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Original Article

Therapeutic outcomes of combined Bupivacaine Liposome, 1,4-Butanediol Diglycidyl Ether-crosslinked sodium hyaluronate, and arthroscopic debridement in knee osteoarthritis management

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Abstract: Objective: To assess the effectiveness of arthroscopic debridement (AD) combined with Bupivacaine Liposome and 1,4-Butanediol Diglycidyl Ether (BDDE)-Crosslinked Sodium Hyaluronate in treating knee osteoarthritis (KOA). Methods: A total of 195 KOA patients were recruited and assigned to two groups based on the treatment modality: a control group (n=95) receiving standard AD and a research group (n=100) receiving the combined therapy. The efficacy of the treatment, inflammatory biomarkers (including tumor necrosis factor-alpha [TNF-α], interleukin [IL]-1β, and IL-6), quality of life (QOL), and patient-reported satisfaction were assessed. Besides, multiple scales were employed, including the Visual Analog Scale (VAS) for pain intensity, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for symptom severity, as well as the Hospital for Special Surgery (HSS) Knee Score and Lysholm Knee Score for functional recovery. Results: The research group demonstrated significantly superior overall efficacy and treatment satisfaction compared to the control group (P<0.05). Post-intervention improvements were observed in knee function scores (HSS and Lysholm) and QOL in both cohorts, with the research group showing greater enhancements (P<0.05). Furthermore, the combination therapy led to more pronounced reductions in WOMAC subscale scores (dysfunction, pain, and stiffness), VAS scores, and inflammatory markers (TNF-α, IL-1β, and IL-6) compared to the control group (P<0.05). Conclusions: The combination of Bupivacaine Liposome, BDDE-Crosslinked Sodium Hyaluronate, and AD shows great therapeutic potential in the management of KOA, supporting its broad clinical generalization.

Keywords: Bupivacaine Liposome, 1,4-Butanediol Diglycidyl Ether-crosslinked sodium hyaluronate, arthroscopic debridement, knee osteoarthritis

Introduction

Osteoarthritis (OA) is a chronic and debilitating musculoskeletal condition characterized by the progressive degradation of articular cartilage, leading to subchondral bone breakdown and impairment of surrounding synovial tissues [1]. The gradual erosion of joint cartilage and persistent pain in OA often induce functional impairment, decreased quality of life (QOL), and increased socioeconomic burden on the affected individuals [2, 3]. Global epidemiological data indicate that OA affects roughly 20.0% of the population, with a higher prevalence in females (13.0%) than in males (10.0%) [4, 5]. OA has a multifactorial pathogenesis, driven by factors such as obesity, aging, repetitive joint injuries, and hereditary predispositions, which exacerbate the condition over time [6]. Arthroscopic debridement (AD) serves as a frontline surgical intervention for knee OA (KOA), effectively removing free intra-articular bodies and inflamed synovium. However, its major drawback - synovial fluid depletion - often impairs recovery [7, 8]. This study presents an innovative therapeutic protocol that inte-

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grates AD with Bupivacaine Liposome and 1,4-Butanediol Diglycidyl Ether (BDDE)-Crosslinked Sodium Hyaluronate, designed to minimize synovial fluid depletion while enhancing AD effectiveness.

Bupivacaine Liposome, as an innovative local anesthetic encapsulated in liposomes, delivers prolonged postoperative pain relief, reducing the need for opioid analgesics. When used for post-arthroscopic local infiltration anesthesia, it offers benefits like accelerating rehabilitation and improving patient outcomes [9, 10]. BDDE-Crosslinked Sodium Hyaluronate (Hyruan ONE) is a single-injection exogenous hyaluronic acid (HA)-based treatment that prolongs intra-articular retention time and normalizes synovial fluid viscoelasticity, and ensures safer, more efficient clinical applications [11, 12]. Given their potent pain-relieving and inflammation-reducing properties, both agents are suitable adjuncts to arthroscopic procedures [13].

This study investigates the potential synergistic effects of Bupivacaine Liposome, BDDE-Crosslinked Sodium Hyaluronate, and AD in KOA patients. Through a comprehensive evaluation of therapeutic response, knee joint functionality, pain control, symptom management, inflammatory response, QOL, and patient satisfaction, this research provides strong evidence supporting the combination approach. The findings could optimize KOA treatment strategies and inform clinical practice and future therapeutic developments.

