Micro-graft Theory

applied to orthopedics, traumatology and wound healing

Regenera Activa AMT

RIGENERA Micrografting Technology

hbw human brain wave

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RIGENERA
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Contents

AMT®-RegeneraActiva

AMT® (Autologous Micrografting Technology)
by Rigenera© technology

Autologous Micro-grafts using Rigenera technology. AMT® protocols are based on stimulating self-regeneration by activating native progenitor cells located in the homologous tissues, through a simple process, without risks to the patient and with great therapeutic potential.

In a single session, the patient is a donor and recipient of autologous micro-grafts, allowing the recipient area to benefit from the regenerative activity of the progenitor cells and growth factors extracted from the donor site.

The technique is based on clinical studies that show there is a high concentration of the cells obtained in solid tissues. Through a calibrated mechanical process and filtering, cells and other precursor elements are concentrated.

We care about the health of our patients, that is why we offer the best quality, personalized and safe treatments with cutting-edge technology.

The Rigeneracon is a device designed and approved to mechanically disintegrate any biological tissue obtaining autologous micro-grafts in a minimally invasive way. rigeneracon is a class II sterile and disposable medical device, consisting of a rotation and pressure propeller, a grid with 100 hexagonal holes 80 microns in diameter and 600 micro blades designed for optimal and effective cutting of different types of tissue. Each device is equipped with an RFID microchip that contains product information for security and traceability reasons.

The tissue to be treated is obtained through a biopsy that is introduced into the Rigeneracon device and is gently pressed against the microblades at a constant speed of 80 rpm, without damaging the cellular structure of the disaggregated tissue. The sample is processed between 2 and 4 minutes depending on the type of tissue. The calibrated holes act as a filter, selecting only particles and cells less than

80 microns. The complete procedure occurs in a single surgical time and in a sterile manner.

AMT® obtains injectable micro grafts composed of: cells, extracellular matrix and growth factors derived from the patient's own cells, with no other manipulation than mechanical disaggregation.

AMT® - RegeneraActiva

Our technology is based on two fundamental pillars of regenerative biology:

- **Principle 1**: The side population. Numerous scientific papers have demonstrated that progenitor cells (PC) reside within a population with determined morphological features. The main features are: (1) the size and (2) stem cell marker expression.
- **Principle 2**: The niche concept. Preserving the extracellular matrix (ECM) allows cells to maintain their physiological niche. This specific environment not only improves cell viability, but also gives the progenitor cells the appropriate growth factors that support their role in regenerative processes.


RIGENERA

AMT® (Autologous Micrografting Technology) by Rigenera© technology

PROTOCOLS

Protocol in Osteoarticular Pathology With Chondral Degeneration

Regenerative and biostimulation therapy with auricular cartilage micro-grafts, with perichondrium and dermis obtained with Rigenera® device

BEFORE PROCEDURE:

1. The selected patients must be diagnosed with degenerative joint pathology: knee, hip, etc. With a degree of joint degeneration, no higher than III and therefore conserving part of the articular cartilage. The more recent and less joint degeneration the patient suffers, the better results will be obtained. The existence of joint immune diseases is considered an exclusion factor.
2. It is recommended to conduct a pre-operative analysis with a complete blood count (glycated haemoglobin, ESR, levels of vitamin D3, B12 and cholesterol with their fractions and triglycerides). Also, thyroid hormone (TSH) values and, in males, testosterone levels are required.
3. Patients with inflammatory diseases: familial inflammatory arthrosis, positive antinuclear antibodies, ASLO> 150, positive rheumatoid factor, as well as a history of inflammatory rheumatism cannot be treated with this protocol.
   Patients with morbid obesity, people with unbalanced diabetes or with a severe metabolic pathology should also be excluded. Patients with low levels of vitamin D3, B12, should be treated with supplements of these vitamins.
4. Carry out WOMAC questionnaire and nuclear magnetic resonance (RMN) of the joint for subsequent evaluation and diagnosis for the extent of the injury.
5. Explain and undersign the informed consent for the procedure to perform.
6. For a correct evaluation of the patient, it is recommended to prevent the use of nonsteroidal anti-inflammatory drugs throughout the entire follow-up. Exceptionally, the three days post treatment may be used in case there is any inflammation.

   At the discretion of the physician, 500 mg of Azithromycin orally 6 hours before the procedure and continuing with a daily tablet of 500 mg for two more days may be prescribed.

TECHNICAL PROCEDURE FOR CARTILAGE REMOVAL

NOTE: *It is recommended to watch beforehand the demo video. It is important the collected biopsy to contain: skin, cartilage and perichondrium.*

1. ANAESTHESIA OF RETRO AURICULAR NERVE

1.1. 1. Apply the anaesthesia in the posterior area of the base of the auricular concha (mastoid area).

1.2. Apply the anaesthesia at the posterior and anterior area of the conchal bowl in a superficially manner in order to separate the skin from the cartilage.

1.3. 2,5 ml of 2% lidocaine shall be used, without vasoconstrictor (usually it is sufficient with 0,5 - 0,7 ml for the retro auricular nerve; the rest is used for infiltrating in the skin).

2. REMOVAL OF 3 PUNCH OF 2.5 mm OF CARTILAGE

2.1. The removal of the cartilage is performed with the dermal punch with gently rotating movements for detaching the cartilage, without passing through the skin of the anterior area.

2.2. When removing the punch, turn downwards to release the sample. In case the cartilage remains inside the punch, use an Adson tweezers.

2.3. The obtained specimen must contain skin, perichrodium and cartilage. It will have a cylindrical shape, white in colour and cartilaginous aspect.

2.4. In order to avoid bleeding, perform haemostasis. The most frequent procedure is the mechanical pressure in the affected area with a sterile gauze for 3-5 minutes. In case the bleeding persists, the electrocoagulation of the holes will be performed. No surgical suture is required, as it will heal by secondary intention within a week.

2.5. Once the bleeding is controlled, a sterile dressing is placed, which covers the originated holes during the extraction.

REMOVED CARTILAGE SAMPLES PROCESSING:

1. Once obtained the necessary specimens, they are soaked 2 - 3 minutes in injectable physiological saline for them to soften. Subsequently, the epidermis is separated and they are placed in the metal grid of Rigeneracons (Ref. 7945RS).

