

## Original Research Article

# Novel triple therapy in osteoarthritis of knee joint

Kalyan K. Hukumathirao, Ashok N. Kotha, Venugopal R. Pondugula, Satya K. Koduru\*

NRI Academy of Sciences, Orthocare, Chinakakani, Andhra Pradesh, India

**Received:** 05 January 2023

**Revised:** 12 January 2023

**Accepted:** 13 January 2023

**\*Correspondence:**

Dr. Satya K. Koduru,

E-mail: kodurusk@gmail.com

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ABSTRACT

**Background:** Regenerative medicine may be defined as the process of replacing or regenerating human tissues or cells of humans to restore or to get very near to normal function of human life. Biological tissues found in humans such as blood, fat, bone marrow are the main resources of regenerative medicine which help in natural process of healing of soft tissue. Extracorporeal shock wave therapy (ESWT) is a physical modality that helps in enhancing healing process of soft tissues. Osteoarthritis of the knee joint is a gradually progressive degenerative condition with the loss of articular cartilage. The early stages of disease are managed conservatively with the aim of retarding the rate of cartilage destruction.

**Methods:** A total of 80 patients underwent the novel triple therapy. The objective is to find out the potential of combination therapy in early degenerative disease of knee with the aim of reduction of inflammation. A protocol was developed which involved three injections of platelet rich plasma (PRP), six sessions of combined ESWT and physiotherapy.

**Results:** Evaluation was mainly based on WOMAC/KSS/VAS scores. Patients in stage 1 and 2 (55+15=70) had excellent results for 36 months, patients in stage 3 (10 cases) had satisfactory outcome at 24 months.

**Conclusions:** Triple therapy is an alternative treatment or in few cases a definitive treatment in degenerative disease of knee joint where medical and surgical management has minimal or no role. Triple therapy in mild to moderate osteoarthritis of knee joint has better outcome.

**Keywords:** ESWT, PRP, Physiotherapy, Regenerative orthopedics knee, Orthobiologics

### INTRODUCTION

#### *Regenerative medicine in orthopaedics*

Regenerative medicine is a branch of medicine that deals with replacing or regenerating cells or tissues or organs of humans to restore or to get very near to normal activities of human life.<sup>1,2</sup> Biological tissues found in humans such as blood/fat/bone marrow are the main resources of regenerative medicine which help in natural process of healing of soft tissue structures of human body like muscles, tendons, ligaments and cartilage. "Orthobiologics" refers to the use of biological substances to help musculoskeletal injuries heal quicker. They are used to improve the healing of fractured bones and injured

muscles, tendons and ligaments, healing of degenerative joints and are derived from substances that are naturally found in body.<sup>3-5</sup> When they are used in concentrations many times the normal, they can potentially help speed up the healing processes.

These orthobiologics evolved over last few decades and the following are few examples of them. 1st generation - hyaluronic acid (HA), 2nd generation - platelet rich plasma/autologous conditioned serum (PRP/ACS), 3rd generation - bone marrow aspirate concentrate/mesenchymal stem cells (BMAC/MSC), 4th generation - adipose mesenchymal stem cells (AMSC)/stromal vascular fraction (SVF) and goldic - gold induced cytokines which is used along with stem cells

in few parts of the world with encouraging positive results, and latest is 5th generation - gene therapy – in vivo under trail.<sup>6</sup>

**Physical modes**

Few modalities help in enhancing healing process of soft tissue degeneration and injuries: exercise - helps mobilizing stem cells into peripheral blood circulation, ESWT, and laser therapy.<sup>7</sup>

ESWT and laser therapy helps in acceleration of tissue healing, increased circulation, pain reduction, decreased inflammation.<sup>8</sup>

**Objectives**

To find out the potential of combination therapy with (ESWT/PT/PRP) in early degenerative disease of knee. The staging system for osteoarthritis (OA) of the knee is shown in Table 1.