Materials and methods

General information

This retrospective study was approved by the Institutional Review Board of Changzhou Maternal and Child Health Care Hospital, Changzhou Medical Center, Nanjing Medical University. A total of 195 KOA patients were recruited between January 2024 and January 2025. The participants were divided into two groups: a control group of 95 patients who underwent AD, and a research group of 100 patients who received Bupivacaine Liposome, BDDE-Crosslinked Sodium Hyaluronate, and AD.

Inclusion and exclusion criteria

Inclusion criteria: Diagnosis of KOA in accordance with established criteria [14]; unilateral involvement; presence with clinical symptoms, including recurrent joint pain accompanied by swelling, morning stiffness, quadriceps atrophy, and audible crepitus during knee movement; history of at least three months of conservative management without symptomatic relief, with scheduled unilateral AD; absence of corticosteroid or immunomodulatory therapy within the past month; absence of psychiatric disorders and demonstrate normal cognitive and communicative abilities.

Exclusion criteria: knee varus or valgus deformities, or secondary KOA; severe angular deformities of the knee, lower extremity disability, osseous collapse, or joint deformation; recent treatments such as glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs) that could potentially confound the study results; known hypersensitivity to the pharmacological agents used in this research; concomitant lumbar spine pathologies, neoplasms, tuberculosis, osteoporosis, gout, septic arthritis, rheumatoid arthritis, or other musculoskeletal disorders; a history of knee trauma, systemic infections, or avascular necrosis of the joint; traumatic injuries, neoplasms, congenital malformations, or any other condition that may impair knee functionality; abnormal muscular strength; pregnancy or lactation.

Treatment protocols

Patients in the control group underwent AD of the knee joint, performed as follows: Combined spinal-epidural anesthesia was administered. Upon successful induction, the patient was positioned in the supine position. A sterile tourniquet was applied to the proximal thigh of the operative limb. Routine disinfection, including iodine tincture and alcohol applied to the entire lower limb distal to the tourniquet was performed, followed by the placement of sterile drapes. The surgical field was then covered with a sterile adhesive drape. Following routine exsanguination, the tourniquet was inflated. Standard anteromedial and anterolateral knee portals were established, with supplementary superomedial or superolateral portals utilized as needed. The arthroscope was introduced, and a sequential evaluation of the synovium, articular cartilage, meniscus, and anterior/posterior cruciate ligaments was conducted. Thereafter, hypertrophic synovial tissue was excised using an electric shaver and radiofrequency

ablation. Damaged portions of the meniscus were resected, and the remaining meniscus was contoured to a smooth surface. For areas of irregular or uneven articular cartilage, microfracture techniques were employed to address regions of cartilage detachment. The joint cavity was then copiously irrigated with 0.9% sodium chloride solution to remove residual synovial, meniscal, and cartilaginous debris. Finally, the incisions were meticulously closed with sutures, and a sterile compressive dressing was applied using an elastic bandage. Dressing changes were performed regularly postoperatively, with sutures removed 12-14 days following the procedure.

In addition to the AD protocol, patients in the research group received adjunctive therapy with Bupivacaine Liposome and BDDE-Crosslinked Sodium Hyaluronate. The specific method is illustrated as follows: At the end of the patient's knee arthroscopic procedure, a sterile syringe was used to puncture the previously disinfected area and inject Bupivacaine Liposome (133 mg, AVT (Shanghai) Pharmaceutical Tech Co., Ltd., S10001-1) into the joint cavity. The injection was administered slowly to avoid discomfort caused by rapid injection. Additionally, a 3-mL dose of BDDE-Crosslinked Sodium Hyaluronate (LG Chem, Ltd., HJ2023-3147) was injected into the knee joint cavity. Each treatment consisted of a single injection, with subsequent injections scheduled at intervals of no less than 6 months, adjusted based on clinical response and symptom severity.