NOTE: *Avoid placing the specimen on the propeller of the rotor.*

2. Subsequently, 4 ml of injectable physiological saline is added to the Rigeneracons dispenser, the lid is closed and it is placed in the machine with the corresponding adapters.
3. The content is processed for 6 minutes, pressing 6 time the button (1 minute of processing/pulse).
4. The Rigeneracons is withdrawn from the machine, it is carefully opened and the micro-graft processed solution is extracted by means of a cone syringe through the extraction hole.

ADMINISTRATION OF MICRO-GRAFT SOLUTION:

1. Infiltration of micro-grafts in the area to be treated according to medical criteria.

   NOTE: In the knee treatment video it is observed the use of an intramuscular needle (*Image 10*) with infiltration in the femorotibial compartment.

2. After the injection, the joint is mobilised in order to distribute the micro-graft solution homogeneously across the treated zone.

POST-TREATMENT CARE:

1. Second intention healing of the micro-graft donor areas when using a 2.5 mm punch. In the case of using a punch with a larger diameter, we recommend sutures to approximate the wound and for hemostasis. It is recommended to avoid contact of these areas with dirty water (swimming pool, sea water...).
2. It is usually observed inflammation of joints during the first 24-72 hours. This is why it is recommended the used of analgesics; avoiding NSAID, which may interfere in the micro-graft functionality.
   Apply local cold intermittently or compressive bandage, if required.
3. It is recommended relative rest, which does not require the treated joint overstrain during the following 7 days after the intervention.
   Thereafter, and insofar the inflammation has diminished, it is possible to start doing some physical exercise and rehabilitative physiotherapy. It is recommended quads and hamstring exercises in knee and rotator cuff of the shoulder.

FOLLOW-UP TESTS AND EVOLUTIVE CONTROL MEASURES:

1. The WOMAC questionnaire shall be carried out again (a minimum of twelve weeks later).
2. We recommend reviewing and performing an MRI of the patient every 6 months to see the evolution and if there is a need to repeat the treatment after a few years.

TECHNICAL PROCEDURE IN CASE OF SOFT TISSUE REMOVAL

1. ANAESTHESIA OF MASTOID AREA

1.1. The anaesthesia is infiltrated in the mastoid area.

1.2. 2,5 ml of 2% lidocaine shall be used, without vasoconstrictor (usually it is sufficient with 0,5 - 0,7 ml for the retro auricular nerve; the rest is used for infiltrating in the skin).

2. EXTRACTION OF MICRO-GRAFTS WITH 2.5 mm PUNCH

2.1. The micro-graft extraction is performed in the mastoid area with a dermal punch with gently rotating movements for detaching the soft tissue.

2.2. To extract the micro-graft from the punch, the punch is turned downward. In case it is not released, we should take out the tissue introducing an Adson tweezers in the hole.

2.3. The obtained specimen must contain skin. The epidermis must always be removed from the sample.

2.4. If the is some bleeding, it is possible to perform haemostasis with different methods, the most used one is the mechanical pressure with an sterile gauze done by an assistant or the patient itself. If the bleeding persists, a fine tip forceps shall be used and the holes made by the punch shall be electrocoagulated. Surgical suture should not be necessary, as the holes caused by the 2.5 mm punch will heal by second intention in a week.

2.5. Once the bleeding has stopped, a sterile dressing is placed in order to cover the originated holes during the extraction.

REMOVED SOF TISSUE SAMPLES PROCESSING:

1. Once the samples are obtained, they are placed for 2 or 3 min in a sterile gauze impregnated with physiological saline to soften them. Subsequently, they are introduced into the Rigeneracons for Wound Healing (70450S) in the area of the metal grid. Avoid placing the specimen on the propeller of the rotor.
2. Then, 3 or 4 ml of injectable physiological saline is placed, Rigeneracons is closed and the machine is placed with the corresponding adaptors.
3. If the punch used is the 2.5 mm diameter punch, the content is processed for 2 min, pressing the button as many times as the minutes of processing (since each cycle lasts 1 min). However, if the punch used is 4 mm in diameter, the sample must be divided into two, disintegrated for 3-4 min and check that the material is well disaggregated.
4. Once this period of time is finished, the Rigeneracons is removed from the machine, it is gently opened and 3 or 4 ml of processed solution are collected ready for injection. If it is necessary to add more injectable physiological saline (depends on each pathology), it is mixed with another syringe containing the required amount of injectable serum.
5. The extraction of the processed saline solution is performed with a cone syringe, without the needle.

ADMINISTRATION OF MICRO-GRAFT SOLUTION:

1. The processed sample is administered to the damaged area or peripherally at the discretion of the physician.
2. After the injection, they are is immobilized or covered for spreading the sample.

POST-SAMPLE REMOVAL CARE:

1. HEALING OF MICRO-GRAFT DONOR AREAS

The incisions caused by the 2.5 mm punch heal between 7 and 10 days by second intention. In the case of using a puch with a larger diameter, we recommend sutures to approximate the wound and for hemostasis.

The day after the procedure, the wound dressing can be removed and the wound cleaned maintaining aseptic conditions. It is recommended to avoid contact of these areas with dirty water (swimming pool, sea water...).

1. INTERVENTION EFFECTS

The effects usually appear between 3- and 7-days post-treatment. Sometimes it can be delayed by the presence of other pathologies associated with the injury, the age and general condition of the patient.

