

Regenerative Surgery Unit (RSU) a new model of care

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Abstract

Regenerative Surgery (RS) defines all the *Regenerative Medicine (RM)* treatments that can be applied through minimally invasive surgical procedures. This biomedical approach includes the use of stem cells, various local biochemical mediators, and tissue engineering.

The *Regenerative Surgery Unit (RSU)* is a new model of health care governance integrating clinical, scientific and research activities.

RSU works in a multidisciplinary setting involving surgeon, biologist, immunologist, laboratory technician, radiologist, and physiotherapist.

RSU setting also aims to generate a special relation between doctor and patient. The aim of this relationship is to establish a solid and mutually beneficial *alliance*, founded on medical ethics, between doctor and patient.

RSU organises clinical services through ambulatory care and day surgery settings. The scientific and research activities are integrated as components of daily medical practice.

This article describes some established procedures in *RS* and some refinements that are more recently available as a result of our clinical and research experience in *RM* fields.

Health Tourism is one element of the sustainable growth model we are developing in the *RSU- Villa Aurora Hospital, Foligno (Italy)*.

Introduction

Regenerative Medicine (RM) is a branch of translational research involving tissue engineering and molecular biology. *RM* deals with the process of regenerating and replacing dysfunctional cells, tissues, and organs; the aim is to restore normal healthy function.

RM intervenes on injured tissues and organs by stimulating body self-repair mechanisms to recover structure and functionality. Biomedical approaches within the field of *RM* may involve the use of stem cells, biologically active molecules, and tissue engineering.

Regenerative Surgery (RS) defines all the *RM* treatments that can be clinically applied through minimally invasive surgical procedures. *RS* opens new possibilities for the delivery of ethical and effective care. Realizing the full benefits requires an appropriate clinical setting and management approach. Patient understanding and safety together with clinical understanding of the need for and benefits of continuous improvement are the cornerstones of a robust and positive alliance with patients. This article reports the model we are applying to Villa Aurora Hospital-*Regenerative Surgery Unit- Foligno (Italy)*.

Regenerative Surgery Unit (RSU) model and organization

The *RSU* model integrates clinical, scientific and research activities to create valuable assets. The *clinical asset* is structured to deliver multidisciplinary and minimally invasive procedures with the aim to halt and reverse symptoms and where possible the underlying conditions. This is achieved through tissue recovery and regeneration. The *scientific asset* includes the constant collection, updating and

communication of data, observations, and findings. It also includes education and training, publications, meetings and conferences and development of scientific associations. The *research asset* encompasses *in vitro* investigations, experimental models, and clinical trials. *RSU* works in a multidisciplinary team involving surgeon, biologist, immunologist, laboratory technician, radiologist, and physiotherapist.

RSU clinical activity is centered on ambulatory care or day surgery procedures.

Patients who receive regenerative treatments can 'walk in and out' of *RSU* within few hours. Dedicated facilities allow *RS* specialists to deliver safe minimally invasive procedures.

Areas of intervention in our Regenerative Surgery Unit:

1. Orthopaedic *RS*

- Early Osteoarthritis (OA)
- Advanced OA
- Traumatic and degenerative damage to tendons and ligaments.

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2. Plastic RS

- diabetic foot ulcers (DFU)
- pressure ulcers (PU)
- venous leg ulcers (VLUs).

3. General RS

- PRF- hernia repair
- perianal fistulas
- preliminary experience in faecal incontinence

4. Aesthetic RS

- filling skin defects
- wrinkles
- stimulation for hair regrowth and hair transplantation.

5. Maxillofacial RS

- periodontal bony defects
- PRF- implant surgery

RS procedures

These treatments have the common aim of improving symptoms and restoring homeostasis to local cells and tissue regeneration.

Materials employed

Platelet-rich plasma (PRP) is a concentrate of platelet-rich plasma proteins derived from centrifuged whole blood.