Outcome measures

(1) Therapeutic efficacy: Therapeutic efficacy was assessed based on predefined criteria: Markedly effective: Patients demonstrated normal ambulation without pain at rest, during squatting, or physical activity; absence of swelling or tenderness around the joint; and a joint range of motion (ROM) ≥130°. Effective: Effective treatment was defined as normal ambulation with mild resting pain and discomfort during squatting or physical activities; absence of joint swelling but with mild tenderness; and a joint ROM ≥100°. Ineffective: Ineffective treatment was characterized by difficulty walking, significant pain at rest or during squatting or physical activities, joint swelling and tenderness, and a ROM <100°. The total effective rate was calculated as the combined rate of markedly effective and effective cases.

(2) Pain intensity: Pain intensity was measured using the Visual Analog Scale (VAS; score range: 0-10) at T1 (pre-treatment), T2 (7 days post-treatment), and T3 (28 days post-treatment) [15]. A higher score indicates greater pain severity.

(3) Symptom severity: Pre- and post-treatment symptom severity was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [16], which includes domains for dysfunction (68 points), joint pain (20 points), and joint stiffness (8 points). Scores are proportional to the severity of symptoms.

(4) Knee joint function: Knee function was evaluated using the Hospital for Special Surgery (HSS) Knee Score before treatment and at 4 weeks post-treatment [17]. The score encompasses six domains: pain (30 points), ROM (20 points), function (20 points), stability (10 points), flexion deformity (10 points), and muscle strength (10 points), with a maximum score of 100. Higher scores indicate superior knee function. Additionally, knee recovery was assessed using the Lysholm Knee Score [18], which includes pain and joint instability (25 points each), locking (15 points), swelling and climbing stairs (10 points each), and weight-bearing, limping, and squatting (5 points each), for a total of 100 points. Higher scores reflect better functional recovery.

(5) Inflammatory response: Peripheral venous blood samples were collected from patients after an overnight fast, both before and after treatment. Serum was isolated by centrifugation, and concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 were quantified using enzyme-linked immunosorbent assay (ELISA; Shanghai Genetimes Technology Inc., EH009, EH001, EH004).

(6) QOL: QOL was assessed using the QOL score [19], which evaluates physical function, social function, and material life, with each domain scored out of 100. Higher scores indicate better QOL.

(7) Treatment satisfaction: Treatment satisfaction was evaluated using a hospital-developed satisfaction questionnaire [20]. Scores were categorized as follows: Very Satisfied (80-100 points), Satisfied (60-79 points), Dissatisfied (<60 points). Total satisfaction was compara-

Table 1. Comparison of baseline characteristics between the two groups

Data	Control group (n=95)	Research group (n=100)	χ^2/t	P
Gender (male/female)	44/51	42/58	0.368	0.544
Age (years)	59.62±7.25	60.74±9.49	0.923	0.357
Disease duration (years)	3.20±1.31	3.10±1.66	0.465	0.642
Hypertension (without/with)	40/55	38/62	0.342	0.558
Coronary heart disease (without/with)	35/60	33/67	0.317	0.574

