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Effect of Co-Injection of PRP and Ozone Gas on Growth Factors' Expression in Knee Osteoarthritis: A Therapeutic Evaluation

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ABSTRACT

Osteoarthritis (OA) is a chronic and progressive disease characterized by cartilage and joint degradation, leading to pain and functional impairment. In this study, we aimed to assess the impact of co-injection of Platelet-Rich Plasma (PRP) and ozone gas on the expression of growth factors' genes in patients with knee osteoarthritis, both before and after treatment with the combined therapy. Therapeutic efficacy was evaluated using the Knee injury and Osteoarthritis Outcome Score (KOOS), Intermittent and Constant Osteoarthritis Pain (ICOAP) scale, and the Timed Up and Go (TUG) test. The expression levels of IGF-1, HIF-1, and BMP2 genes, as well as the serum IGF-1 levels, were measured in patients before the initial injection, one month after the first injection, and one month after the second injection. The results demonstrated a significant improvement in the mean scores of KOOS, ICOAP, and TUG tests one month after the first injection compared to the pre-injection phase. Furthermore, one month after the second injection, the mean scores were significantly better than one month after the first injection, indicating the effectiveness of the two-time co-injection therapy for knee OA treatment. Moreover, the mean expression levels of IGF-1, HIF-1, and BMP2 genes were significantly higher one month after both the first and second injections compared to the pre-injection phase, suggesting a potential upregulation of growth factors in response to the treatment. The study also revealed a noticeable increase in the level of IGF-1 in the serum one month after the first injection, further supporting the positive effects of intra-articular PRP and ozone gas injection on knee osteoarthritis by enhancing growth factors' expression. In conclusion, the findings suggest that the co-injection of PRP and ozone gas can lead to improved pain relief, reduced stiffness, and enhanced quality of life in patients with knee osteoarthritis. This positive outcome is likely attributed to the upregulation of growth factors' expression following the combined therapy. Further research and clinical investigations are warranted to validate and extend these promising results.

Keywords: Platelet Enriched Plasma (PRP); Knee Osteoarthritis; IGF-1; Ozone Gas

Introduction

Osteoarthritis (OA) also called degenerative joint disease, is a joint disorder that leads to the degeneration of joint tissues, there by the resulted pain, stiffness, and impaired physical functioning [1]. The World Health Organization asserts that over a global number of 150 million people (2.5% of the world's population) face OA [2,3]. This number can grow up to 10% in people aged over 60. The condition can develop in any of the synovial joints of the body; however, the most severe OA cases tend to occur in the knee joint [4]. Nearly 4.4 million Canadians suffer from knee OA, and it is expected that the number will reach 10 million in the next 30 years as a result of extended life expectancy, diminished physical activity, and weight gain [2,3]. OA is characterized by pain and disability in the form of reduced participation in activities and diminished temperament, sleep, and,

consequently, resulting in negative effects on the overall quality of life [5]. Pain has a multifactorial mechanism, and it seems to be nociceptive and neuropathic in patients with OA. Pain treatment is thought to be of importance in the cost of OA care. OA treatment is aimed at controlling pain and maintaining/improving physical functioning [6]. Evidence-based international management guidelines suggest a blend of non-pharmacological and pharmacological options for the treatment of OA pain which is highly complicated as pain is a bio psychosocial multifactorial phenomenon [7,8]. Moreover, no treatment has been identified thus far for OA treatment or a way to stop the damage caused to joint tissue. However, the use of platelet-rich plasma (PRP) is viewed as a new treatment for osteoarthritis [9].

PRP is a plasma fraction from autologous blood with a platelet concentration above the baseline. Platelets contain a variety of growth factors (GFs) and many important bioactive proteins and anti-inflammatory cytokines that mediate cartilage healing [10]. Different types of GFs are released from platelets, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), basic fibroblast growth factors (bFGF), insulin-like growth factor (IGF), epidermal growth factors (GF), and many other factors [11]. Due to the importance of these GFs, PRP has been used in several clinical studies for treating diseases. In addition to PRP, ozone therapy which is the administration of ozone gas into the patient's body has recently been proposed as a safe, inexpensive, convenient therapeutic method for treating different types of diseases [12]. Ozone therapy is practiced for different varieties of musculoskeletal and joint pain such as knee joint pain and there is a 75% probability that the patients' chronic pain would be completely and permanently alleviated [13].