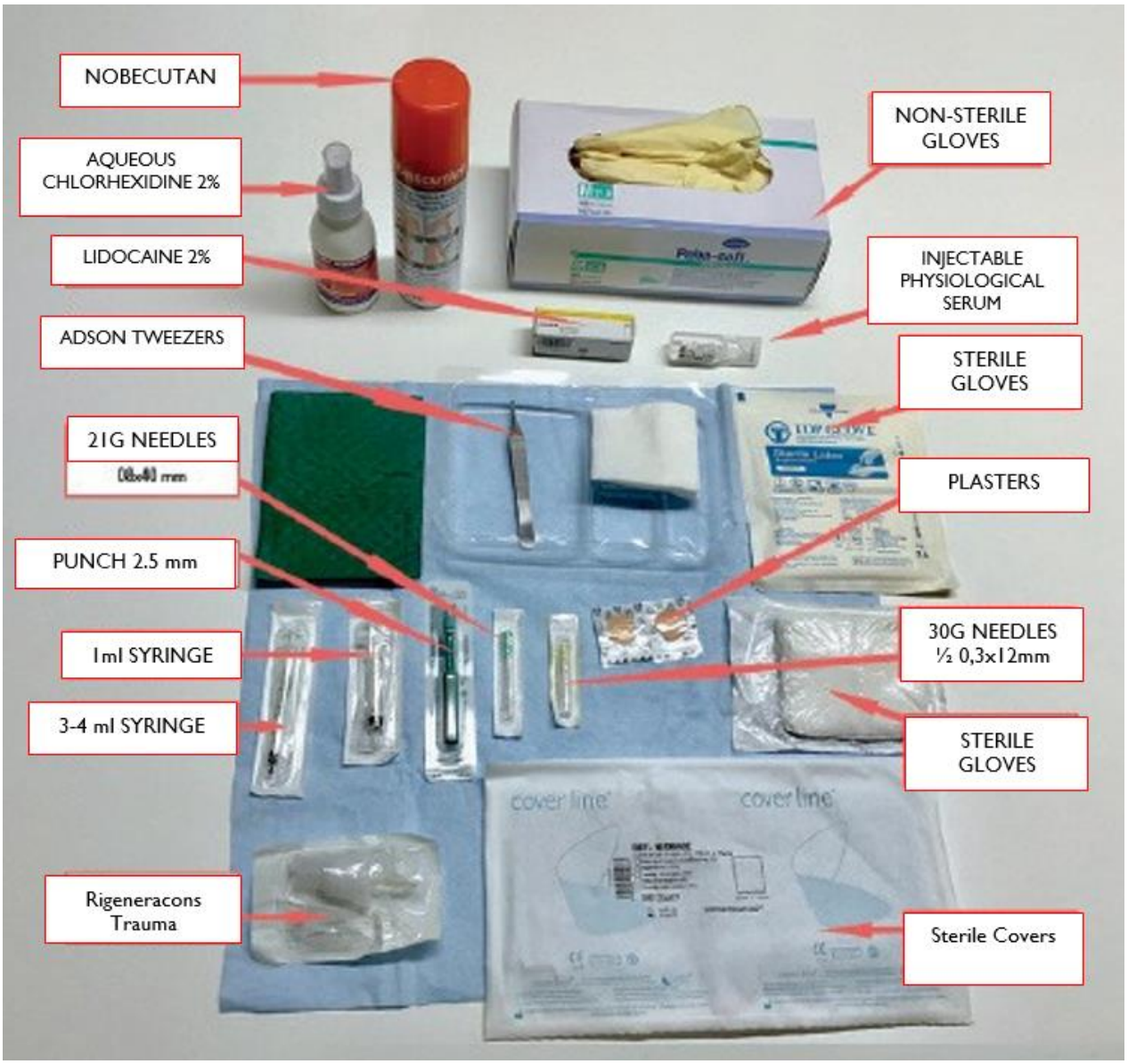
POST-SAMPLE REMOVAL CARE:

It is usually observed inflammation of joints during the first 24-72 hours. This is why it is recommended intermittently apply cold locally the used of analgesics; avoiding NSAID, which may interfere in the micro-graft functionality.

1. INTERVENTION DURATION AND PERFORMANCE

Cases which have been treated after 24 months they continue without requiring any further intervention. We recommend checking up the patient every 6 months to see the evolution and the need to repeat the treatment after a few years.

REQUIRED MATERIAL: FULL TRAUMA KIT



REQUIRED MATERIAL LISTING:

1. Rigenera Machine (Ref: 80118 o N4SAcolour)
2. Rigeneracons for Trauma 7945RS, Rigeneracons for Wound healing (70450S).
3. 2% Aqueous chlorhexidine
4. 2% Lidocaine (anaesthesia)
5. Nobecutan©
6. 1 ml syringe (for anaesthesia administration)
7. 3-5 ml syringe (for grafts administration)
8. Syringe adapter (transfer/pin)
9. 30G x ½, 0.3x12 mm and 18G,1.2x40 mm needles
10. 21G x ½, 0.8x40 mm needles (for articular infiltration and physiological saline administration)
11. Surgical drapes
12. 2.5 mm punch
13. Adson Tweezers
14. Injectable physiological saline
15. Sterile and non-sterile gloves
16. Sterile gauzes
17. Round sticking plasters

Regenerative and biostimulation therapy with:

- Soft tissue micro-graft of mastoid area
- Bone micro-graft of iliac crest and/or cancellous area
- Cartilage micro-graft of auricular cartilage area with perichrodium and dermis

TRAUMATOLOGY PROTOCOL FOR BONE PATHOLOGY

Application of SVF injection of REGENERA ACTIVA	
Direct extraction	With cannulated drill
Processing volume	4 ml
Processing time	6 min
Extraction area	Iliac and/or spongy crest
Sample composition	Cancellous bone and periosteum
Bone Pathology	Bone edema fractures
Injection site	At the focus of the injury

METHOD:

1. Fill Rigeneracons Trauma device (Ref. 7945RS) with 4 ml of injectable physiological saline.
2. Put the extracted micro-grafts of the bone specimen (extracted with the drill) on the grid with holes, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Infiltration of micro-graft solution in the affected area.

TRAUMATOLOGY PROTOCOL
of SHOULDER PATHOLOGY

Application of SVF injection of REGENERA ACTIVA	
Punch Number	3 punch of 2.5 mm
Processing volume	4 ml
Processing time	6 min
Extraction area	Conchal bowl
Sample composition	Cartilage and perichondrium, the dermis and epidermis are discarded
Shoulder Pathology	Arthrosis Injuries of humerus cartilage
Injection site	Intra-articular area

METHOD:

NOTE: *ALWAYS remove epidermis and dermis from the sample*

1. Fill Rigeneracons Trauma device (Ref. 7945RS) with 4 ml of injectable physiological saline.
2. Introduce the 3 punch without epidermis on the grid with holes, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Infiltration of micro-graft solution in the affected area.