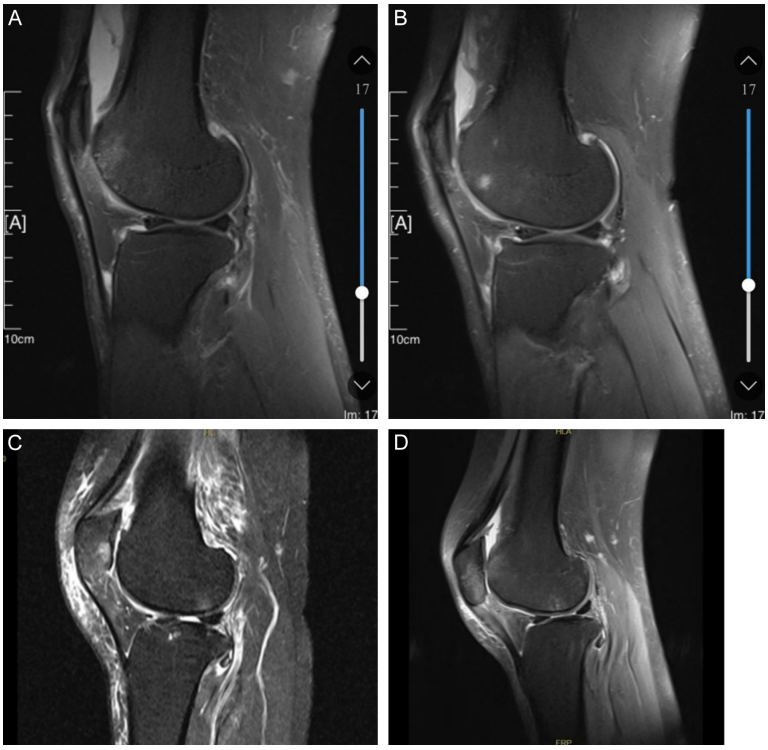

Figure 1. Comparative presentation of typical imaging findings. A. Pretreatment imaging of a patient in the control group. B. Posttreatment imaging of the same control group patient. C. Pretreatment imaging of a patient in the research group. D. Posttreatment imaging of the same research group patient (The effusion of suprapatellar bursa is significantly reduced, and the inflammation is alleviated).

tively analyzed. The overall satisfaction rate was calculated as the sum of very satisfied and satisfied cases, expressed as a percentage of the total cohort.

Statistical analysis

The data in this research were processed and analyzed using the SPSS 22.0. Categorical variables were expressed as frequencies and percentages (n/%), while continuous variables were presented as mean ± standard error of the mean (SEM). The chi-square (χ^2) test was used to compare categorical data between groups. Continuous data were analyzed using the independent t-test for intergroup comparisons and the paired t-test for intragroup comparisons before and after treatment. Statistical significance was defined as a *P*-value <0.05.

Results

Comparison of baseline characteristics between the two groups

No significant differences were observed between the control and research groups in baseline characteristics, including gender distribution, age, disease duration, comorbid hypertension, and comorbid coronary heart disease (*P*>0.05). This indicates that the two groups were comparable in a clinical context, as presented in **Table 1**.

Comparison of typical imaging findings between the two groups

Typical joint imaging findings before and after treatment in both patient groups can be seen in **Figure 1**. Prior to treatment, both groups exhibited characteristic radiographic features of OA, including joint space narrowing and subchondral bone sclerosis (**Figure 1A**, **1C**). Posttreatment evaluation revealed no significant radiographic improvement in joint pathology in the control group (**Figure 1B**). However, in the research group treated with bupivacaine liposome and BDDE-Crosslinked Sodium Hyaluronate therapy, there was marked radiographic improvement (**Figure 1D**), particularly in terms of reduced suprapatellar bursa effusion and alleviated synovial inflammation.

Table 2. Comparison of therapeutic efficacy between the two groups

Efficacy	Control group (n=95)	Research group (n=100)	χ^2	P
Markedly effective	38 (40.00)	58 (58.00)		
Effective	39 (41.05)	36 (36.00)		
Ineffective	18 (18.95)	6 (6.00)		
Overall effective rate	77 (81.05)	94 (94.00)	7.567	0.006

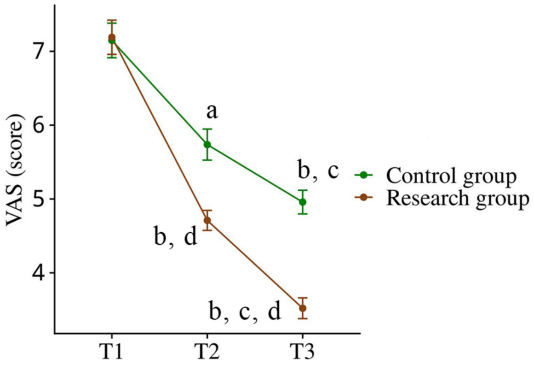

Figure 2. Comparison of pain intensity between the two groups. T1: Pre-treatment; T2: 7 days post-treatment; T3: 28 days post-treatment; VAS, Visual Analog Scale. Notes: [a]*P*<0.05, [b]*P*<0.01, compared to T1; [c]*P*<0.05, compared to T2; [d]*P*<0.05, compared to the control group.

Comparison of therapeutic efficacy between the two groups

In the control group, the number of cases classified as markedly effective, effective, and ineffective was 38, 39, and 18, respectively. In contrast, the research group had 58 markedly effective, 36 effective, and 6 ineffective cases. The overall effective rate was significantly higher in the research group than in the control group (*P*<0.05). For further details, see **Table 2**.

