, with significantly higher scores in the treated group at 8 weeks. Overall, ELHLD peptide administration resulted in reduced postoperative inflammation and significantly enhanced recovery of stifle joint function compared to the control group.

Key words: Degenerative joint disease, Dog, ELHLD peptide, Intra-articular injection, Patellar luxation.

INTRODUCTION

In patellar luxation surgery, procedures such as incision of soft tissues, resection of cartilage and bone and curettage are performed. These interventions induce severe pain and swelling, which can temporarily lead to a marked decline in joint function. In the long term, they may also contribute to degenerative changes within the joint. Such degenerative joint diseases frequently lead to significant morphological and biomechanical alterations if not adequately managed (Kataru *et al.*, 2022). These changes can result in chronic pain and discomfort and increase the risk of cranial cruciate ligament rupture. Therefore, continuous management is required after surgical correction of patellar luxation to delay the progression of degenerative joint disease (Roy *et al.*, 1992; Alam *et al.*, 2007).

The most commonly used management approach is the administration of nonsteroidal anti-inflammatory drugs (NSAIDs). In the immediate postoperative period, NSAIDs are administered at analgesic and anti-inflammatory doses, whereas long-term management of chronic osteoarthritis involves low-dose maintenance therapy (Autefage *et al.,* 2011; Henrotin *et al.,* 2005; KuKanich *et al.*, 2012; Lee *et al.*, 2019). However, due to their

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mechanism as cyclooxygenase (COX)-inhibiting agents, NSAIDs can cause adverse effects on the gastrointestinal tract and kidneys, making them less suitable for use in geriatric dogs. Moreover, NSAID therapy alone is often insufficient to fully control degenerative joint disease (Ryan *et al.*, 2006; Gowan *et al.*, 2011; Kim *et al.*, 2016). Furthermore, alternative and integrative therapies are increasingly evaluated for the management of joint inflammation and osteoarthritis in canines (Ashwath *et al.*, 2021). Accordingly, recent studies have focused on various intra-articular therapeutic agents for the treatment of osteoarthritis (Chevalier, 2010; Cook *et al.*, 2016; Cabon *et al.*, 2019; Kim *et al.*, 2019; Jeong *et al.*, 2021).

Transforming growth factor-beta 1 (TGF-β1) is a cytokine known to play an important role in cartilage homeostasis by promoting chondrogenesis and the synthesis of extracellular matrix components in articular cartilage (18, 26, 28). Under normal physiological conditions, TGF-β1 acts through the Smad 2/3 pathway to suppress changes in chondrocytes. However, in osteoarthritis, TGF-β1 is overexpressed and activates the Smad 1/5/8 pathway instead of the Smad 2/3 pathway, leading to the transformation of chondrocytes into macrophage-like or apoptotic cells (Li *et al.*, 2021). These changes result in the formation of osteophytes within the joint and degeneration of the subchondral bone, causing discomfort during movement and a reduced range of motion. Recent studies have reported that inhibition of TGF-β1 has cartilage-protective and regenerative effects in osteoarthritis in both rodents and humans (Ping *et al*, 2021). The ELHLD peptide was developed as an inhibitor of TGF-β1 (Kim *et al.*, 2016) and selectively blocks the Smad 1/5/8 pathway by binding to TGF-β1 in joint cells, thereby suppressing inflammatory responses and pain while promoting cartilage regeneration (Mobasheri and Henrotin, 2010; Kim *et al.*, 2016).

In this study, the TGF-β1 inhibitor ELHLD peptide was administered in the early phase following surgical correction of patellar luxation, with the aim of evaluating its effects on post-operative pain, inflammation and degenerative changes, as well as its potential to facilitate early recovery of joint function.