PRP variably contains several growth factors including Platelet derived growth factor (PDGF); Vascular endothelial growth factor (VEGF); Transforming growth factor beta-1 (TGF- β 1); Epidermal growth factor (EGF); Basic fibroblast growth factor (FGF- β) and Insulin-like growth factor-1 (IGF-1) [1].

Preparations have been categorized by content into four main groups: PPRP (pure PRP), L-PRP (leukocyte and PRP), P-PRF (pure platelet-rich fibrin) and, L-PRF (leukocyte and platelet-rich fibrin) [1].

Literature shows that PRP can stimulate an antiinflammatory, proliferative and remodelling response inducing mesenchymal tissue regeneration [2].

Specifically, in osteoarthritis (OA), chondrogenic differentiating properties were found *in vitro* as well as *in vivo* in mice and rabbits, indicating a major role in regeneration of cartilage [3-7].

These PRP biological properties are increasingly used for OA treatments, maxillofacial and dental procedures, plastic surgery and aesthetic treatments and their use has recently been expanding in general surgery [8,9].

The final goal is the stimulation of resident MSCs to promote a regenerative microenvironment.

MSCs stimulate local inflammatory-immune modulation and trophic effects and ultimately facilitate tissue regeneration [10-14].

MSCs Therapy

In 2001 the FDA issued a set of regulations governing cellular and tissue-based therapies. The basic principle of these guidelines was that

cellular and tissue therapies that require *minimal to no manipulation* of autologous tissue do not require FDA approval [15].

MSCs isolated from different sources such as bone marrow, adipose tissue, cord blood, amniotic fluid, omentum, peripheral blood etc, showed *in vitro* capacity to differentiate in all mesenchymal lineages: fibroblasts, chondroblasts, adipocytes, muscle-cells, osteoblasts and other mesenchymal lineages [14-17].

Autologous ASCs offer advantages from regulatory, histocompatibility, and infectious perspectives.

Autologous MSCs are the most frequently used in clinical practice.

For autologous MSCs treatments in OA and plastic-aesthetic surgery the use of adipose tissue-derived stem cells (ASCs) is the most common and the most studied. The use of peripheral blood stem cells (PBSCs) is becoming popular [2].

Modern therapeutic strategies rely on the combination of MSCs and tissue engineering so that MSCs suspensions combined with biodegradable materials may improve cell survival and tissue regeneration capacity [18]. As with other MSCs it has been supposed that ASCs delivered into injured tissue induce repair and regeneration via paracrine effects. The ASCs stimulate the resident stem cells and promote their differentiation along the required lineage pathway. Furthermore, ASCs similar to BM-MSCs can deliver new mitochondria to damaged cells, thereby rescuing aerobic metabolism [10,11,12,19].

Therefore, against the initial assumption that MSCs might *in vivo* reproduce the *in vitro* findings, evidence increasingly suggests that the main therapeutic function of MSCs could be the paracrine effect to induce a local regenerative microenvironment [10,20].

In degenerative OA, ASCs can be culture-expanded and then injected into the joint or they can be harvested and directly injected as stromal vascular fraction SVF [14,21,22]. Further, ASCs have been used as mixed injections in combination with GFs, cytokines and scaffolds in order to improve their effectiveness. The most common scaffolds used are hyaluronic acid and fibrin gel. PRP has been applied as a nutrient fluid containing chondrogenic and osteogenic growth factors (e.g., TGF- β and PDGF) to support the survival and differentiation of transplanted MSCs [23,24].

Who are the RSU Patients? A focus on OA and hernia repair

Joint and back pain is often the result of degenerative OA and is one of the most frequent causes of patient visits for assessment. Degenerative Osteoarthritis (OA) is the most common chronic musculoskeletal disorder. Whilst OA can affect all joints, the knee, spine, hip, hands, feet, and shoulder are most frequently involved. Chronic pain leading to disability is the most common direct consequence. OA is the single most common cause of disability in older adults [2].