Comparison of pain intensity between the two groups

At time point T1, no marked differences were observed in VAS scores between the two groups (*P*>0.05). However, at T2 and T3, VAS scores decreased significantly in both groups, demonstrating a progressive decline (*P*<0.05). Notably, the research group exhibited significantly lower VAS scores than the control group at both T2 and T3 (*P*<0.05). See **Figure 2** for details.

Comparison of symptom severity between the two groups

Based on the WOMAC data, no statistical intergroup differences were observed in dysfunction, joint pain, or joint stiffness before treatment (all *P*>0.05). After treatment, significant reductions were observed in all WOMAC subscale scores (*P*< 0.05), with the research group achieving significantly lower scores than the control group (*P*<0.05). Refer to **Figure 3** for a detailed breakdown.

Comparison of knee joint function between the two groups

Prior to treatment, there were no significant disparities in the HSS and Lysholm Knee Score between the two groups (*P*>0.05). However, following treatment, both scores showed significant improvement (*P*<0.05), with the research group achieving significantly higher scores compared to the control group (*P*< 0.05). Refer to **Figure 4** for a visual representation.

Comparison of inflammatory response between the two groups

The data on inflammatory response-related markers, such as TNF-α, IL-1β, and IL-6, revealed no notable differences between the two groups before treatment (*P*>0.05). Post-treatment, these inflammatory marker levels were significantly decreased (*P*<0.05), with the research group showing significantly lower levels compared to the control group (*P*<0.05). See **Figure 5** for a detailed comparison.

Comparison of QOL scores between the two groups

No evident intergroup differences were observed in QOL scores for physical functioning, social functioning, or material life before treatment (all *P*>0.05). After treatment, all QOL scores improved significantly (*P*<0.05), with the research group achieving significantly higher scores than the control group (*P*<0.05). Refer to **Figure 6** for further details.

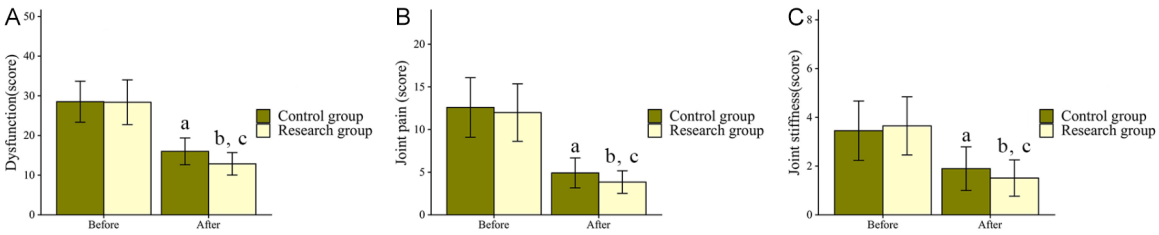

Figure 3. Comparison of symptom severity between the two groups before and after treatment. A. Pre- and post-treatment dysfunction scores. B. Pre- and post-treatment joint pain scores. C. Pre- and post-treatment joint stiffness scores. Notes: [a]*P*<0.05, [b]*P*<0.01, compared to the pre-treatment values; [c]*P*<0.05, compared to the control group.

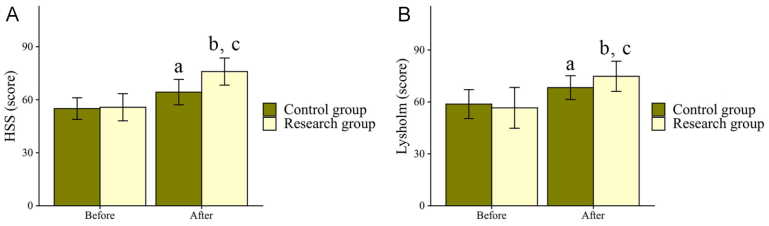

Figure 4. Comparison of knee joint function between the two groups before and after treatment. A. Pre- and post-treatment HSS Knee Scores. B. Pre- and post-treatment Lysholm Knee Scores. Note: [a]*P*<0.05, [b]*P*<0.01, when compared to the pre-treatment values; [c]*P*<0.05, when compared to the control group; HSS Knee Score, the Hospital for Special Surgery Knee Score.