**Table 1: Staging of knee osteoarthritis.**

Stage	Knee pain	Radiographic osteophytes	Age	Morning stiffness	Creptus	Bony enlargement on physical examination
<b>I</b>	√	√	<40	-	-	-
<b>II</b>	√	√	>40	<30	√	-
<b>III</b>	√	√	>40	>30	√	-
<b>IV</b>	√	√	>40	>30	√	√

-Findings absent, √ findings

**METHODS**

This is a prospective study conducted on patients suffering from OA of the knee joint.

The study period was from April 2018 to March 2021. Selection of cases was done mainly from January 2018 to March 2018.

The study was conducted at Orthocare, Vijayawada and follow up was done at the department of orthopaedics at NRIGH.

70 females & 10 males were recruited for the study based on inclusion criteria. The patients were aged between 45 to 60 years. Among the 80 patients, 55 cases were in stage 2 OA, 15 cases in stage 1 OA and remaining 10 cases were in stage 3 OA. Out of 55 in stage 2, we had 50 females and 5 males, 12 females and 3 males in stage 1 and 8 females and 2 males in stage 3.

**Inclusion criteria**

The study included: KL grade 1 to grade 3 OA, primary OA, pain at least for 3 months, and age between 45 and 60 years.

**Exclusion criteria**

The study excluded: KL grade 4 OA, secondary OA, coagulation disorders, immunodeficiency patients, pregnant women, and uncontrolled diabetes.

All the patients were asked to attend a formal meeting and explained about the study we are going to perform on them and after taking consent from 80 cases we started doing the study from April 2018.

We analyzed all the 80 cases at the end of 36 months.

The intensity of knee pain was evaluated using the visual analogue scale (VAS) after the patients have remained in a weight-bearing state for 5 minutes (walking or standing). The pain level was rated by each patient from 0 to 10 cm, where 0 represented ‘no pain’, and 10 represented ‘unbearable pain’.

The patients’ disability was evaluated using the valid and reliable modified Western Ontario and MacMaster Universities osteoarthritis index (WOMAC). It is a questionnaire that evaluates disabilities in performing daily living activities. This method is relevant and appreciated for its simplicity and allows assessment of the patients’ opinions of their functional disabilities. WOMAC/KSS/VAS scores were taken on the day of starting of the study and results were mainly based on these scores.

Clinical evaluation along with radiological grading was done before enrolling the cases into study after taking informed consent from patients.

**Protocol of novel triple therapy of degenerative knee**

Day 01 – PRP, day 03 - ESWT + physiotherapy, day 05 - ESWT + physiotherapy, day 07 - ESWT + physiotherapy, day 10 – PRP, day 12 - ESWT + physiotherapy, day 14 - ESWT + physiotherapy, day 16 - ESWT + physiotherapy, and day 20 – PRP.

**ESWT**

It is a non-invasive method that uses acoustic waves to treat a wide variety of musculoskeletal conditions. Total 6 sessions of ESWT given for the cases enrolled for this study, and non-focused - radial or dispersive type is used

on the day 3, 5, 7, 12, 14 and 16 at frequency of 9 Hz and energy used 2.5 bar with 2500 shocks per session.