TRAUMATOLOGY PROTOCOL
of SPINE COLUMN

Application of SVF injection of REGENERA ACTIVA	
Punch Number	3 punch of 2.5 mm
Processing volume	4 ml (0.2 - 0.5 (ml/facet))
Processing time	6 min
Extraction area	Conchal bowl
Sample composition	Cartilage and perichondrium, the dermis and epidermis are discarded
Spinal Pathology	Facet syndrome
Injection site	Intra-articular area
Special Material	Cannulated Kirschner needles Suitable trocars for infiltration of spinal column Operating room

METHOD:

NOTE: *ALWAYS remove epidermis and dermis from the sample*

1. Fill Rigeneracons Traumatology device (Ref: 7945RS) with 4 ml of physiological saline.
2. Introduce the 3 punch without dermis nor epidermis on the grid with holes, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Infiltration of micro-graft solution in the affected area. (In case the intervertebral disc, inject passing through the fibrous ring and infiltrate in the nucleus pulposus between 0,5 to 1 ml)

TRAUMATOLOGY PROTOCOL
of HIP PATHOLOGY

Application of SVF injection of REGENERA ACTIVA	
Punch Number	4 or 5 punch of 2.5 mm
Processing volume	7-10 ml
Processing time	6 min
Extraction area	Conchal bowl
Sample composition	Cartilage and perichondrium, the dermis and epidermis are discarded
Hip Pathology	Chondromalacia Grade I, II and III Arthrosis Necrosis
Injection site	Intra-articular area
Special Material	Needles for articular infiltrations

METHOD:

NOTE: *ALWAYS remove epidermis and dermis from the sample*

1. Fill Rigeneracons Trauma device (Ref. 7945RS) with 4 ml of injectable physiological saline.
2. Introduce the 4 or 5 punch without dermis nor epidermis on the grid with holes, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Repeat procedure injecting again another 3 or 4 ml of physiological saline and mixing both solutions by a transfer to obtain a homogeneous solution.
6. Thus, we obtain 2 syringes with 4 ml each one.
7. Infiltration of micro-graft solution in the affected area. (In necrosis, tunnel without passing through the femoral head)

TRAUMATOLOGY PROTOCOL
of KNEE PATHOLOGY

Application of SVF injection of REGENERA ACTIVA	
Punch Number	3 punch of 2.5 mm
Processing volume	4 ml
Processing time	6 min
Extraction area	Conchal bowl
Sample composition	With cartilage and perichondrium, the dermis and epidermis are discarded
Knee Pathology	Degenerative chondropathy Chondromalacia
Injection site	Intra-articular

METHOD:

NOTE: *ALWAYS remove epidermis and dermis from the sample Not injecting in total or partial breaking of meniscus, until performing arthroscopy with its corresponding cleaning.*

1. Fill Rigeneracons Trauma device (Ref. 7945RS) with 4 ml of injectable physiological saline.
2. Introduce the 3 punch without dermis nor epidermis on the grid with holes, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Infiltration of micro-graft solution in the affected area.

TRAUMATOLOGY PROTOCOL
of FOOT PATHOLOGY

Application of SVF injection of REGENERA ACTIVA	
Punch Number	3 punch of 2.5 mm
Processing volume	4 ml
Processing time	3 min
Extraction area	Conchal bowl
Sample composition	Cartilage and perichondrium, the dermis and epidermis are discarded
Foot Pathology	Degeneration of the foot joints
Injection site	Injury area- Intraarticular

METHOD:

NOTE: *ALWAYS remove epidermis from the sample.*

1. Fill Rigeneracons for Trauma (Ref. 7945RS) with 4 ml of injectable physiological saline.
2. Introduce the extracted micro-grafts with the punch without epidermis in the corresponding department of Rigeneracons, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Infiltration of micro-graft solution in the affected area.

PROTOCOL of MAXILLOFACIAL PATHOLOGY OF TEMPOROMANDIBULAR JOINT

Application of SVF injection of REGENERA ACTIVA	
Punch Number	1 or 2 punch of 2.5 mm
Processing volume	1-2 ml
Processing time	6 min
Extraction area	Conchal bowl
Sample composition	Cartilage and perichondrium, the dermis and epidermis are discarded
Maxillofacial Pathology	Temporomandibular Dysfunction Syndrome (TMDS)
Injection site	Intra-articular

METHOD:

NOTE: ALWAYS remove epidermis and dermis from the sample.

1. Fill Rigeneracons Trauma device (Ref. 7945RS) with 3 ml of injectable physiological saline.
2. Introduce the 1 or 2 punch without dermis nor epidermis on the grid with holes, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Infiltration of micro-graft solution in the affected area.

TRAUMATOLOGY PROTOCOL of

MUSCULOTENDINOUS SHOULDER PATHOLOGY

Application of SVF injection of REGENERA ACTIVA	
Punch Number	3 punch of 2.5 mm
Processing volume	3 ml
Processing time	2 min
Extraction area	Retroauricular mastoid area (without hair follicle)
Sample composition	Dermis, epidermis and subcutaneous cellular tissue
Shoulder Pathology	Rotator cuff Recent injury of no more than 6 months
Injection site	At the focus of the injury

METHOD:

NOTE: *ALWAYS remove epidermis from the sample*

1. Fill Rigeneracons Wound Healing device (Ref. 7945OS) with 3 ml of injectable physiological saline.
2. Introduce the 3 punch without epidermis on the grid with holes, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Infiltration of micro-graft solution in the affected area.

TRAUMATOLOGY PROTOCOL of

TENDON AND LIGAMENT PATHOLOGY

Application of SVF injection of REGENERA ACTIVA	
Punch Number	2 punch of 2.5 mm
Processing volume	3 ml
Processing time	2 min
Extraction area	Retroauricular mastoid area (without hair follicle)
Sample composition	Dermis, epidermis and subcutaneous cellular tissue
Tendon and Ligament Pathology	Ligamentous Tendinosis
Injection site	Ligament and/or tendon at the focus and around the injury

METHOD:

NOTE: ALWAYS remove epidermis and dermis from the sample..

1. Fill Rigeneracons Wound Healing device (Ref. 7945OS) with 3 ml of injectable physiological saline.
2. Introduce the 2 punch without epidermis on the grid with holes, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Infiltration of micro-graft solution in the affected area.

WOUND HEALING PROTOCOL in ULCERS, SCARS and BURNS PATHOLOGY

Application of SVF injection of REGENERA ACTIVA	
Punch Number	2 or 3 punch of 2.5 mm
Processing volume	3 ml
Processing time	3 min
Extraction area	Retroauricular mastoid area (without hair follicle)
Sample composition	Dermis, epidermis and subcutaneous cellular tissue
Tendon and Ligament Pathology	Chronic ulcers, scars or cuts and burns grade I, II, III
Injection site	Infiltration in edges and within the wound

METHOD:

NOTE: *ALWAYS remove epidermis from specimen*

1. Fill Rigeneracons Wound Healing device (Ref. 7945OS) with 3 ml of injectable physiological saline.
2. Introduce the extracted micro-grafts with the punch without epidermis in the corresponding department of Rigeneracons, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Application to the area to be treated.
6. For large wounds, repeat the procedure as many times as necessary.