MATERIALS AND METHODS

Dog selection and study protocol

This study was conducted using 15 client-owned dogs diagnosed with bilateral grade II medial patellar luxation that underwent corrective surgery. Exclusion criteria included the presence of concurrent musculoskeletal disorders, asymmetrical damage between the stifle joints and a history of receiving pharmacological treatments that affect the musculoskeletal system (26). Prior to the procedure, the owners were provided with detailed information regarding the surgical procedure and the administration of ELHLD peptide and written informed consent was obtained. Preoperative evaluations included a physical examination (body weight, blood pressure, body temperature, heart rate, respiratory rate and body condition score) as well as routine blood tests.

The surgical procedure included trochleoplasty, tibial tuberosity transposition and fascia imbrication as required. After these procedures were completed, the joint capsule and fascia were sutured, followed by intra-articular injection of ELHLD peptide. Subsequently, subcutaneous and skin sutures were performed to complete the surgery (Roy *et al.*, 1992). The contralateral stifle joint underwent the same surgical procedures but without ELHLD peptide administration.

ELHLD peptide administration

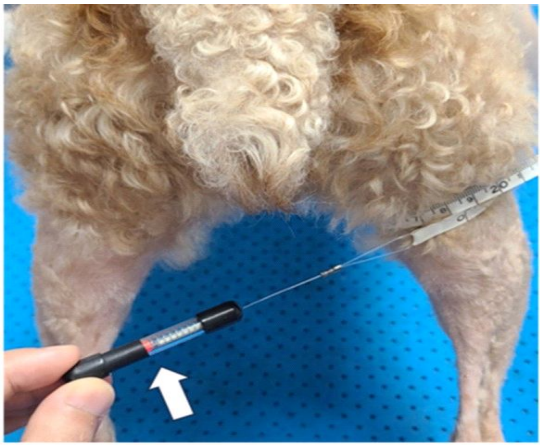
For intra-articular injection, JointVex® (Vexpert, Korea) was used. The ELHLD peptide (0.5 mg/vial), provided as a white powder formulation, was mixed with sterile normal saline prior to administration. The solution was then injected intra-articularly at a dose of 100 µg/kg, adjusted according to the body weight of the patient.

Inflammation index evaluation

All dogs were evaluated by the same experienced veterinarian to ensure consistency. The inflammation index was assessed based on several clinical parameters, including weight-bearing status, joint mobility, pain on palpation, swelling, heat and redness. These parameters were scored before injection and at 2, 4, 6 and 8 weeks after injection (Waxman *et al.*, 2008; Hielm-Björkman *et al.*, 2009).

Muscle circumference of femur

Femoral muscle circumference was measured by an experienced veterinarian with the dog in a standing position (Bascuñán *et al.*, 2016). The circumference of the thigh was measured at 50% of the thigh length, defined as the midpoint between the greater trochanter and the patella. Measurements were obtained using a Gulick II tape measure (Fig 1). The values were recorded preoperatively and at 2, 4,



Thigh circumference was measured using a Gulick II tape measure. The measurement was taken while maintaining constant tension, ensuring that one red bead on the handle (white arrow) was fully exposed.

Fig 1: Measurement of thigh circumference.

6 and 8 weeks postoperatively (Hielm-Björkman *et al.*, 2009, Baker *et al.*, 2010, Mobasheri and Henrotin, 2010).

Radiographic muscle width of the femur (MWF)

To complement the subjectivity of MCF measurements, thigh width was also assessed (Bascuñán *et al.*, 2016). Ventrodorsal radiographs of the hindlimbs were obtained and the width of the thigh muscle, perpendicular to the femur, was measured at the mid-thigh (50% TL). Measurements were performed using a PACS DICOM viewer (Weview, Woorien, Korea) (Fig 2). Thigh circumference was quantified preoperatively and at 2, 4, 6 and 8 weeks postoperatively.

Range of motion of the stifle joint

ROM of the stifle joint was measured by an experienced veterinarian using a goniometer (MP-90, SB®, Korea) with the dog in a standing position (Fig 3). Measurements were taken preoperatively and at 2, 4, 6 and 8 weeks postoperatively to quantify changes in joint mobility (Waxman *et al.*, 2008).

