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Research Article

Viscogel Technology for Enhanced Cartilage Repair: Preliminary Evidence of High Performance and Feasible In-Office Use

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Abstract

Because articular cartilage heals poorly, restoring damaged knee cartilage remains clinically difficult. Established non-cell-based procedures, including microfracture and mosaicplasty, frequently produce repair tissue with limited mechanical competence, durability, and integration. More advanced strategies, such as autologous chondrocyte implantation and stem-cell-based approaches, have their own limitations, notably loss of cells from the target site and nonuniform cell distribution. Sustained localization of therapeutic biological material is essential to the success of these treatments. Achieving reliable union between the implant and intact neighboring cartilage, however, remains unresolved, particularly when bone-marrow-derived products or autologous adipose tissue are used.

We investigated a viscogel intended for cartilage restoration, with particular attention to its adhesive behavior, tissue integration, and regenerative potential. The formulation demonstrated substantial adhesive strength and exceeded the performance reported for commercially available alternatives such as fibrin sealants.

Adhesion and long-term incorporation were examined *in vivo* in full-thickness caprine cartilage defects over a six-month period. Acellular viscogel treatment produced better continuity with adjacent tissue and more extensive repair than the untreated condition. A uniform intra-articular distribution was observed after infrapatellar administration and after medial or lateral knee approaches.

Complementary *in vitro* experiments showed that cells remained highly viable after encapsulation, were distributed successfully throughout the viscogel, and generated abundant matrix. Together, these observations support adhesive viscogels as delivery matrices capable of strengthening cell-based treatment strategies for knee cartilage injury.

Keywords: *Adhesive Viscogel; Articular Cartilage; Tissue Integration; Cartilage Repair*

Abbreviations

AB: Alcian Blue; ACI: Autologous Chondrocyte Implantation; cDNA: Complementary DNA; CS: Chondroitin Sulfate; DMEM: Dulbecco's Modified Eagle Medium; DMMB: 1,9-Dimethylmethylene Blue; DNA: Deoxyribonucleic Acid; DPBS: Dulbecco's Phosphate-Buffered Saline; ECM: Extracellular Matrix; EDTA: Ethylenediaminetetraacetic Acid; FBS: Fetal Bovine Serum; GAG: Glycosaminoglycan; HA: Hyaluronic Acid; H&E: Hematoxylin and Eosin; LAP: Lithium Phenyl-2,4,6-Trimethylbenzoylphosphinate; PBS: Phosphate-Buffered Saline; PCR: Polymerase Chain Reaction; PS: Penicillin-Streptomycin; PS: Phosphoserine; RNA: Ribonucleic Acid

Introduction

Treating focal knee-cartilage damage continues to pose technical and therapeutic difficulties. Selection of an intervention is influenced by lesion dimensions and severity, including the presence of chondromalacia, osteoarthrosis, or osteoarthritis. The clinical objectives are to restore or replace the damaged articular surface, reduce symptoms, and limit further osteoarthritic deterioration. Although the number of cartilage-restoration procedures has grown, the tissue's avascular nature and intrinsically weak healing response continue to constrain treatment effectiveness [1,2].

Small chondral defects, generally below 2 cm^2, are commonly managed by microfracture or osteochondral autograft transfer (mosaicplasty). The resulting repair tissue may nevertheless be mechanically inadequate for sustained loading, and subsequent procedures can become necessary. Larger lesions are often approached with cell-based methods, including successive generations of autologous chondrocyte implantation (ACI). Newer ACI techniques have improved long-term repair, yet important problems persist: suspensions may escape through membrane sutures, cells may distribute unevenly within the lesion, and complications such as infectious arthritis or severe synovitis may occur. Clinical responses also remain variable [3,4]. Another persistent limitation is inadequate lateral bonding between repair tissue and the healthy cartilage border [5,6].

Adhesive viscogels have therefore emerged as candidate biomaterials for cartilage engineering [7-9]. When adhesion is sufficient, a gel can be retained within a chondral defect while supporting cellular entry and continuity with neighboring tissue. Such scaffolds may also reproduce key features of the native extracellular matrix (ECM), thereby favoring cell survival, differentiation, and matrix synthesis [10]. Existing systems, however, do not consistently integrate with the defect margins. Contributing factors include insufficient adhesion, unsuitable molecular-weight profiles, application by inadequately trained operators, and a mismatch between viscosity and lesion size. Highly fluid formulations with low molecular weight or limited crosslinking generally bond slowly and weakly.