TRAUMATOLOGY PROTOCOL
of FISTULAS PATHOLOGY

Application of SVF injection of REGENERA ACTIVA	
Punch Number	3 punch of 2.5 mm
Processing volume	3 ml
Processing time	2 min
Extraction area of Punch	Close to fistula (healthy tissue)
Sample composition	Dermis, epidermis and subcutaneous cellular tissue
Pathology	All fistulas
Injection site	Around fistula and at the clean focus

METHOD:

NOTE: ALWAYS remove epidermis and dermis from the sample.

1. Fill Rigeneracons Wound Healing (Ref. 7945OS) with 3 ml of injectable physiological saline.
2. Introduce the 3 punch without epidermis on the grid with holes, below the rotor propeller.
3. Process the specified time.
4. Extract the result of the process with a cone syringe.
5. Infiltration of micro-graft solution in the affected area.

AMT® (Autologous Micrografting Technology) by Rigenera© technology

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Biostimulation of Knee Cartilage Using Autologous Micro-Grafts: A Preliminary Study of the Rigenera Protocol in Osteochondral Lesions of the Knee

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Abstract: Osteochondral pathologies are associated with cartilage loss. Autologous micro-grafts, obtained from various tissues containing mesenchymal stem cells, has proven regenerative properties in various tissues. The study included patients with osteochondral pathology not responding to conventional therapies and considered suitable for treatment with autologous micro-graft. Fifteen days before the intervention, patients started treatment with chondroitin sulfate and supplementary vitamin C and zinc. Autologous micro-grafts were obtained from ear skin and cartilage, disaggregated using the Rigenera system, and injected into the knee under local anesthesia. After the intervention, patients underwent six-week rehabilitation program based on non-weight bearing exercises. Nine patients were enrolled into the study. The autologous graft transfer was successful in all patients, and no severe complications were recorded, including aesthetical defects in the donor site. Eight patients (88.9%) experienced an improvement in all subdomains of the WOMAC scale. The median (IR) improvement in the WOMAC scale was 22.0 (10.0 – 40.0) points. The MRI examination revealed the absence of space-occupying lesions in the knee and the surrounding soft tissues in all patients. An edema reduction was observed in 8 of 9 patients (88.9%); 3 patients (33.3%) showed a thickening of the cartilage line. Autologous micro-graft transfer using the Rigenera system is safe and has promising results in the treatment of chondral injuries associated with pain and function limiting.

Keywords: Rigenera, Osteoarthritis, Osteochondral Regions, Mesenchymal Stem Cells, Tissue Regeneration

1. Introduction

Osteochondral pathologies may result from trauma or sports injuries or be the consequence of disorders associated with cartilage degeneration, such as chondromalacia and osteoarthritis [1, 2]. Irrespective of the etiology of the osteochondral pathology, the loss of cartilage, evidenced in magnetic resonance images (MRI) as a thinning of the cartilage line, causes pain and physical disability [3–5]. In addition to surgery, the traditional management of degenerative cartilage diseases is based on physical therapy and pain relief. However, some patients do not respond well to pain relievers, and the regeneration of the damaged cartilage may last for a long time, thus compromising the complete functional recovery.

In the recent years, many efforts have been made in developing complementary strategies aimed at either regenerating the damaged cartilage or enhancing the natural regeneration process. In addition to the intra-articular use of hyaluronic acid, various approaches have been proposed to stimulate the production of new cartilage. Biostimulation techniques include physical approaches, such as the use of high-frequency biostimulation during surgery [6] or low-power laser targeting the osteochondral defect [7, 8], and biological approaches, such as autologous chondrocyte implantation [9] and the use of platelet-rich plasma to stimulate the production of new cartilage [10].

The finding of stem-like cell populations with multipotent features in various tissues has motivated the use of these cells

3. Results

3.1. Patients and Procedure

The autologous graft transfer was performed in nine patients meeting all the selection criteria. The mean (SD) age was 51.7 (6.2), 56% were male, and none of them were active smokers. In all cases, the procedure was successful, and none of them experienced infections or severe complications after the procedure. Two patients experienced joint effusion, manifested at a few days after the procedure. No aesthetical defects were observed at the donor site in any patient and none of them complained about the result on the donor site. One patient with a history of blood dyscrasias experience retromuscular bruising which healed without other interventions than vitamin K supplementation and any aesthetical defect.

3.2. Symptoms and Functional Outcome

Except one patient who experienced edema associated with cell infiltration, all patients referred a remarkable pain decrease during the few days following the procedure. At the end of the follow up all patients all patients returned to their activities performed before the worsening of the cartilage injuries. Table 1 shows the details of the functional and pain assessment at baseline and the end of the follow-up. Eight patients (88.9%) experienced an improvement in all subdomains of the WOMAC scale. Median (IR) total WOMAC score in the study population was 39.0 (19.5 – 59.0) before intervention and 9 (3.0 – 23.5), a median improvement of 22.0 (10.0 – 40.0) points. Patient 3 improved her stiffness and functional impairment but worsened pain associated with her knee condition. Overall, the median (IR) pain, stiffness, and function improvement were 5.0 (3.3 – 9.0) on a 20-point scale, 3.0 (1.3 – 3.8) on an 8-point scale, and 19.5 (9.3 – 30.0) on a 68-point scale, respectively.

The MRI examination revealed the absence of space-occupying lesions in the knee and the surrounding soft tissues in all patients. An edema reduction was observed in 8 of 9 patients (88.9%) (Figure 1A). The woman in case 9 displayed more edema in the post-intervention than in the pre-intervention MRI. Chondromalacia showed a partial regression in 5 of 7 cases (71.4%) in which the progress of the chondromalatic signs was reported. Three patients (33.3%) showed a thickening of the cartilage line (Figure 1B). Of 8 patients with visible cartilage tear at baseline, 4 maintained the injury, 1 showed a remarkable improvement, and 2 showed no signs of the injury at the post-intervention MRI. Three patients showed a Baker's cyst at baseline: one remained unchanged, one reduced the cyst size, and one had no visible cysts at post-intervention MRI. The patient who experienced a worsening in knee stiffness had a cartilage injury before the procedure which was maintained after the procedure.