Owner's assessment score of gait analysis

Owner-based gait evaluation was conducted using a questionnaire developed with reference to the Canine Brief Pain Inventory and the Helsinki Chronic Pain Index. Additional detailed items were included to evaluate the dog's functional limb use in various daily situations, such as limb positioning at rest, posture while sitting, standing posture during feeding and posture during urination and defecation. The questionnaire was completed by the owners before surgery and at 2-, 4-, 6- and 8-weeks during follow-up examinations and the results were quantified for analysis (Brown *et al.*, 2013; Belshaw *et al.*, 2016).

Statistical analysis

Statistical analysis was performed using IBM SPSS version 25.0 (IBM Corporation, Armonk, New York, United States). The inflammation score, MCF, MWF, ROM and gait score were evaluated using repeated measures ANOVA before surgery and during follow-up visits at 2-week intervals (2, 4, 6 and 8 weeks). Statistical significance was set at $p<0.05$. Significance levels were indicated in the graphs as (*$p<0.05$) and (**$p<0.01$).

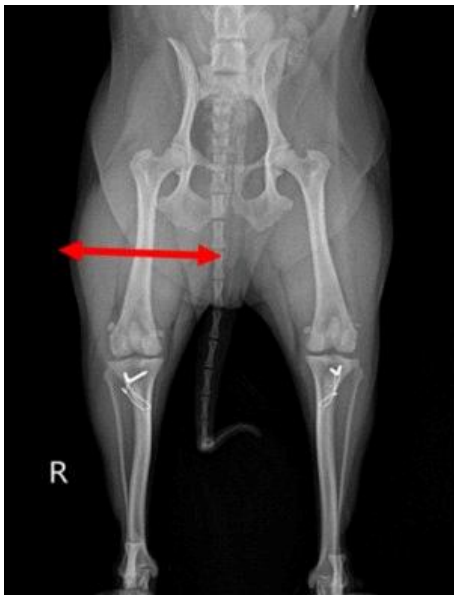
RESULTS AND DISCUSSION

Inflammatory index

Two weeks after surgical correction of patellar luxation, an increase in the inflammatory index-comprising postoperative pain, swelling, redness, lameness, heat and functional impairment-was observed in both the ELHLD peptide-treated and untreated groups. Compared to the untreated group, the ELHLD peptide-treated group showed a relatively smaller increase in the inflammatory index at 2 weeks postoperatively. The inflammatory index was measured at 2-week intervals and a gradual decrease was observed in both groups over time. At 6 and 8 weeks postoperatively, the inflammatory index in the ELHLD peptide-treated group was significantly lower than that in the untreated group (Fig 4).

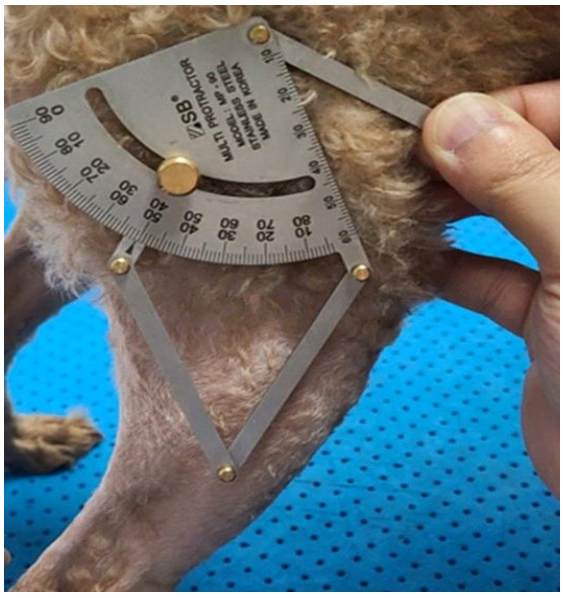
Muscle circumference of femur (MCF)

Two weeks after patellar luxation surgery, a decrease in MCF was observed in both the non-treated group and the



The width of the thigh muscle (red arrow) was measured using a PACS DICOM viewer.

Fig 2: Thigh width on radiographic imaging.