Progress in synthetic and animal-derived hyaluronic-acid hydrogels and other bioactive gels has not eliminated the need for an injectable material that cures rapidly, adheres firmly under knee loading, and produces few adverse effects [11,12]. Fibrin glues and preparations rich in platelets or fibrin, whether relatively fluid or dense, tend to provide limited mechanical fixation and may require repeated application, exposing the patient to additional procedures [13]. A clinically useful viscogel must therefore balance intrinsic adhesion, injectability, and load-bearing behavior. The formulation evaluated here was selected because its reported biophysical and biomechanical profile meets these requirements while showing a favorable tolerability profile relative to the compared marketed products.

One recently reported platform consists of injectable, intrinsically adhesive viscogels whose physicochemical characteristics can be tuned and whose curing is activated by light [12]. Its clinical accessibility may be restricted, however, when repeated exposure to high-power laser equipment is required, because both the material and the necessary device add substantial cost.

The present proof-of-concept study examined whether this viscogel can function as an adhesive support for articular-cartilage restoration. Homogeneous incorporation of the acellular device was assessed in a caprine *in vivo* model. In parallel, bovine chondrocytes were encapsulated *in vitro* to determine whether the matrix could serve as a cell-delivery vehicle and promote a regenerative response. These experiments were designed to evaluate the formulation's capacity to improve chondrocyte-based treatment of knee-cartilage defects.

Materials and Methods

In vivo study

Animal model and surgical procedures

The animal experiment included three healthy, two-year-old male Anglo-Nubian goats weighing approximately 70 kg. The Institutional Animal Care and Use Committee of Assis Gurgacz College (FAG) authorized the protocol. Eligibility was confirmed through clinical assessment and blood and urine testing. Food was withheld for 18h before surgery, while water remained available.

Ketamine (3 - 5 mg/kg) and diazepam (0.2 mg/kg) were administered to induce general anesthesia, and meloxicam (0.2 mg/kg) was given pre-emptively for analgesia. Each goat was intubated, supplied with oxygen, and maintained under isoflurane anesthesia. Ophthalmic ointment protected the corneas. The left knee was exposed through a medial parapatellar approach. A chondrotome was then used to produce 5-mm-diameter, full-thickness defects in the femoral trochlear groove. Experimental lesions received sterile BIOVISC ORTHO SINGLE precursor containing 15 wt% polymer. Immediately after filling, the material was polymerized in situ for 1 min with a portable 405-nm light source. Control defects received no material. Postoperatively, the animals were allowed unrestricted weight bearing without immobilization and received meloxicam at 0.1 mg/kg once daily for five days. One animal was euthanized seven days after implantation and three animals at six months for comprehensive examination. At each assessment time, one animal was designated as a control.

Histological analysis

After euthanasia, the operated knees were harvested to examine repair tissue and determine whether the implanted viscogel remained intact within the lesions. Specimens were fixed overnight in 10% buffered formalin and decalcified in formic acid. They were then passed through graded ethanol (70 - 100%), cleared with xylene, and embedded in paraffin. Sections cut through the center of each defect were stained with hematoxylin and eosin to assess tissue architecture and with alcian blue to evaluate glycosaminoglycan-rich matrix.

Primary cell culture

Bovine articular chondrocytes were isolated from knee joints and expanded at 37°C in conventional T75 culture flasks. Dulbecco's Modified Eagle Medium containing 10% fetal bovine serum, 1% penicillin-streptomycin, and 1% L-glutamine served as the expansion medium. Cells were mixed with 5.5% polymer viscogel precursor at 1 × 10^7 cells/mL. The cell-gel mixtures were cast in cylinders measuring 5 mm in diameter and 2.2 mm in height, then exposed to 405-nm light at 10 mW/cm^2 to induce polymerization. Constructs were subsequently maintained for as long as four weeks in freshly prepared, serum-free chondrogenic DMEM supplemented with 50 µg/mL vitamin C, 10 ng/mL TGF-β3, diluted ITS IV, 1% penicillin-streptomycin, and 1% L-glutamine. Medium was replaced every third day. Cellular behavior, matrix accumulation, and microtissue formation were monitored throughout culture.