OA risk factors include obesity, sedentary lifestyle, chronic postural defects, bone density, occupational injury, trauma, and genetic predisposition.

The 2010 Global Burden of Disease Study estimated that 10% to 15% of all adults aged over 60 had some degree of symptomatic OA, with prevalence higher among females than males [25,26].

Most of the current medical treatments are palliative and work on pain management and symptom control. In advanced OA, total knee and hip replacement are the current standards to alleviate pain and improve function. However, the risks associated with the operation

and the finite life span of joint prosthesis exclude this option for a significant group of patients.

Joint replacement cannot often be offered to **frail elderly patients** (ASA III-IV) due to high risks of complications and increased mortality. Likewise, surgeons are reluctant to offer to **younger patient's** joint replacement due to the limited life span of prosthesis and chronic postural imbalance induced by the new joint [2]. The result is the increasing consumption of chronic medications such as NSAIDs and opioids in so-called *pain management*. This palliation has a severe systemic backlash on patient care and health systems due to the complications related to chronic NSAIDs and opioids intake and addiction [2].

Dilemmas can arise when we seek to offer patients the greatest benefits along with minimal risks. The basic medical principles *primum non nocere, secundum cavere, tertium sanare* (first do not harm, second be careful, third cure) should always guide and inspire medical practice [2].

The latest knowledge about the biological processes involved in the **early OA**, has given general awareness that this disease can be curbed and reversed if addressed at the early stage [2].

Early OA is defined by recurrent joint pain together with no or minimal changes detectable by *X-ray* imaging. Only MRI and USS can identify early markers of early OA in the synovial membrane and some superficial cartilage erosions [27-29].

These methods and criteria enable early identification of joint disease and this facilitates early therapeutic approaches to halt and reverse the normal progress of the disease [2,30].

The development of regenerative medicine procedures has facilitated a major change in *early OA* treatments as well as in *advanced OA*. These therapies provide persistent analgesia through tissue repair for frail elderly patients as well as younger patients who are currently offered simple palliation [2].

In addition, regenerative surgery minimally invasive procedures are non-toxic, very low risk and have minimal adverse side effects.

Inguinal hernia repair is the most frequently performed operation in General Surgery. Over 20 million hernia repair procedures per year are performed worldwide [8].

Complications including chronic inguinal pain (12%) and recurrence rate (11%) have significant negative impact on surgical results. The 4 main impacting factors affecting hernia repair results are: 1) *mesh material and design*; 2) *mesh fixation*; 3) *tissue healing and regeneration* and 4) *the surgical technique* [8].

PRF-hernia repair is a new physiologic and genuinely "tension-free technique" that follows the sound principles of both regenerative and conventional surgery. *L-PRF* mesh fixation removes the need for stitches, the usual cause of "nerve entrapment syndrome" due to the snaring by stitches of inguinal nerves. Further, the *PRF* anti-inflammatory and tissue regeneration properties both speed and 'streamline' the process of mesh integration.

The surgical technique, mesh material choice, biological method of fixation and the regenerative properties of *PRF* work synergistically to minimize wound site inflammation and assist correct integration of the mesh. These result in postoperative advantages. The short-term benefits are less pain and shorter time of recovery [8,9].

The mid-long-term benefits are lower incidence of chronic pain due to a correct process of wound healing and minimizing the risk of nerve entrapment [8,9].

Better integration and minimization of scar tissue may lead to a stronger repair and associated reduction in recurrence. This can be confirmed by long-term studies conducted by the research asset.

Other areas of expertise in the RSU

As reported in the *RSU* model, patients affected by chronic wound and skin ulcers such as diabetic foot ulcers (DFU), pressure ulcers (PU); venous leg ulcers (VLUs) have been treated. Significant benefit resulted from treatments of debridement together with the application of *PRF membrane* enriched with *HSPs* (supercharged-*PRF*).