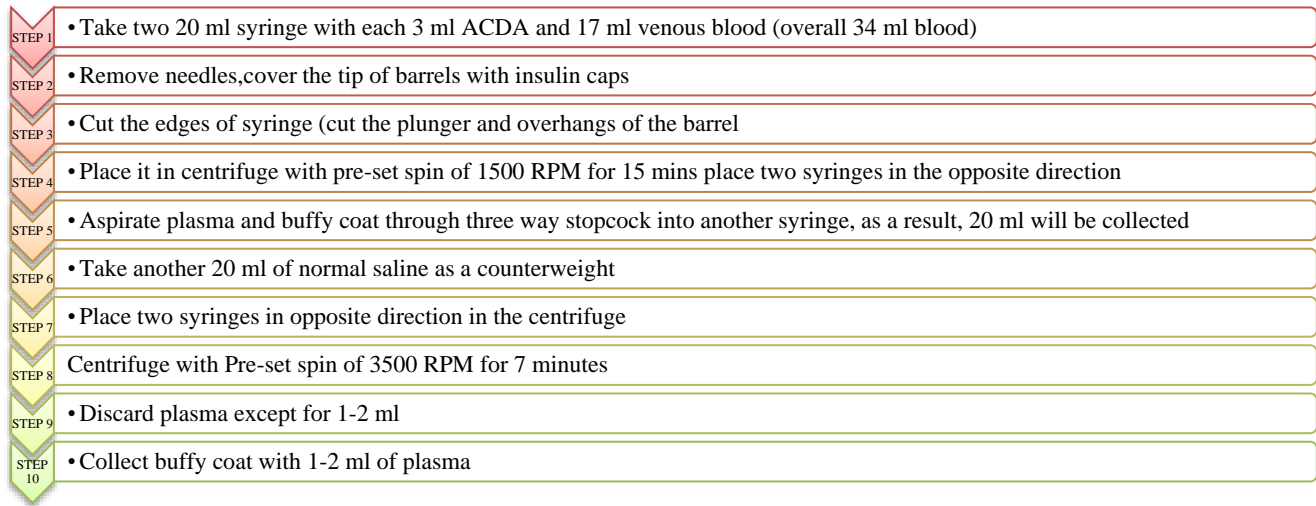
in all knee OA groups for 6 days especially on the day when ESWT was planned (day 3, 5, 7, 12, 14 and 16).

**Physiotherapy**

The rehabilitation program designed to decrease the pain intensity and improve the knee range of motion, isometric quadriceps strength, and level of functional performance

**Statistical analysis**

Data entry was done using Microsoft excel, and it statistically analyzed using statistical package for social sciences (SPSS version 16) for M.S. Windows.



**Figure 1: Steps in the preparation of platelet rich plasma.**

**RESULTS**

Based on WOMAC/KSS/VAS scores, pre-treatment and post treatment responses were evaluated. Follow up was done for 36 months (3 m/6 m/12 m/18 m/24 m/30 m and 36 m).

Stage 1 and 2 (55+15=70) had excellent results for 36 months, stage 3 (10 cases) had satisfactory outcome for 24 months.

In Table 2 of Womac score the results are clearly showing the advantage patients received especially in stage 1 and 2

compared to stage 3. In stage 3 after 24 months score was getting into higher side.

In Table 3 of KSS score the results are clearly showing the advantage patients received especially in stage 1 and 2 compared to stage 3. In stage 1 and 2 upto 36 months score was getting into higher score which indicates good result.

In Table 4 of VAS the results are clearly showing the advantage patients received especially in stage 1 and 2. In stage 3 after 24 months score was getting into higher side which indicates patients are getting back into pre therapy status.

**Table 2: Pre and post therapy WOMAC Scores.**

Pre	Post 03	Post 06	Post 09	Post 12	Post 18	Post 24	Post 36
<b>Pre and post therapy scores – stages 1 and 2 - WOMAC</b>							
<b>82</b>	0-5	0-5	0	0	0	10-15	20-30
<b>Pre and post therapy scores – stage 3 - WOMAC</b>							
<b>78</b>	0-5	0-5	0	0	0	35-40	40-50

**Table 3: Pre and post therapy knee society score.**

Pre	Post 03	Post 06	Post 09	Post 12	Post 18	Post 24	Post 36
<b>Pre and post therapy scores – stages 1 and 2 - knee society score</b>							
<b>59.9±13.5</b>	67.7±14.2	69.3±16.8	78.2±10.0	80±6.8	87.9±11.1	90.8±5.2	92.5±14.4
<b>Pre and post therapy scores – stage 3 - knee society score</b>							
<b>58.7±12.6</b>	62.4±11.7	69.9±8.3	75.7±7.9	85.6±11.0	88.9±16.7	86.5±13.3	85.1±13.7