Cell viability and distribution analysis

Viability was measured with the Live-Dead Assay kit (Biotium, Fremont, CA, USA) according to the supplier's instructions. Calcein AM and ethidium homodimer were diluted in PBS to final concentrations of 0.2 µL/mL and 0.4 µL/mL, respectively. Each construct was bisected, exposed to the staining mixture for 20 min, rinsed with PBS, and examined at 20× magnification with a Zeiss LSM 700 confocal microscope (Carl Zeiss, Jena, Germany). Green- and red-fluorescence channels were recorded with the corresponding filters. Cell survival was additionally quantified from confocal Z-stacks with a custom script in FIJI.

Biochemical analysis

DNA and sulfated glycosaminoglycan contents were determined biochemically at predefined sampling times. Specimens were minced, placed in 1.5-mL tubes, and digested overnight at 60°C in 500 µL of buffer containing papain at 6 µL/mL (Sigma P-3125). The buffer was prepared in 500 mL deionized water with 7.1 g Na_2HPO_4, 1.86 g EDTA, and 870 mg L-cysteine HCl, and adjusted to pH 6.5. For the dimethylmethylene-blue assay, performed against shark chondroitin sulfate, 20 µL of each digest and 130 µL of dye were dispensed in triplicate into a 96-well plate. Absorbance was read at 590 nm on a Wallac 1420 Victor2 reader (PerkinElmer, Ramsey, MN, USA). DNA was measured separately with Hoechst 33258 (Thermo Fisher Scientific): 10 µL of digest was combined with 140 µL of dye in a black 96-well plate, fluorescence emission was recorded at 460 nm, and concentrations were derived from a calf-thymus-DNA calibration curve.

Gene expression analysis

At every collection point, RNA was recovered from the constructs for real-time PCR analysis. Hydrogels were placed in microcentrifuge tubes with 300 µL Trizol and disrupted on ice using a pestle. RNA purification followed the NucleoSpin RNA protocol (Macherey-Nagel,

Düren, Germany), and yield was measured on a NanoDrop Lite spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). One microgram of RNA was reverse-transcribed with TaqMan Reverse Transcription reagents (Applied Biosystems). Quantitative PCR was performed using SYBR Green Master Mix on a StepOnePlus instrument (Applied Biosystems, Waltham, USA). Targets comprised the chondrogenic genes COL2A1 and ACAN and the catabolic gene ADAMTS5; RPL13A served as the reference. Thermal cycling began with 1 minute at 95°C and continued for 40 cycles of 5s at 95°C and 30s at 60°C. Relative transcript abundance was calculated by the ΔΔCT method.

Results and Discussion

Tensile adhesion was quantified for BIOVISC ORTHO SINGLE, BIOVISC ORTHO PLUS, and BIOVISC ORTHO at polymer contents of 5%, 10%, and 15% by weight. Adhesive strength rose with polymer concentration for BIOVISC ORTHO SINGLE and BIOVISC ORTHO PLUS. Despite containing 95 wt% water, both formulations exceeded approximately 14 kPa, the value associated with fibrin glue commonly used to retain cells during ACI or secure them within a defect. Fibrin material prepared from platelet-rich plasma has limited mechanical resistance in addition to weak adhesion and undergoes rapid degradation *in vivo* [14]. These properties can permit early loss of fixation or migration of implanted material before adequate healing has occurred.

Increasing polymer content also increased compressive stiffness. At 15 wt%, the compression modulus was approximately 468.2 ± 44.2 kPa for BIOVISC ORTHO SINGLE and 264.9 ± 25.6 kPa for BIOVISC ORTHO PLUS. Both measurements indicate considerably greater structural support than is ordinarily expected from platelet-rich-plasma-derived fibrin glue.

We next combined an *in vivo* proof-of-concept experiment with *in vitro* molecular analyses to assess longer-term behavior, biological compatibility, and interactions between the viscogels and cells.

Male goats were chosen for the *in vivo* experiment because their joint loading and cellular characteristics were considered relevant to the intended human application. A veterinarian created a cartilage lesion by a mosaic-type procedure and placed the viscogel into the defect (Figure 1a). Histology at two days compared an untreated cavity with a viscogel-filled lesion (Figure 1b). Whereas the control remained clearly unfilled, the treated site already showed contact and early continuity with the cartilage margins. This finding indicates that the material was retained locally during the initial repair phase. The matrix may also support cell movement and ECM deposition at the interface. In combination with progressive mechanical accommodation and the scaffold's material properties, these processes could contribute to durable incorporation into native cartilage.