The angle of the stifle joint formed by the femur and tibia was measured using a goniometer in a normal standing position.

Fig 3: Range of motion of the stifle joint.

ELHLD peptide-treated group. MCF measurements were performed at two-week intervals and a gradual increase in MCF values was observed in both groups over time. However, the increase in MCF was more pronounced in the ELHLD peptide-treated group. In particular, a clear increase was observed between weeks 4 and 6 in the ELHLD-treated group (Fig 5).

At 8 weeks after surgery, the MCF value in the ELHLD peptide-treated group had increased to a level nearly comparable to the preoperative MCF measurement.

Radiographic muscle width of the femur (MWF)

Two weeks after surgical correction of patellar luxation, both the untreated group and the ELHLD peptide-treated group showed a decrease in thigh width (MWF) compared to preoperative values.

MWF was measured at 2-week intervals and a gradual increase was observed in both groups over time. The degree of increase in MWF was significantly greater in the ELHLD-treated group than in the untreated group at 6 and 8 weeks (Fig 6).

Range of motion of the stifle joint

Two weeks after surgical correction of patellar luxation, a decrease in the range of motion (ROM) of the stifle joint was observed in both the untreated group and the ELHLD peptide-treated group. In both groups, ROM gradually increased over time. The degree of increase in ROM was significantly greater in the ELHLD peptide-treated group than in the untreated group starting from 4 weeks, with more pronounced differences at 6 and 8 weeks (Fig 7). At 8 weeks postoperatively, the ELHLD peptide-treated group showed ROM values that were nearly restored to preoperative levels.

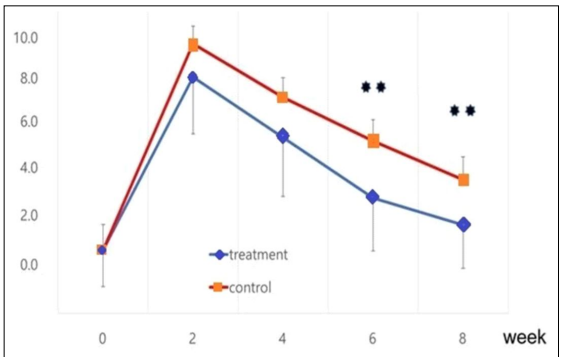
Owner's assessment of walking evaluation score

Two weeks after surgical correction of patellar luxation, gait scores based on owner questionnaires decreased in both the untreated group and the ELHLD peptide-treated group.

Gait scores were assessed at 2-week intervals and a gradual increase was observed in both groups over time. The degree of improvement was more pronounced in the ELHLD peptide-treated group, with a significantly higher gait score compared to the untreated group at 8 weeks (Fig 8).

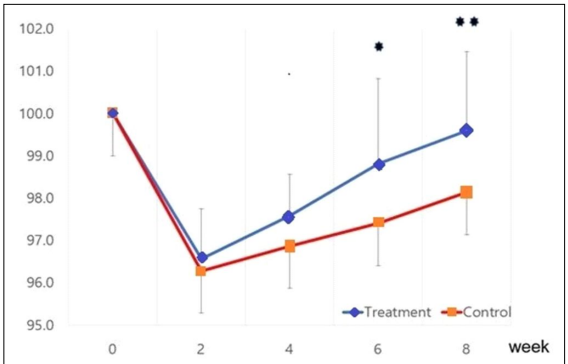
At 8 weeks postoperatively, gait scores in both groups had increased to levels higher than those observed preoperatively.