**Table 4: Pre and post therapy Visual Analogue Scale scores.**

Pre	Post 03	Post 06	Post 09	Post 12	Post 18	Post 24	Post 36
<b>Pre and post therapy scores – stages 1 and 2 - VAS</b>							
8/10	2/10	2/10	0/10	0/10	2/10	2/10	2/10
<b>Pre and post therapy scores – stage 3 - VAS</b>							
8/10	2/10	2/10	0/10	0/10	2/10	6/10	8/10

**DISCUSSION**

Osteoarthritis is a disorder of synovial joints caused mainly by the uncoupling of balance between cartilage regeneration and degeneration due to focal loss of hyaline cartilage leading to proliferation of cells and the formation of new bone and remodeling of joint surfaces. Osteoarthritis is a dynamic repair process of synovial joints that may be triggered by a wide variety of causes. It is a result of the imbalance between various factors.

**Table 5: Molecules.**

Bad molecules	Good molecules
<b>MMPs – matrix metalloproteinases – collagenases, gelatinases, stromelysins – degrade collagen, proteoglycans, elastin; IL-1, TNF – interleukins – inflammatory – enhance MMPs; ADAMTS – disintegrins – prevent platelet function</b>	TGF –transforming growth factor; TIMP 1 and 2 – tissue inhibitor of metalloproteinases; IRAP – interleukin receptor antagonist protein; A2M – alpha 2 macroglobulin

**ESWT in degenerative arthritic condition**

ESWT is a non-invasive method that uses acoustic waves to treat various musculoskeletal conditions.<sup>9</sup> It promotes neovascularization at the tendon-bone junction, stimulate proliferation of tenocytes and osteoprogenitor differentiation, increase leukocyte infiltration, and amplify growth factor and protein synthesis to stimulate collagen synthesis and tissue remodelling.<sup>10,11</sup> These waves create compression and shear loads on the surface of the material. This rapid interaction between compression and shear forces results in cavitations. This is the basic principle behind ESWT.<sup>12</sup> It helps in healing, improves blood supply, and helps in pain reduction.

There are 2 types: focussed - for lithotripsy, and non-focussed - radial or dispersive used in orthopaedics. An electromagnetic source by passing an electric current through a coil to produce a magnetic field generates a shockwave, which results in sudden membrane deflection and generation of pressure waves in a fluid. Subsequently, a lens is applied to focus these waves onto the diseased area of the body, and the length of the lens can be used to determine the therapeutic point.<sup>13</sup> Piezoelectric sources can produce shockwaves via a high-voltage discharge

across piezoelectric elements mounted in a sphere, which induces a pressure pulse in the surrounding water that increases to a shockwave. The expansion of each element generates a pressure pulse that enables the self-focusing of waves toward the target, creating an extremely precise focus and high level of energy. The various features of these shockwave devices like energy density, pressure distribution, and total energy at the second focal point, are used to treat a variety of diseases like musculoskeletal disorders and urolithiasis.<sup>14</sup> Chronic OA pain appears to be related closely to an increase in the growth of nonvascular, substance P-positive sensory nerve fibres.<sup>15</sup> Many studies have demonstrated the ability of ESWT to reduce OA pain. This effect is because of the neovascularization, and by repairing inflamed tissues via tissue regeneration. In a previous study, Ochiai et al applied treatment to the medial sides of knees in a rat model of OA.<sup>16</sup>



