A New Injectable Cartilage Void-filler-defect Repair for Osteoarthritis or Trauma Injuries

Nicolas DUVAL*, Cyril CHAPUT, Abdellatif CHENITE**, Amine SELMANI**§**

***Clinique Nicolas Duval**, 1457 Bd des Laurentides, Laval (Quebec) H7M 2Y3 Canada; ****Oligo-Medic Inc**., CQIB, suite 113, 500 Bd Cartier, Laval (Quebec) H7V 5B7 Canada.

§Contact: A. Selmani; selmani@oligomedic.com

Introduction

In the recent years, thermo-gelling biopolymeric systems have elicited much interest for biomedical applications such as tissue repair, delivery systems, tissue engineering and cell encapsulation matrices (1). An aqueous solution of Polyglucosamine (PG) can be neutralized by using a buffering solution of Glucosamine Carbonate (GC). The thermo-gelling Polyglucosamine/Glucosamine Carbonate (PG/GC) system is obtained by admixing appropriate amounts of GC solution to a PG solution at room temperature, preferably between 5 and 20℃, under vigorous stirring. The resulting solution, even at pH between 6.7 and 7.2, has been found to remain liquid at room temperature and turns rapidly into a solid hydrogel when heated up to 37℃ or above. This novel injectable Polyglucosamine-based (PG/GC) composition, ***JointRep™***, is proposed as Cartilage void-filler matrix for Osteoarthritis or Trauma injuries.

Characteristics of the thermo-gelling PG/GC system, *JointRep™*

The PG/GC system is a pH-triggered temperature-stimulated hydrogel-forming composition, and as such, the thermo-gelling characteristics are mainly influenced by the final pH in the PG/GC solution and by the gelling temperature. Among many possible PG/GC compositions, we determined that a PG/GC solution with a concentration of 53.3 mM in Glucosamine and 77.6 mM in Carbonate, and with a final pH between 6.8 and 7.4 has ideal thermo-gelling characteristics: when poured in a test tube and incubated at 37℃, it gels within approximately 1 minute. Moreover this PG/GC system has a dual gelation property: it gels at high and at low temperatures (***Figure 1***).

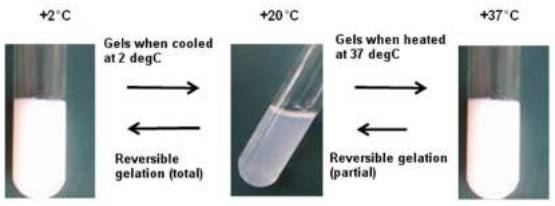


Figure 1

Figure 2 illustrates the evolution of the elastic modulus and viscous modulus with the temperature of a thermo-gelling composition having a pH value around 6.7 (PG, dda=98%) as described herein.

The ***JointRep™*** PG/GC device is prepared as a sterile 3-component kit, generally 3 sterile component syringes: Polyglucosamine (PG), Glycosamine chloride (G) and (sodium) carbonate salts (C). The thermo-gelling PG/GC device is reconstituted just a few minutes before its use of administration.

The ***JointRep™*** PG/GC device has been tested for toxicity and biocompatibility (cytotoxicity, irritation, mutagenicity, skin sensitization, acute systemic toxicity, animal implantation in cartilage defects) as per ANSI/AAMI/ISO 10993 international standards. All test results show that the ***JointRep™*** PG/GC device is fully non-toxic and biocompatible.