The pathobiology of OA is still not well known. Meanwhile, various genes have been recognized to play a crucial role in the prevention of OA [14]. Hypoxia-inducible factor 1-alpha, also known as the HIF-1α is among the key genes that keep chondrocytes alive and grow throughout cartilage development. Insulin-like growth factor 1, also called somatomedin C (IGF-1) is an essential anabolic growth factor for the cartilage that not only is of great significance in cartilage homeostasis but also balances proteoglycan synthesis [15]. Likewise, bone morphogenetic protein 2 (BMP2) is a strong bone/cartilage-inducing molecule capable of stimulating proteoglycan synthesis and bone formation. It has also anabolic effects on cartilage metabolism [16]. Therapies utilized as analgesics have not been as effective thus far, and the overall failed treatments remain a major gap in osteoarthritis treatment management. Likewise, there are a few studies conducted to assess the disease progression, the response to new treatment options and mechanism of action [17]. Hence, this study was executed to evaluate the effectiveness of injection of PRP and ozone gas in the treatment of knee OA based on its effect on the expression of genes involved in cartilage formation and repair.

Methods

Preparation of PRP and Co-Injection of PRP/Ozone Gas in Knee of OA Patients

Autologous PRP was derived from blood samples taken from 30 patients diagnosed with knee osteoarthritis. Aseptically, a total of 35 ml of blood was collected to produce PRP, following the manufacturer's protocol (Rooyagen Kit, Arya Mabna Tashkis Corporation, RN: 312569). The purity of platelets was assessed by counting blood cells before and after PRP purification. Intra- articular injection of 7 mL of purified autologous PRP was performed using a 22-gauge needle, with the assistance of a local anesthetic agent administered by a Physiatrist. Subsequently, ozone gas, ranging from 10 to 20 cc, generated by the Ozomed device, was injected into the same knee joint.

Osteoarthritis Improvement Questionnaires

This study employed a comprehensive assessment approach to evaluate the effects of PRP and ozone gas injection on knee osteoarthritis (OA) treatment. The evaluation was based on the Knee Injury and Osteoarthritis Outcome Scores (KOOS), The Intermittent and Constant Pain Score (ICOAP), and the Timed Up and Go Test (TUG). The ICOAP consisted of 11 items that measured two types of pain: constant pain and intermittent pain. Constant pain refers to pain that persists continuously, albeit not necessarily severe, whereas intermittent pain occurs based on the patient's condition. In ICOAP, a higher score of 100 indicated a greater degree of pain, while lower scores represented reduced pain levels. The KOOS was designed to assess the consequences of knee OA and injuries, consisting of 42 items across five separate subscales: Pain, other Symptoms, Function in daily living (ADL), Function in Sport and Recreation (Sport/Rec), and knee-related Quality of Life (QOL). Each item offered five alternatives ranging from "No Recovery" (None) to "Full Recovery" (Extreme). The TUG test focused on evaluating mobility, balance, walking ability, and fall risk in adults, making it a sui instrument for individuals with OA or stroke. During this test, the patient started in a seated position and, upon the therapist's command, stood up, walked three meters, turned around, returned to the chair, and sat down. Patients undergoing the test were not allowed to seek assistance from others for walking, although they could use assistive devices. There was no time limit for the test, and the time recorded from the start to the end of the process (i.e., when the patient turned back and sat down) constituted the TUG score. A score of less than 10 seconds indicated normal mobility without issues, while scores ranging from 10 to 20 seconds denoted good mobility, allowing patients to perform daily tasks independently. TUG scores between 20 and 30 seconds indicated severe mobility problems, highlighting the need for assistance in daily tasks. Similarly, scores above 14 seconds indicated an increased risk of falling, necessitating appropriate treatment.

RNA, Reverse Transcription-Polymerase Chain Reaction, and Real-Time Polymerase Chain Reaction

RNA was collected from the patients' blood before PRP and ozone gas injection, one month after the first PRP and ozone gas injection, and one month after the second PRP and ozone gas injection by means of RNeasy blood mini kit (Qiagen, Germany) according to the manufacturer's protocol. The quality and quantity of RNA were analyzed using optical density measurements of 260/280 nm ratio. Complementary DNA (cDNA) was prepared from purified RNA for each sample using the cDNA synthesis kit (Add Bio, South Korea). The relative expressions of responsible genes for cartilage synthesis were determined using the Real-Time PCR approach. Primer specifications are shown in Table 1. To this end, 1µg synthesized cDNA was mixed with 2x SYBR Green Master Mix (Genetbio, South Korea) and then the mixture was subjected to the Corbet 6000 Real-Time PCR Detection System (Qiagen, Germany). Amplification conditions were as follows: 1 min at 94ºC, 35 cycles of 45 s at 94ºC, 60 s at 72ºC, and 10 s at 72°C. The data were normalized to GAPDH gene expression, and relative expression was then calculated using formula. Gene expression experiments were performed in triplicate.