**Figure 2: Handle of ESWT (clicked in the clinic orthocare).**

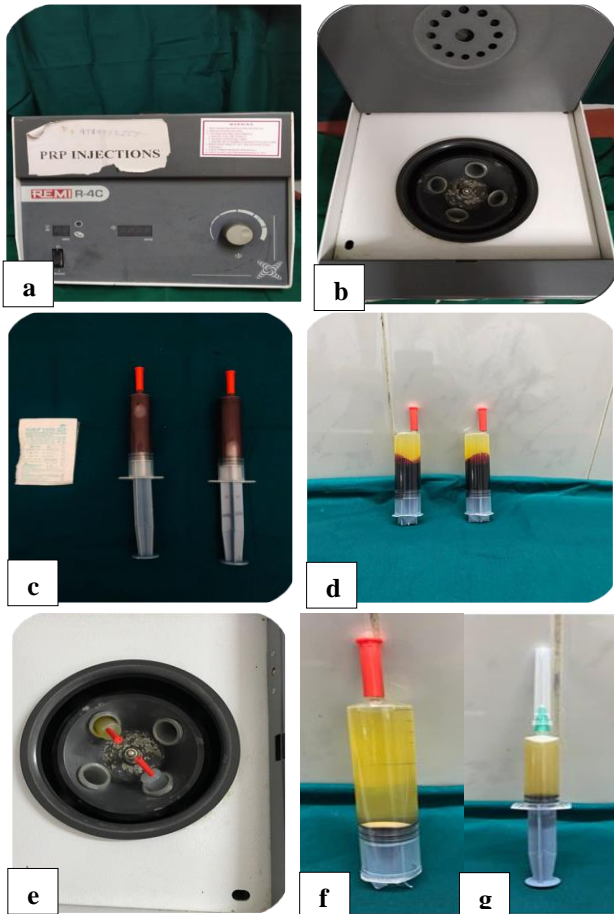


**Figure 3: Shockwave system (clicked in the clinic orthocare).**



**PRP in degenerative disease of knee**

It helps in environmental rebalancing in an arthritic joint, stimulates regeneration of damaged articular cartilage, stem cell migration can be mobilized.<sup>17</sup> The use of biological agents, including PRP in orthopaedics, has increased exponentially over the previous years because of its autologous nature, lack of side-effects, and supposed effectiveness. Platelet-rich plasma is an autologous blood product with platelet concentrations much more than the normal.



**Figure 4: Steps in preparation of PRP (a) centrifuge machine, (b) centrifuge rotor at centre, (c) 3 ml ACDA+17 ml blood in each syringe, (d) after first spin 1500 rpm for 15 minutes in centrifuge, (e) second spin 3500 rpm for 7 minutes, (f) after second spin—remove platelet poor plasma leaving 3-4 ml at the bottom, and (g) final PRP.**

Tissue repair is a complex process comprising chemotaxis, cell proliferation, angiogenesis, and matrix formation. Platelets play a crucial role in all these functions by releasing growth factors. High concentrations of proteins such as endothelial cell growth factor, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) have led to the conclusion that PRP may be useful in conditions requiring tissue healing. Conversely, transforming growth

factor (TGF-β1), present in PRP, has a negative effect and can lead to non-predictable results. Keeping all the above in mind we decided to combine all these 3 modalities in degenerative knee disease and following protocol was designed by our group.

The rehabilitation program decreased the pain intensity and improved the knee ROM, isometric quadriceps strength, and level of functional performance in all knee OA groups.<sup>18</sup>

The study was conducted on a small group of patients and hence cannot be generalised. Though it is a prospective study, there is no comparison group to the participants. It is an observational study with no blinding techniques followed.

**CONCLUSION**

Our triple therapy is an alternative treatment or in few cases a definitive treatment in degenerative disease of knee joint. Orthobiologics is definitely a game changer in managing degenerative diseases of knee or any other chronic inflammatory pathologies where medical and surgical management has minimal or no role. Triple or multidimensional treatment in mild to moderate OA has better outcome and definitely changed the outcome better than NSAIDs and Intraarticular steroids which are just symptom relievers.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

**REFERENCES**

1. Zamborsky R, Kilian M, Csobonyeiova M, Danisovic L. Regenerative Medicine in Orthopaedics and Trauma: Challenges, Regulation and Ethical Issues. *Ortop Traumatol Rehabil.* 2018;20(3):173-80.
2. Gómez-Barrena E, Rosset P, Müller I, Giordano R, Bunu C, Layrolle P, Kontinen YT, Luyten FP. Bone regeneration: stem cell therapies and clinical studies in orthopaedics and traumatology. *J Cell Mol Med.* 2011;15(6):1266-86.
3. de Graeff JJ, van den Bekerom MPJ, van Meer BL, Zijl JAC; Dutch Arthroscopy Society. Orthobiologics and hyaluronic acid usage in the Netherlands: an electronic survey of 265 orthopaedic surgeons and sports physicians. *J Exp Orthop.* 2021;8(1):66.
4. Sezgin EA, Atik OS. Are orthobiologics the next chapter in clinical orthopedics? A literature review. *Eklemler Hastalik Cerrahisi.* 2018;29(2):110-6.
5. Roberts TT, Rosenbaum AJ. Bone grafts, bone substitutes and orthobiologics: the bridge between basic science and clinical advancements in fracture healing. *Organogenesis.* 2012;8:114-24.