Figure captions

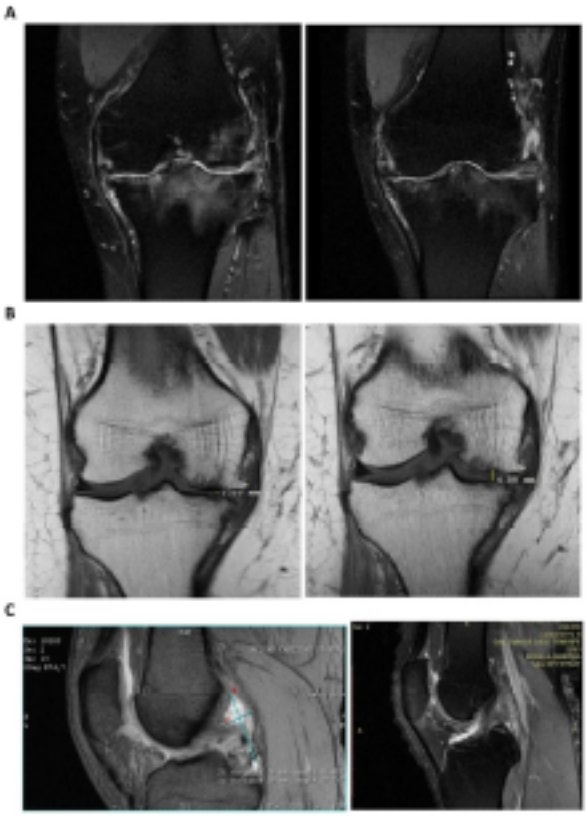

Figure 1. Highlights of MRI findings before and after procedure. A: case 4 at presentation (left) and sixteen weeks after (right): the images show an edema reduction and an increase in the definition of the cartilage line. B: case 7 at presentation (left) and twelve weeks after the intervention (right): the cartilage thickness experienced an increase of 2.78 cm. C: case 1 at presentation (left) and 17 weeks after: the Baker's cyst of 56 mm length x 16 mm width identified at presentation showed a complete remission 17 weeks after the procedure.

Table 1. Patient characteristics and results of the WOMAC scale.

			WOMAC scores* pain | stiffness | function limitation	
Patient no.	Sex	Age (years)	Before the intervention	After the intervention
1	male	44	4 | 1 | 8	0 | 0 | 0
2	male	44	2 | 3 | 4	0 | 0 | 2
3	female	54	3 | 5 | 19	7 | 2 | 15
4	male	63	11 | 5 | 45	6 | 2 | 18
5	male	50	7 | 2 | 30	4 | 2 | 17
6	male	48	12 | 6 | 29	3 | 2 | 4
7	female	56	18 | 8 | 63	1 | 2 | 4
8	female	56	12 | 5 | 40	3 | 3 | 9
9	female	50	6 | 3 | 17	1 | 0 | 3

*Scores ranges for the assessment of pain, stiffness, and functional limitation are 0-20, 0-8, and 0-68, respectively.

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Journal of Regenerative Medicine

Research

A SCITECHNOL JOURNAL

A combined use of Chondrocytes Micro Grafts (CMG) Mixed with Platelet Rich Plasma (PRP) in Patients Affected by Pinch Nose Deformity

Gentile P*, Scioli MG, Bielli A, Orlandi A and Cervelli V

Abstract

Background: The combined use of autologous chondrocytes micro-grafts (CMG) mixed with Platelet Rich Plasma (PRP) is an alternative that opens a new era in this field.

Materials and Methods: At the Department of Plastic and Reconstructive Surgery, University of Rome "Tor Vergata", Italy, 15 patients, affected by pinch nose deformity underwent nasal alar reconstruction with chondrocytes micro-grafts gentle poured onto PRP in solid form. A CT scan control was performed after 12 months. Pearson's Chi-square test was used to investigate difference in cartilage density (CD) between native and newly formed cartilage.

Results: The constructs of CMG-PRP subcutaneously injected resulted in cartilage tissue with adequate central nutritional perfusion. Postoperative follow-up evaluation has shown optimal aesthetic results and improvement of nasal obstruction. These composite grafts provide functional support to the alar cartilages, usually collapsed in pinch nose deformity because of excessive resection during previous surgery.

Conclusion: This report demonstrated that chondrocytes micro-grafts derived from nasal septum poured onto PRP in solid form are a useful method for cartilage regeneration in patients affected by external nasal valve collapse.

Keywords

Chondrocytes auto-graft; Cartilage regeneration; Cartilage tissue engineering

Introduction

For therapeutic cartilage regeneration, the use of chondrocytes micrografts (CMG) mixed with platelet-rich plasma (PRP) has not been studied for cryopreserved chondrogrants. PRP has been demonstrated to be effective in the treatment of soft tissue defects and patterns hair loss [1-4]. It has been demonstrated that three-dimensional culture system in type I collagen scaffold and the addition of multiple growth factors contained in PRP, in the culture medium induced proliferation and a robust chondrogenesis of adult stem cells in vitro [5,6]. Direct mixing of chondrocytes with PRP leads to shielding and delivered cartilage formation in vivo [7] owing to poor mechanical stability and rapid degradability. In particular the use of chondrocytes micrografts represents a micro-invasive procedure and grafts are more flexible to fill the lesions with various shapes. Today the main problem to transferring the experimental protocols of tissue engineering in the routine clinical practice is the identification of accessible sites where an adequate amount of stem cells are collected [8,9]. In addition, the need to specifically define technical procedure and its safety is an essential factor, as occurring for stem cell application in breast reconstruction and soft tissue defects [10-13].

Although within the human body there are several "niches" inhabited by a significant number of stem cells [14-16], often these are not easy to access. The nasal septum represents a niche housing chondrocytes easily accessible without limited morbidity of the anatomical site after collection of the micrografts. Rafat Bet al. [17] developed the cell brick technique, which cultured a chondrocyte sheet and cut such a cell–Extra Cellular Matrix complex into multiple small fragments (cell bricks). They found that chondrocyte bricks significantly inhibited vascular infiltration into PRP gels and slowed their degradation, thus maintaining the framework and shape of the PRP grafts [18]. They hypothesized that the cell brick-enriched PRP gel could be an ideal injectable niche for adults stem cells, which is expected to regenerate histological cartilage tissue with persistent cartilaginous phenotype, less deformation and uniform histological structure [18].

Currently, in this study, we investigated the in vivo performance of chondrocytes in cell brick-enriched PRP gels, and evaluated the persistence of a stable chondrogenic phenotype.