Six-month histology further distinguished the treated and control defects (Figure 1c). Hematoxylin-and-eosin sections showed lateral continuity between the viscogel scaffold and surrounding cartilage in treated samples, as indicated by the arrows. Untreated lesions instead retained conspicuous interfacial spaces and fissures. Alcian-blue staining likewise demonstrated more extensive repair, matrix deposition, and better alignment at the margins after viscogel application. Staining intensity remained low, consistent with limited glycosaminoglycan content and a predominantly fibrocartilaginous repair response, which was expected because the implanted gel contained neither cells nor a biological agent. No inflammatory or immune adverse response was identified, supporting intra-articular biocompatibility.

These adhesive and physicochemical properties also support evaluation of the formulation as an injectable carrier for cells, drugs, platelet-rich plasma, or bone-marrow-derived products. To examine cell-related performance directly, bovine chondrocytes were embedded in BIOVISC ORTHO SINGLE and BIOVISC ORTHO PLUS and evaluated *in vitro*. Both matrices supported survival, proliferation, and extracellular-matrix formation. BIOVISC ORTHO SINGLE, which is based on hyaluronic acid, displayed the stronger mechanical and chondroinductive profile. Increased expression of chondrogenic markers together with suppression of the catabolic marker ADAMTS5 reinforced the regenerative potential of the systems.

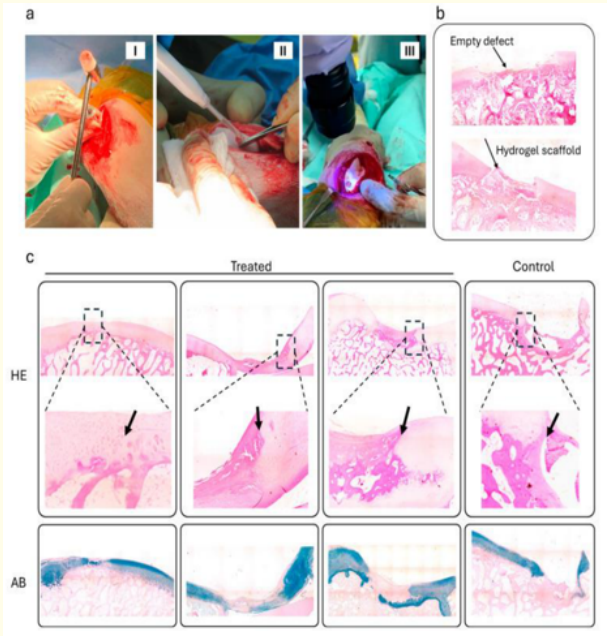

Figure 1: *Operative creation of cartilage defects and histological findings in viscogel-treated and untreated sites.*

Conclusion

The caprine findings indicate that BIOVISC ORTHO SINGLE may address important limitations in articular-cartilage treatment. The formulation adhered to the defect and established continuity with neighboring tissue, two requirements for stable repair. Its material characteristics also created a three-dimensional environment compatible with cellular growth, differentiation, and matrix formation. Notably, the homogeneous incorporation seen *in vivo* may help overcome the weak interface frequently observed after conventional cartilage-restoration procedures. These observations justify further investigation of viscogel-assisted cell therapy for knee defects.

Several characteristics of the observed response may be relevant to future clinical translation.

Firm union between native and newly formed tissue could improve restoration of joint-surface function. In advanced ACI, an adhesive injectable carrier may reduce reliance on retention membranes while limiting both cell escape and uneven distribution. By holding therapeutic cells within the injured region, the viscogel could prolong their local activity, including extracellular-matrix synthesis and other reparative processes. With appropriate patient selection and a validated protocol, combining these materials with intra-articular biological agents or drugs may therefore improve tissue repair, mobility, and quality of life.

Additional *in vitro* and *in vivo* investigations using human cells and intra-articular administration have been completed to refine the therapeutic protocol and further characterize the efficacy and safety of BIOVISC ORTHO SINGLE and BIOVISC ORTHO PLUS.

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Editorial Note

This manuscript was rewritten in English from the supplied source while retaining its reported numerical values, product nomenclature, methodological details, and apparent internal inconsistencies. These items should be verified by the authors before submission.

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