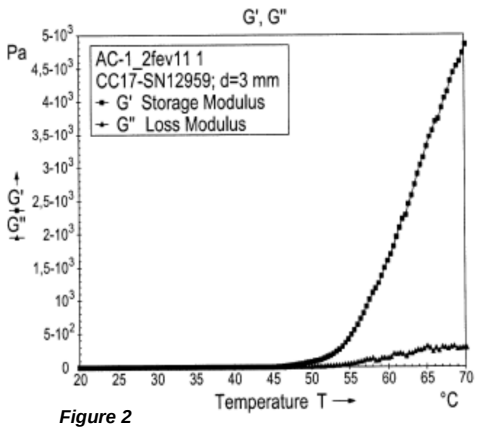


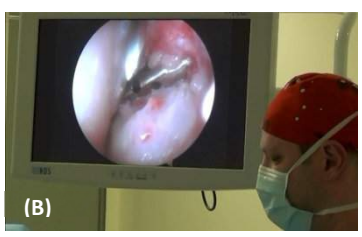
Figure 2

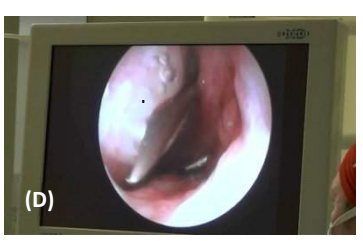
Clinical Applications of *JointRep™* as Cartilage void-filler matrix for Osteoarthritis or Trauma injuries

The clinical application of the ***JointRep™*** PG/GC device to repair articular cartilage defects related to osteoarthritis and trauma injuries was performed under control by the Regulatory Authorities of Canada, Health Canada (HC), under its Special Access Program (SAP). Applications were done using a ***JointRep™*** PG/GC device to be administered to human patients supplied as a kit of 3 sterile sealed syringes and 1 sterile sealed connector (total product volume 4.2 mL).

No specific exclusion criterion was applied for this clinical administration and evaluation, except the exclusion criteria that normally apply to an arthroscopic procedure. Once treated with the ***JointRep™*** PG/GC device, the patient was allowed to leave the clinical center, with a physiological rehabilitation program for 2-3 weeks. The clinical evaluations focussed on parameters such as the administration technique, the adverse events related to the device and the short-term efficacy of the treatment. The patients and knee joints arthroscopically treated with the ***JointRep™*** PG/GC device were evaluated pre-operatively (t = 0) and post-operatively at 6 months (t = 6), by using the Western Ontario MacMaster (WOMAC) Index of Osteoarthritis questionnaire.

Results & Observations





(A) Positioning of the percutaneous needle(s) and needle tip(s) in the knee joint;

(B) air-drying of the cartilage defect and injection zone;

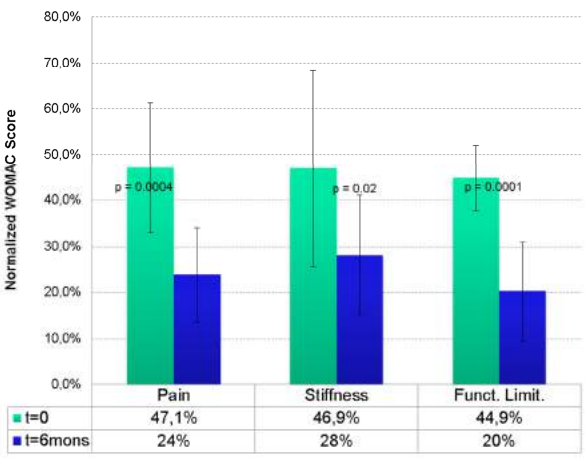
(C) Preparation of the final ***JointRep™*** syringe; the ***JointRep™*** device is injected through the positioned needle;

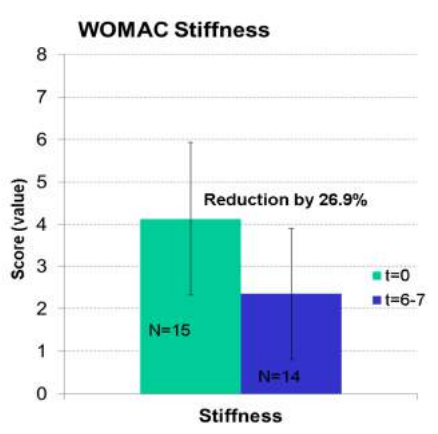
(D) Injection of the ***JointRep™*** device to fill the defect; the hydrogel forms rapidly *in situ* (**).

The surgical procedure is a normal arthroscopic procedure for articular cartilage defects in the knee joint. The first part of the procedure was a knee joint arthroscopy where the cartilage defects are investigated and cleaned as necessary. Then, during the course of the arthroscopy, the specialist prepares for the administration of the ***JointRep™*** device. Briefly, the specialist located each defect with a gauge #14, 1½ inch IV needle: several needles can be disposed to locate and treat several defects. Then, the inflow irrigation is stopped, the arthroscope is taken out but the sleeve is left in. An air circulation is created inside the joint with an inflow sleeve and an outflow succion canula, and is allowed to run for a few minutes. The arthroscope is then put back in. Whilst the installed needles are double checked, the thermo-gelling PG/GC device to be administered is prepared by an assistant. The specialist injects the desired volume(s) of the ***JointRep™*** device in the defect(s), starting with the largest defect and under a constant direct vision (arthroscopic imaging). Finally, after 2-3 minutes with the knee still in position, the arthroscopic procedure is ended and the knee joint skin is closed.