Chondrocytes can be obtained by enzymatic digestion and/or mechanical disaggregation: in the first method, the cartilage tissue is harvested under sterile conditions, digested with appropriate enzymes, and then the resulting cell suspensions are seeded in culture dishes containing a special medium supplemented with necessary additives and then incubated. Finally, the resulting colonies are sub-cultured before confluence and the cells are stimulated to differentiate. In the second procedure, chondrocytes are isolated by the mechanical centrifugation of cartilage (Rigenera Method) in which the cartilage is treated as any other connective tissue subjected to grafts, with a phase of collection and a phase of mechanical disaggregation of the tissue without manipulating the matrix. Rigenera protocol produces millions of viable micro-grafts and fibers them with a cut-off of 50 microns, in order to promote the discharging of old differentiated cells and the enrichment of young progenitors cells contained within the cartilage.

Materials and Methods

Patients

A total of 15 patients aged 29-67 years, affected by external nasal valve collapse, the so-called pinched nose deformity, were treated from January 2014 to September 2015 at the Plastic and Reconstructive Surgery Department of "Tor Vergata" University, Rome.

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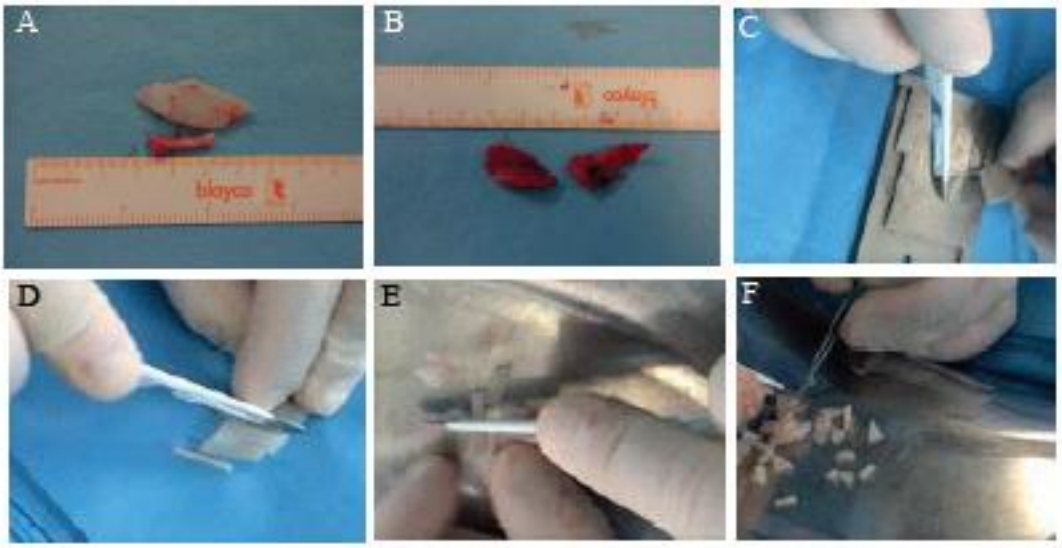

Figure 3: (A) Original fragment of the cartilage extracted from the septum during rhinoplasty; (B) Fragment of the septum cartilage remodeled; (C) Plane of the septum cutting; (D) Strips of the cartilage septum; (E) Selection of the strips; (F) Selected 2 mm X 2 mm strips.

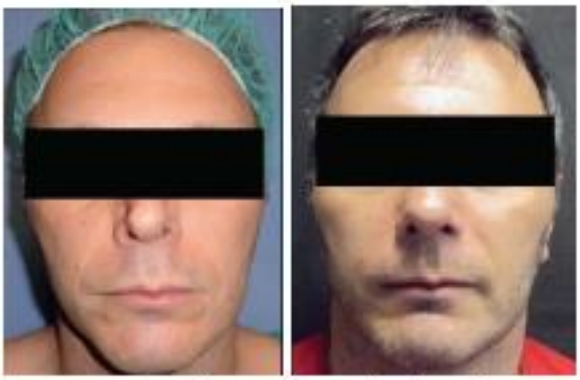

Figure 4: (A) Pre-operative in frontal projection with right nasal valve collapse; (B) Post-operative situation after 1 year in frontal projection.

pharmaceuticals

Article

In Vitro and In Vivo Studies of Alar-Nasal Cartilage Using Autologous Micro-Grafts: The Use of the Rigenera® Protocol in the Treatment of an Osteochondral Lesion of the Nose

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Abstract: Cartilage defects represent a serious problem due to the poor regenerative properties of this tissue. Regarding the nose, nasal valve collapse is associated with nasal blockage and persistent airway obstruction associated with a significant drop in the quality of life for patients. In addition to surgical techniques, several cell-based tissue-engineering strategies are studied to improve cartilage support in the nasal wall, that is, to ameliorate wall insufficiency. Nevertheless, there are no congruent data available on the benefit for patients during the follow-up time. In this manuscript, we propose an innovative approach in the treatment of cartilage defects in the nose (nasal valve collapse) based on autologous micro-grafts obtained by mechanical disaggregation of a small portion of cartilage tissue (Rigenera® protocol). In particular, we first analyzed in vitro murine and human cartilage micro-grafts; secondly, we analyzed the clinical results of a patient with pinched nose deformity treated with autologous micro-grafts of chondrocytes obtained by Rigenera® protocol. The use of autologous micro-graft produced promising results in surgery treatment of cartilage injuries and could be safely and easily administrated to patients with cartilage tissue defects.