Table 1: The sequence of primers used in molecular testing.

Product Length	Beginner Sequence	Gene
106 bp	F: TCTACCTGGCACTCTGCTTG	IGF-1
	R: GGTCCACACACGAACTGAAG	
101 bp	F: TCAAGCCAAACACAAACAGC	BMP-2
	R: CCACGATCCAGTCATTCCA	
125 bp	F: CGATGACACGGAAACTGAAG	HIF-1α
	R: CAGATTCAGGTAATGGAGACA	
123 bp	F: TGAACCATGAGAAGTATGACAA	GAPDH
	R: CATGAGTCCTTCCACGATAC	

Serum IGF-1 Measurement

Serum IGF-1 levels were assessed to verify the overexpression of the IGF-1 gene in the co-injected groups compared to the pre-injection phase. The measurements were conducted one month after the first injection and one month after the second injection using a chemiluminescence analyzer, specifically the siemens IMMULITE 2000 xpi, following the manufacturer's protocol.

Statistical Analysis

Statistical analysis was conducted using the SPSS software program. The results were compared using the one-way ANOVA. If the difference between the groups was significant, the Tukey post- hoc test as employed. The results were reported as mean ± standard deviation (SD) and P value <0.05 was considered as a significant difference.

Results

The Number of Platelet were Evaluated Before and After Purification

This study comprised 30 patients with knee osteoarthritis. There were 15 male and 15 female patients. Patients' mean age was 65 years and their age ranged from 55 to 74 years. The mean body mass index (BMI) of the participants in this study was 67 kg / m2. The number of blood cells was counted before and after PRP purification in order to confirm the PRP purification process. The results of blood cell counting are indicated in Table 2.

Table 2: The result of cell blood counting.

Cell type	Before Purification	After Purification
Platelets	$194*10^6$ µl	$1067*10^6$ µl
White blood cell	$6*10^6$ µl	$7*10^5$ µl
Lymphocytes	49%	Not Detected
Monocytes	5%	Not Detected
Neutrophils	42%	Not Detected
Basophils	Not Detected	Not Detected
Eosinophils	3%	Not Detected
Red Blood Cell	$13.1*10^3$ µl	$0.05*10^3$ µl

The Therapeutic Efficiency of Co-Injection of PRP/Ozone Gas was Evaluated by KOOS, ICOAP, and TUG Tests

The findings of the KOOS, ICOAP, and TUG tests conducted before PRP and ozone gas injection, one month after the first injection, and one month after the second injection are summarized in Table 3. Regarding pain assessment, the results demonstrated a statistically significant reduction in pain levels one month after both the first and second PRP and ozone gas injections when compared to the pain experienced before the injection. Similarly, a significant improvement in symptoms was observed one month after each injection, compared to the symptoms reported prior to the treatment (P<0.0001). Moreover, patients exhibited enhanced mobility and reduced pain levels one month after both injections, indicating substantial improvement (P<0.0001). Notably, patients' daily activity significantly improved one month after each injection, compared to their activity level prior to the treatment (P<0.0001). The ICOAP test results indicated a significant reduction in pain experienced by patients after each injection phase (P<0.0001). Additionally, the TUG test outcomes demonstrated that PRP and ozone gas injection had a significant positive impact on mobility and gait in individuals with osteoarthritis (P<0.0001).

Table 3: KOOS, ICOAP, And TUG Tests result before PRP 448 and ozone gas injection, one month after the first PRP and ozone gas injection and one month after the second PRP and ozone gas injection. KOOS: Knee Injury and Osteoarthritis Outcome Scores, ICOAP: The Intermittent and Constant Pain Score, TUG: Timed Up and Go Test.

	Variables	Before PRP and ozone gas Injection (±SD)	1 Month after the first PRP and ozone gas Injection (±SD)	1 Month after the second PRP and ozone gas Injection (±SD)	p- value
KOOS	Pain	76.54±7.51	46.81±3.57	30.18 ±1.88	0.0001
	Symptoms	61.8±8.22	27.8± 1.30	26 ±1.58	0.0001
	Function in daily living	69±1.41	27± 1.41	23 ±1.41	0.0001
	Function in Sport and Recreation (Sport/Rec)	74.77±10.54	47± 3.47	31.33± 1.58	0.0001
	knee-related Quality of Life (QOL)	24.88±2.30	45.73± 3	53.42 ±4.10	0.0001
ICOAP		77.26 ±1.86	59.11± 3.17	48.05 ±2.35	0.0001
TUG		29.14 ±3.48	18.89 ±2.65	17.25± 2.12	0.0001