Conventional pain and anti-inflammatory management using NSAIDs has clear limitations and associated side effects (Mobasheri and Henrotin, 2010). Accordingly, recent studies have explored various intra-articular therapies for the treatment of arthritis. Hyaluronic acid (HA), platelet-rich plasma (PRP), mesenchymal stem cells (MSC) and corticosteroids have been used as intra-articular agents (Cook *et al.*, 2016; Lee *et al.*, 2019). In studies involving



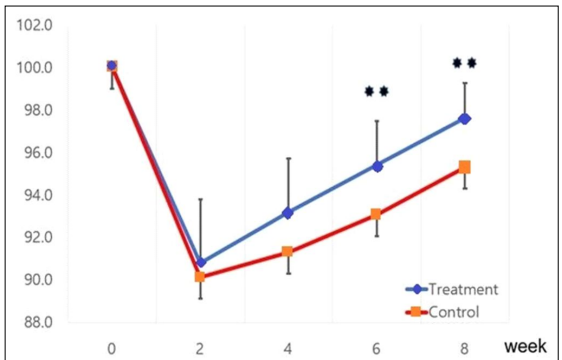
Following a peak at 2 weeks, inflammation scores decreased in both groups. However, the treatment group exhibited significantly lower inflammation scores compared to the control group at 6 and 8 weeks. Data are presented as mean ± SD. **p<0.01 vs. control group.

Fig 4: Changes in inflammation scores over time.



Thigh circumference (cm) was measured at 0, 2, 4, 6 and 8 weeks. The treatment group showed significantly higher values compared to the control group at 6 and 8 weeks. Data are presented as mean ± SD. * p<0.05, **p<0.01 vs. control group.

Fig 5: Changes in thigh circumference over time.



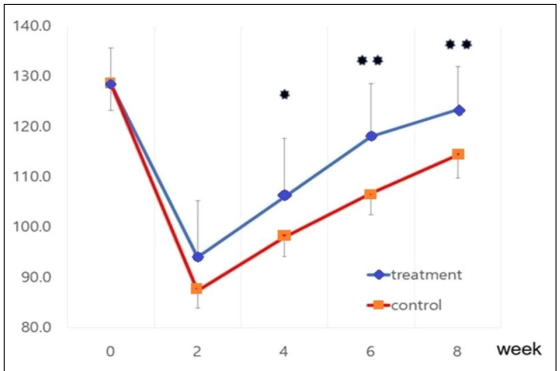
Following an initial decrease at 2 weeks, thigh circumference gradually increased in both groups. Notably, the treatment group demonstrated significantly higher values compared to the control group at 6 and 8 weeks. Data are presented as mean ± SD. **p<0.01 vs control group.

Fig 6: Changes in thigh circumference over time.

MSC administration, improvements in pain and joint range of motion were reported (Henrotin *et al.*, 2005). In another study using PRP and HA, joint function in dogs improved by 57% to 81% (Lee *et al.*, 2019). Additionally, administration of triamcinolone in dogs with hip dysplasia demonstrated a 95% improvement in pain (Autefage *et al.*, 2011).

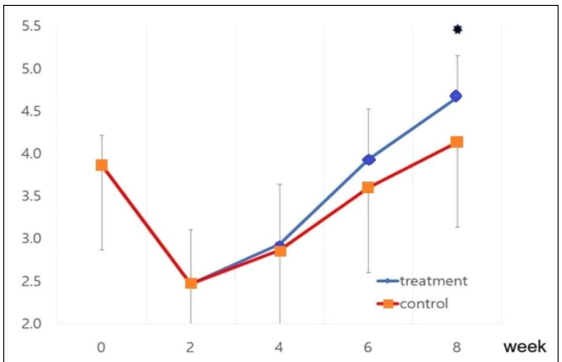
In this study, the selective TGF-β1 inhibitor ELHLD peptide was administered intra-articularly to evaluate its effectiveness as an analgesic and anti-inflammatory agent in osteoarthritis that inevitably develops after surgical correction of patellar luxation. The inflammatory index, thigh circumference, thigh width, ROM and gait score were measured at 2-week intervals over an 8-week period.

The inflammatory index increased sharply at 2 weeks in both the experimental and control groups. Although the increase was relatively smaller in the treated group, no statistically significant difference was observed compared to the control group. Due to the nature of patellar luxation surgery, which involves incision of soft tissues, resection of cartilage and bone and curettage, severe inflammation is induced, leading to a rapid decline in joint function. However, at 6 and 8 weeks, the inflammatory index in the experimental group was significantly lower than that in the control group.