Keywords: Rigenera® protocol; autologous micro-grafts; chondrocytes; tissue engineering approaches; nasal valve collapse

1. Introduction

Osteochondral pathologies may result from trauma or sports injuries or be the consequence of disorders associated with cartilage degeneration, such as chondromalacia and osteoarthritis [1,2]. Irrespective of the etiology of the osteochondral pathology, the loss of cartilage, evidenced in magnetic resonance images (MRI) as a thickening of the cartilage line, causes pain and physical disability [3–5]. In addition, regarding nasal cartilage, obstruction at the level of the nasal valve is a common and long-recognized cause of nasal blockage [6,7]. It is estimated that about 40% of nasal obstruction is

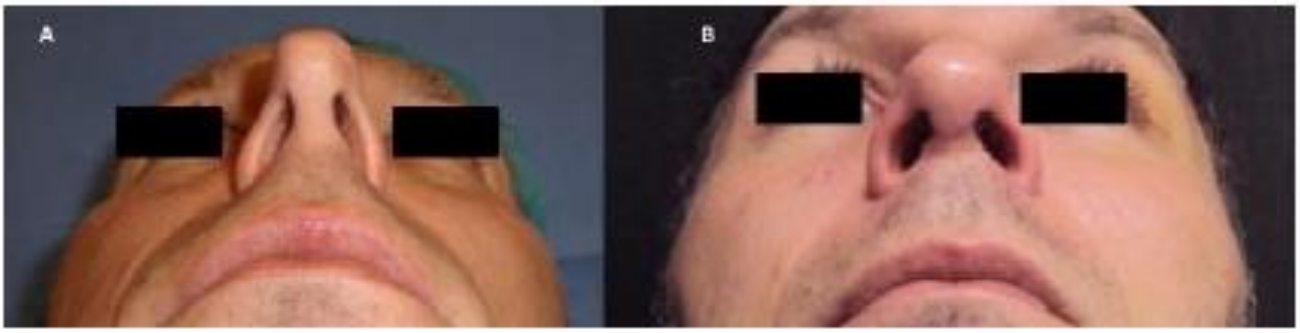

Figure 3. (A) Pre-operative situation of patient affected by bilateral external and internal nasal valve collapse with nasal obstruction produced by excessive resection during previous surgery. (B) Post-operative situation after 12 months of the same patient treated with conchocyte micro-grafts obtained by Rigenerazione® (CE certified Class I) mixed with platelet-rich plasma (PRP) in mild form. The authors used septum cartilage cut in the strips, processed by Rigenera® Centrifuge. These composite grafts provided functional support to the alar cartilages. Trans-columellar open-tip access was necessary to allow for better visualization of the valve collapse, alar cartilage, and for the fixation of the cartila.

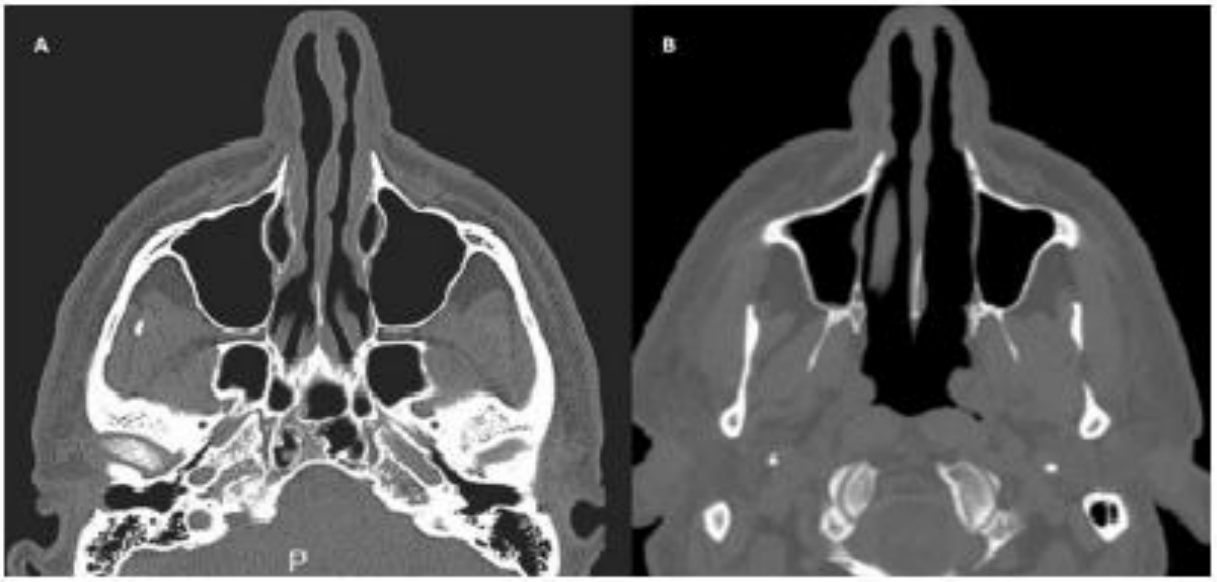

Figure 4. (A) CT scans show the pre-operative situation with bilateral soft tissue defect of nasal tip and cartilage collapse. In addition, nasal septum deviation was detected. (B) CT scans of the same area after 12 months show the regenerated site in the post-operative image with soft tissue volume improvement and the correction of the nasal septum deviation.

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Journal of Orthopaedic Surgery and Research

RESEARCH ARTICLE Open Access

Rationale and pre-clinical evidences for the use of autologous cartilage micrografts in cartilage repair

Marco Viganò[1†], Irene Tessaro[1†], Letizia Trovato[2*], Alessandra Colombini[1], Marco Scala[3], Alberto Magi[4], Andrea Toto[4], Giuseppe Peretti[1,5] and Laura de Girolamo[1]

Abstract

Background: The management of cartilage lesions is an open issue in clinical practice, and regenerative medicine represents a promising approach, including the use of autologous micrografts whose efficacy was already tested in different clinical settings. The aim of this study was to characterize in vitro the effect of autologous cartilage micrografts on chondrocyte viability and differentiation and perform an evaluation of their application in racehorses affected by joint diseases.

Materials and methods: Matched human chondrocytes and micrografts were obtained from articular cartilage using Rigenera® procedure. Chondrocytes were cultured in the presence or absence of micrografts and chondrogenic medium to assess cell viability and cell differentiation. For the pre-clinical evaluation, three racehorses affected by joint diseases were treated with a suspension of autologous micrografts and PRP in arthroscopy interventions. Clinical and radiographic follow-ups were performed up to 4 months after the procedure.

Results: Autologous micrografts support the formation of chondrogenic micromasses thanks to their content of matrix and growth factors, such as transforming growth factor β (TGFβ) and Insulin-like growth factor 1 (IGF-1). On the other hand, no significant differences were observed on the gene expression of type II collagen, aggrecan, and SOX9. Preliminary data in the treatment of racehorses are suggestive of a potential in vivo use of micrografts to treat cartilage lesions.

Conclusions: The results reported in this study showed the role of articular micrografts in the promoting chondrocyte differentiation suggesting their potential use in the clinical practice to treat articular lesions.

Keywords: Micrografts, Cartilage repair, Regenerative medicine, Cartilage defects, Rigenera

AMT® (Autologous Micrografting Technology) by Rigenera© technology

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