Patient Statistics		
Total Number of Patients		N=21
Patients included in WOMAC Evaluation		N=20
Patients with WOMAC		N=17
Patients, age		48.71 ± 10.69
Patients	Male	Female
	76.5%	23.5%
Treated Knee	Right	Left
	58.8% (10/17)	41.2% (7/17)
Associated lesions	Menisectomy	21.4%
	LCA	21.4%
	Microfractures	11.8%

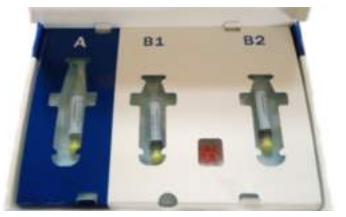
WOMAC Score and Sub-scores, mean (±SD)		
WOMAC, t = 0	N=15	
	Mean value (±SD)	
WOMAC Pain sub-score	10,1±3,24	-
WOMAC Stiffness sub-score	4,1±1,81	-
WOMAC Physical sub-score	32,2±5,65	-
WOMAC Total	46,4±9,50	-
Pain Score, treated knee	2.3±0.7	-
WOMAC, t = 6 months	N=14	
	Mean value (±SD)	Mean reduction, % (±SD)
WOMAC Pain sub-score	5,0±3,05	39,0±38,7%
WOMAC Stiffness sub-score	2,4±1,55	26,9±42,8%
WOMAC Physical sub-score	14,3±10,3	48,0±35,9%
WOMAC Total	21,7±14,5	45,1±34,8%
Pain Score, treated knee	1.2±1.0	20.0±27.1%





JointRep™ PG/GC device is easily and rapidly administered to defects during the course of a normal knee joint arthroscopy: it takes only 4-5 minutes to prepare the device. The device is injected percutaneously through gauge #14 needle(s), directly to cartilage defect(s).

During the study, no adverse event or undesirable effect was observed or reported by patients. In the study, ***JointRep™*** was also administered, with no problem, to knee joints with associate lesions: micro-fractures, ACL lesions, menisectomy.



JointRep™ device kit

At t = 6 months, most patients, except two, experienced positive clinical impacts. For the two patients, WOMAC scores were almost unchanged (Qty=1) or increased (Qty=1). Preliminary clinical data by WOMAC show that WOMAC total score is reduced by 45%, pain sub-score by 39%, stiffness sub-score by 26.9% and physical sub-score by 48%. Overall, the WOMAC data and patient

JointRep™ PG/GC device proves to be a very attractive injectable cartilage void-filler matrix to complete or improve arthroscopic cartilage defect procedures

Conclusion

The ***JointRep™*** PG/GC device is a three-part formulation liquid at room temperature and solid at body temperature with attractive features: Non-toxic and highly biocompatible; Onsite preparation within two (2) minutes; Administered during arthroscopic surgery; No defect size limitation; Gels in minutes; Application to any joints.

Initial clinical evaluation with WOMAC suggests significant reduction of pain and stiffness and improved function at 6 months post-op. However more complete clinical data and further clinical trials with ***JointRep™*** PG/GC device will have to confirm the good preliminary clinical results for this cartilage void-filler matrix for Osteoarthritis or Trauma injuries.

JointRep™ is a patent protected CE-marked device developed by **Oligo-Medic Inc**. an ISO 13485 certified company (2).

(1) Chenite A, Chaput C, Wang D, Combes C, Buschmann M D, Hoemann CD, Leroux JC, Binette F and Selmani A. Novel injectable neutral solutions of chitosan form biodegradable gels *in situ*. *Biomaterials*, 2000; 21 (21): 2155-2161.

(2) US8,506,972, Highly Biocompatible Dual Thermogelling Chitosan/Glucosamine Salt Compositions. Chenite *et al*.