Comparison of treatment satisfaction between the two groups

In the control group, the number of patients reporting very satisfied, satisfied, and dissatisfied was 36, 40, and 19, respectively. In the research group, the corresponding numbers were 55, 37, and 8. The research group demonstrated a statistically higher overall treatment satisfaction rate than the control group (*P*<0.05). See **Table 3** for a detailed comparison.

Discussion

Research on the efficacy of combining Bupivacaine Liposome, BDDE-Crosslinked Sodium Hyaluronate, and AD in the treatment of KOA patients remains limited. This study seeks to address this gap by providing robust clinical evidence to enhance therapeutic outcomes for individuals with KOA.

In this investigation, 195 KOA patients were enrolled to compare the clinical efficacy of AD alone versus AD combined with Bupivacaine Liposome and BDDE-Crosslinked Sodium Hyaluronate. The combined approach was found to be significantly more effective than AD alone (94.00% vs. 81.05%). This superior efficacy may be attributed to BDDE-Crosslinked Sodium Hyaluronate's ability to restore viscoelastic properties and physiological balance of synovial fluid, as well as its prolonged therapeutic actions versus conventional HA, thereby providing stronger joint protection by reducing mechanical vibrations [21, 22]. Furthermore, its sustained pain-alleviating effects can persist for over six months, and reinjections maintain efficacy while being well tolerated [21]. Regarding Bupivacaine Liposome, its unique sustained-release properties enable continuous drug release at the target site, providing prolonged pain relief while minimizing systemic absorption and thereby reducing adverse effects compared to traditional local anesthetics [23]. Through their complementary mechanisms of sustained analgesia, the two agents work synergistically to enhance AD's therapeutic benefits, leading to superior treatment performance.

Additionally, patients receiving the combined treatment demonstrated significantly reduced pain intensity, alleviated symptoms (such as joint stiffness, functional impairment), improved joint functionality, and enhanced QOL, including physical function, social function, and material life. All these beneficial outcomes were markedly superior to those achieved with AD alone. This superiority might be ascribed to the immediate postoperative injection of BDDE-Crosslinked Sodium Hyaluronate, which promptly adheres to the surfaces of the trimmed meniscus and cartilage to form a protec-

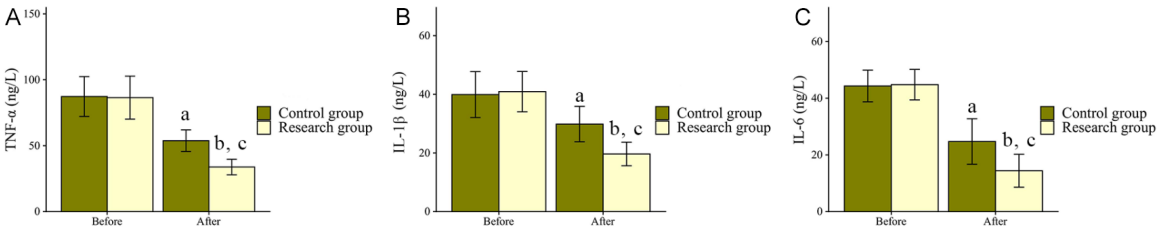

Figure 5. Comparison of the inflammatory response between the two groups before and after treatment. A. Pre- and post-treatment TNF-α levels. B. Pre- and post-treatment IL-1β levels. C. Pre- and post-treatment IL-6 levels. Notes: [a]*P*<0.05, [b]*P*<0.01, compared to the pre-treatment values; [c]*P*<0.05, compared to the control group; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1β; IL-6, interleukin-6.

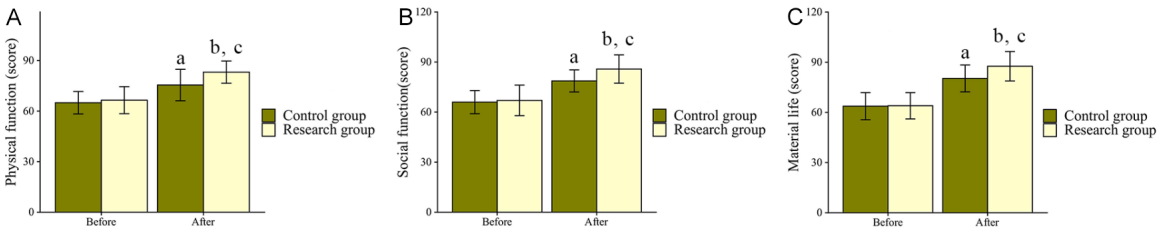

Figure 6. Comparison of QoL between the two groups before and after treatment. A. Pre- and post-treatment physical function scores. B. Pre- and post-treatment social function scores. C. Pre- and post-treatment material life scores. Notes: [a]*P*<0.05, [b]*P*<0.01, compared to the pre-treatment values; [c]*P*<0.05, compared to the control group; QoL, quality of life.