PPRP and *ASCs* aesthetic regenerative fillers have been used to treat skin defects and to minimize wrinkles. *PRP* in combination with *HSPs* has been applied for hair regrowth and to aid transplantation.

These procedures involve different specialists and health professionals working cooperatively in the *RSU* multidisciplinary model.

Establishing an alliance between doctor and patient

The relationship between doctor and patient should be based on ethics, professionalism, competence, trust, honesty and especially on empathic communication.

The current process to gain the informed consent of patients has focused on medico-legal aspects. In daily practice, a doctor is mostly dedicated to defending his/her-self from potential complaints. The consent goal is to get permission to deliver medical treatments and the patient's acceptance of complications; these are usually stated in a long list. In the end, doctors effectively request the patient's permission to accept treatments and possible adverse events.

This is quite different to a relationship based on awareness and trust. In our model, the consent process is an essential step to establish a relation of *partnership* with the patient. Open and honest communication will satisfy patients that regenerative surgery procedures are the safest of the current medical options and effective enough to attempt them before considering major invasive procedures. This is in accordance with the first basic medical principle *first do no harm*. Doctors must mention that failure of treatment is a possible outcome. It is also proper to mention that the primary ethical aim is to attempt to remove suffering by improving patient symptoms with the least invasive and least harmful treatment that is currently available and has strong indications of efficacy.

The overall goal is to establish an *alliance* between the doctor and patient to pursue the common goal of best result and patient satisfaction.

RSU ambulatory care and day-surgery settings

Most of the *RS* procedures can be delivered in ambulatory care settings. This model has been applied in *Villa Aurora Hospital-Regenerative Surgery Unit*- Foligno (Italy). The essential parts are summarized below.

A dedicated laboratory area hosts centrifuges, fridge, oven-dryer and homogenizer where the patient's blood or adipose tissue can be sterilely manipulated and prepared.

Adjacent clinical rooms are arranged to deliver *RS* procedures. These need to be set as a surgical ambulatory care facility, each tailored for the specialist services to be provided: e.g. orthopedics, plastic surgery, dental service etc.

USs with a linear probe should be always available for OA treatments.

Main areas in the RSU ambulatory care settings:

- Reception and waiting room
- Blood Sample collection
- RS laboratory to prepare individual medication
- RS ambulatory care treatments
- Recovery, refreshment, and discharge

Procedures that can be delivered by ambulatory services are mainly *PRP/PRF-derivatives* and *monocytes*. These treatments provide valid therapeutic options in OA patients, implantology and plastic/aesthetic procedures.

To elicit best results in OA, particular care must be taken over the method of *PRP* production and application and the accurate positioning of the bio-stimulator in the affected joints. Centrifuge characteristics, centrifugation speed/ time, manipulation of the resulting product(s) and positioning in the joint tissue can all change the effectiveness and therefore the results of *PRPs* procedures [31].

We have used autologous adipose stem cells (*ASCs*) procedures for OA in various combinations with *PRP* and scaffolds to improve clinical results. *ASCs* procedures are generally delivered under general anesthetic in a day surgery facility. *PRF-inguinal hernia repair* is a day surgery new technique delivered in theatre setting. The centrifuge to produce the *L-PRF* used to fix the mesh is based in theatre.

Our research and innovative procedures

Stimulation of resident MSCs. Most joint tissue regeneration treatments have targeted cartilage tissue. However, literature on the physiopathology of *early OA* has shown the essential role played by the synovial membrane and synovial fluid to trigger the disease together with articular cartilage modifications [2]. Joint pain is firstly initiated by changes to non-cartilaginous components such as the joint capsule, synovial membrane, tendons and ligaments where there is a significant innervation [32,33].

Since 2012 the author has published work on procedures whose core effect is stimulation of *joint resident MSCs* [34,35]. A study mentioned in the work aimed to show long-term symptom control through the recovery of local cell homeostasis and tissue repair. The study examined an individual medication comprised of *polydeoxyribonucleotides (PDRN)*, a specific set of *Heat Shock Proteins (HSPs)* and a *glycerol scaffold*. The *HSPs* were derived from the patient's blood through a process of thermic stress.