Following a decrease at 2 weeks, the ROM gradually improved in both groups. Notably, the treatment group demonstrated a significantly greater ROM compared to the control group at 4, 6 and 8 weeks. Data are presented as mean ± SD. *p<0.05, **p<0.01 vs control group.

Fig 7: Changes in range of motion of the stifle joint over time.



Following a decrease at 2 weeks, gait scores gradually improved in both groups. Notably, the treatment group demonstrated a significantly higher gait score compared to the control group at 8 weeks. Data are presented as mean ± SD *p<0.05 vs control group.

Fig 8: Changes in gait scores over time.

MCF and MWF are indicators used to evaluate the degree of disuse muscle atrophy of the thigh caused by reduced weight-bearing on the hindlimb due to postoperative pain, inflammation and joint fibrosis. Consistent evaluation of lameness and weight-bearing is crucial for determining functional recovery following major orthopedic surgeries in dogs (Pravalika *et al.*, 2022). In some cases, these measurements can more accurately reflect the continuous contribution of each hindlimb to weight-bearing during daily activity than momentary clinical assessments, making them widely used indicators (Baker *et al.*, 2010). However, MCF measurements may be subject to variability due to factors such as patient posture, tension, joint flexion/extension and sedation, even when performed by experienced examiners (McCarthy *et al.*, 2018). To compensate for this limitation, MWF was measured using ventrodorsal radiographs of the hindlimbs (Bascuñán *et al.*, 2016).

Both the experimental and control groups showed marked decreases in MCF and MWF at 2 weeks. Although MCF showed a rapid increase between 4 and 6 weeks, its trend appeared more pronounced compared to other measurements, suggesting potential measurement-related variability. From 4 to 8 weeks, both MCF and MWF showed statistically significant differences between the experimental and control groups.

ROM decreased by approximately 30% on average in both groups between the preoperative period and 2 weeks postoperatively. The experimental group treated with ELHLD peptide showed a 26% decrease, whereas the control group showed a 34% decrease. During the 4- to 8-week evaluation period, the experimental group demonstrated a continuous and statistically significant increase in ROM compared to the control group.

Gait scores based on owner questionnaires were similarly low in both groups at 2 weeks postoperatively. However, from 2 to 8 weeks, gait frequency and activity levels gradually increased, resulting in a steep improvement in scores. At 8 weeks, the gait score in the treated group was significantly higher than that in the control group.

This study evaluated the recovery pattern of stifle joint function over 8 weeks following a single intra-articular administration of ELHLD peptide after surgical correction of patellar luxation. However, several limitations exist. First, the 8-week evaluation period is insufficient to assess chronic osteoarthritic changes. To more clearly verify the effects of ELHLD peptide on degenerative joint changes, long-term monitoring over at least one year-including radiographic evaluation of degenerative changes and assessment of repeated administration-would be

necessary. Second, comparisons with other treatment modalities were not performed. Comparative or combination studies involving NSAIDs, HA, PRP, MSC and corticosteroids are expected to contribute to establishing more effective strategies for improving joint function and preventing or mitigating degenerative changes in osteoarthritis.

CONCLUSION

This study was conducted in a total of 15 dogs, with the right hindlimb assigned to the treatment group and the left hindlimb serving as the untreated control. Following surgical correction of patellar luxation, the selective TGF-β1 inhibitor ELHLD peptide was administered to only one joint and outcomes were compared with the contralateral untreated joint. Various parameters in the treated group showed less deterioration in joint function immediately after surgery compared to the untreated group.

Over the 8-week evaluation period, the treated group demonstrated a consistently better recovery trend in stifle joint function than the control group, which was confirmed to be statistically significant. These findings suggest that ELHLD peptide is effective as an analgesic and anti-inflammatory agent in mitigating postoperative complications such as severe swelling and pain in the early phase after patellar luxation surgery, thereby promoting recovery of joint function.

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Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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