Table 3. Comparison of treatment satisfaction between the two groups

Satisfaction	Control group (n=95)	Research group (n=100)	χ^2	P
Very satisfied	36 (37.89)	55 (55.00)		
Satisfied	40 (42.11)	37 (37.00)		
Dissatisfied	19 (20.00)	8 (8.00)		
Total	76 (80.00)	92 (92.00)	5.881	0.015

tive barrier. This barrier prevents proteoglycan loss, preserves vascular integrity, and effectively inhibits the proliferation of bone cells, chondrocytes, and vascular endothelial cells. As a result, the progression of KOA is impeded, symptom severity is reduced, and the overall QOL is enhanced [24, 25].

TNF-α and IL-6 are closely associated with cartilage degradation in the knee joints of the elderly and serve as reliable indicators of disease severity in conditions involving knee cartilage damage [26, 27]. Among these cytokines, IL-1β plays a pivotal role in the progression of post-traumatic KOA. Selective IL-1 inhibitors have been shown to alleviate cartilage damage and reduce lesion severity by downregulating IL-1β concentrations [28]. In our study, the combined therapy significantly reduced the abnormally elevated levels of inflammatory markers such as TNF-α, IL-1β, and IL-6, outperforming the effects of AD alone. Notably, BDDE-Crosslinked Sodium Hyaluronate is known to envelop the synovial membrane through a combination of biological, chemical, and physical barriers, thus suppressing synovial inflammation and preventing hyperplasia and effusion. These mechanisms contribute to the anti-inflammatory effects observed with the combination therapy [12]. Furthermore, research has reported that Hyruan Plus can suppress inflammatory responses in KOA by partially inhibiting the Mitogen-Activated Protein Kinase (MAPK) pathway in chondrocytes and the p65/Nuclear Factor κB (NF-κB) signaling pathway in macrophages, providing insight into the potential mechanisms underlying the anti-inflammatory properties of BDDE-Crosslinked Sodium Hyaluronate [29].

The study ultimately revealed that patients undergoing the combination therapy reported

significantly higher treatment satisfaction (92.00% vs. 80.00%). This elevated satisfaction likely stems from the superior therapeutic outcomes achieved with the combined approach, which not only improved knee joint function but also reduced pain intensity, alleviated symptom severity, and enhanced overall QOL. These benefits collectively contributed to the marked increase in patient satisfaction. Supporting this, Blicharski T et al. [30] demonstrated that BDDE-Crosslinked Sodium Hyaluronate is both effective and safe for treating mild to moderate KOA, with pain relief comparable to that of active controls.

This study has several limitations that should be addressed. First, the satisfaction assessment survey was institutionally developed and evaluated only by our specialists, without undergoing reliability and validity testing. Future investigations should incorporate thorough psychometric evaluations, such as assessing content validity through expert review. Second, we did not explore the mechanisms underlying the combined therapy in depth. More detailed mechanistic research is needed to identify novel targets that could enhance treatment effectiveness. Finally, a key limitation is the lack of univariate and multivariate analyses to determine efficacy-related factors. Future work should conduct such analyses to identify predictors associated with treatment outcomes, which would facilitate the development of patient-specific clinical strategies.

In summary, the integration of Bupivacaine Liposome, BDDE-Crosslinked Sodium Hyaluronate, and AD significantly enhances therapeutic outcomes in KOA patients. This combined approach improves knee joint function, reduces pain, alleviates symptoms, suppresses inflammation, and increases treatment satisfaction. It offers novel insights for optimizing AD outcomes in KOA and presents a superior treatment option for this patient population.

Disclosure of conflict of interest

None.

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