This product named *Gel repair® (GR)* has shown to be a biological activator able to stimulate the *resident MSCs* located in the capsule and synovial tissue.

An observational clinical trial with 3 years follow-up showed a persistent improvement of symptoms together with a radiologic recovery of joints affected by degenerative Osteoarthritis. Lower pain level and increased joint mobility were observed in almost 80% treated patients and imaging often showed a downgrading of the degenerative OA [34,35]. Besides cartilage and bone regeneration, *Gel Repair®* (in some preliminary experiences) has shown wound healing properties on chronic skin ulcers that did not respond to traditional treatments. Following the same biological principles, we have been using thermic stressed *L-PRF* membranes to produce a pool of *HSPs*. The process aims

to activate *SM-MSCs* (Synovial Membrane-MSCs) in OA. The resulting product, termed '*supercharged L-PRF*' when used in a *procedure*, supplements the stimulation of *SM-MSCs* with a pool of *HSPs* that are slowly released by the treated membranes when applied on the surface of capsule-bursa tissues.

Omentum adipose stem cells (OASCs) transplantation has been successfully used for muscle regeneration, for degenerative osteoarthritis and to prevent colorectal anastomotic leak [17].

Scientific activity

RSU implements data collection and statistical analysis to measure the quality of services and their performance. Data and results will eventually be published in scientific journals.

This approach improves the quality of health care in any sector of *RSU* activities. The *clinical activity* is set by default as a longitudinal, observational, or comparative study to constantly deliver research results on the ground. This is the basis for CQI/TQM best practice in clinical settings [36]. This measurable systematic approach generates quality, high performance, and value. The *RSU-members website* promotes regenerative surgery information and updating, interactive communications, e-learning, and training. The *website* will outline and enable members to explore options for a scientific society/association model.

One option has a board of scientists, academics, experts in biology, immunology, regenerative surgery, longevity, and regulatory professionals. The association may elect to establish partnerships with universities and other institutions to promote educational events and research.

Other services associated with the RSU

In orthopedics, *RSU* works in a team with physiotherapists and advises long term swimming-pool-physio to improve the quality and duration of results. Furthermore, *OA* patients may be obese and /or frail and/or with multiple chronic comorbidities. Therefore, we offer specialistic consultations and treatments to tackle these problems and prevent *OA* recurrence.

Health tourism

Health or Medical tourism refers to people travelling abroad to obtain medical treatments or health care services. Historically, patients and people have always travelled from developing countries to developed countries to receive medical treatments unavailable in their countries [37].

However, in recent years, *health tourism* has become a two-way flow. Social and economic motivations have pushed people from developed countries to seek treatments in developing countries that promise high performance at lower prices. Moreover, tourism boards of some countries offer medical care together with touristic/ cultural excursions and entertainment. There are significant differences between the medical regulatory agencies in various countries (FDA; EMA etc.). As a consequence, a drug or a procedure may be approved in some countries and not in others. Therefore, another reason for *Medical tourism* is to receive medical care unavailable or non-licensed in the home country.

Medical tourism most often is for plastic and cosmetic surgeries, dental and fertility procedures [38]. More recently, 'longevity' therapies involving stem cells and associated treatments are rapidly

expanding in several medical fields. Again, the core aim is regeneration of dysfunctional cells, tissues, organs and structures. *Medical Tourism* offers ought to warrant safety, effectiveness, quality of services, high performance, assessment should be handled by an independent quality commission.

Our RSU located at Villa Aurora Hospital- Foligno (Italy) is fully accredited by the National Health System (SSN) and rated by external commissioners. Foligno is a medieval town close to Perugia in the central heart of Italy (Umbria) which offers beauty and peace in enchanting scenarios together with art and culture.

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