6. Steven S, Hunter V, Mary AA, Edwin A. Orthobiologics: Where are we Now? *Nov Tech Arthritis Bone Res.* 2017;2(1):555576.
7. De Lisio M, Parise G. Characterization of the effects of exercise training on hematopoietic stem cell quantity and function. *J Appl Physiol* (1985). 2012;113(10):1576-84.
8. Apostolopoulos AP, Angelis S, Kaitatzi M. The Facts and Myths for the Use of Lasers in Orthopedic Surgery. *J Long Term Eff Med Implants.* 2021;31(2):55-69.
9. Zhao Z, Jing R, Shi Z, Zhao B, Ai Q, Xing G. Efficacy of extracorporeal shockwave therapy for knee osteoarthritis: a randomized controlled trial. *J Surg Res.* 2013;185(2):661-6.
10. Li W, Pan Y, Yang Q, Guo ZG, Yue Q, Meng QG. Extracorporeal shockwave therapy for the treatment of knee osteoarthritis: A retrospective study. *Medicine (Baltimore).* 2018;97(27):e11418.
11. Wang YC, Huang HT, Huang PJ, Liu ZM, Shih CL. Efficacy and Safety of Extracorporeal Shockwave Therapy for Treatment of Knee Osteoarthritis: A Systematic Review and Meta-analysis. *Pain Med.* 2020;21(4):822-35.
12. Vetrano M, Ranieri D, Nanni M, Pavan A, Malisan F, Vulpiani MC, Visco V. Hyaluronic Acid (HA), Platelet-Rich Plasm and Extracorporeal Shock Wave Therapy (ESWT) promote human chondrocyte regeneration in vitro and ESWT-mediated increase of CD44 expression enhances their susceptibility to HA treatment. *PLoS One.* 2019;14(6):e0218740.
13. Moya D, Ramon S, Schaden W, Wang CJ, Guiloff L, Cheng JH. The Role of Extracorporeal Shockwave Treatment in Musculoskeletal Disorders. *J Bone Joint Surg Am.* 2018;100:251-63.
14. Wang CJ, Yang YJ, Huang CC. The effects of shockwave on systemic concentrations of nitric oxide level, angiogenesis and osteogenesis factors in hip necrosis. *Rheumatol Int.* 2011;31:871-7.
15. Lian O, Dahl J, Ackermann PW, Frihagen F, Engebretsen L, Bahr R. Pronociceptive and antinociceptive neuromediators in patellar tendinopathy. *Am J Sports Med.* 2006;34:1801-8.
16. Ochiai N, Ohtori S, Sasho T, Nakagawa K, Takahashi K, Takahashi N, et al. Extracorporeal shock wave therapy improves motor dysfunction and pain originating from knee osteoarthritis in rats. *Osteoarthritis Cartilage.* 2007;15:1093-6.
17. Dhillon MS, Behera P, Patel S, Shetty V. Orthobiologics and platelet rich plasma. *Indian J Orthop.* 2014;48:1-9.
18. Abdel-Aziem AA, Soliman ES, Mosaad DM, Draz AH. Effect of a physiotherapy rehabilitation program on knee osteoarthritis in patients with different pain intensities. *J Phys Ther Sci.* 2018;30(2):307-12.

**Cite this article as:** Hukumathirao KK, Kotha AN, Pondugula VR, Koduru SK. Novel triple therapy in osteoarthritis of knee joint. *Int J Res Orthop* 2023;9:xxx-xx.