Injection of PRP/Ozone Gas Induced the Expression of Responsible Genes for OA Treatment

Real-Time PCR was utilized to determine the expression of responsible genes in the cartilage Synthesis, before PRP & ozone gas injection and after the first and second injections. The expressions of IGF-1, HIF-1α and BMP2 in relation to GAPDH are revealed in Figure 1. The results revealed that the expression of IGF-1, HIF-1α, and BMP2 genes rise significantly after the first and second injections compared to gene expression before the injection in patients with knee osteoarthritis. Although the expression of all three genes lowered inconsiderably one month after the second injection compared to one month after the first injection, this reduction was not significant, and the expression of these genes was significantly higher than before the injection (Figure 1). Due to the high overexpression of the IGF-1 gene after co-injection than before injection, we analyzed the level of IGF-1 in the serum. The results indicated the level of IGF-1 expression significantly increased one month after the first PRP/ozone gas co-injection rather that before injection in patients with OA. However, one month after re-injection of PRP/ozone gas the serum level of IGF-1 decreased again (Figure 2).

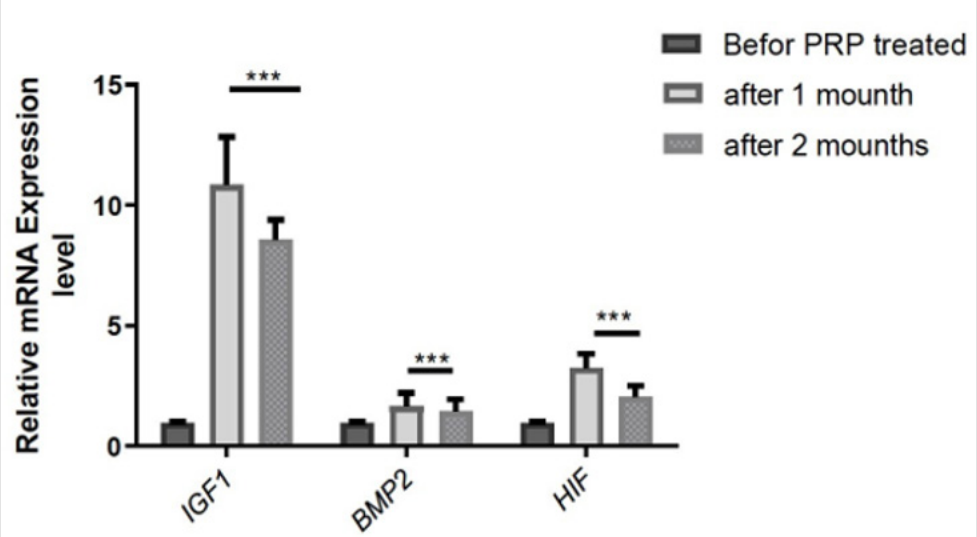

Figure 1: The expression of IGF-1, BMP2, and HIF-1α genes involved in cartilage stiffness and repair of knee osteoarthritis before injection, one month after the first injection, and one month after the second injection. IGF1: Insulin-like growth factor 1, BMP2: Bone morphogenetic protein 2, HIF-1α: Hypoxia-inducible factor 1-alpha.

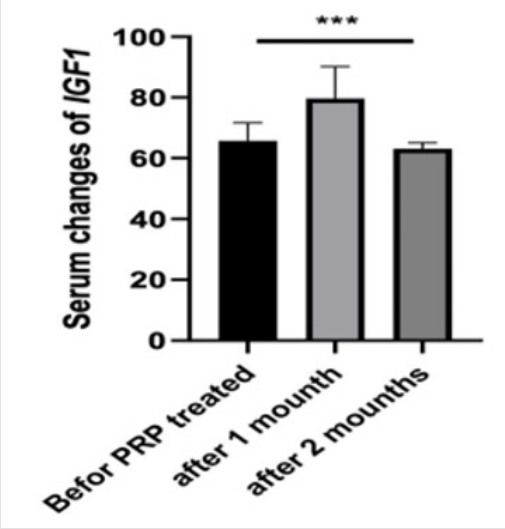

Figure 2: IGF-1 levels in the serum. IGF1: Insulin-like growth factor 1.

Discussion

Osteoarthritis (OA) is a joint condition characterized by the degeneration of joint tissues, leading to pain, stiffness, and impaired physical function [11]. This study aimed to assess the impact of co-injection of autologous PRP obtained from patients with knee OA, followed by ozone gas injection, on gene expression related to cartilage formation. The evaluation involved measurements taken before injection, one month after the first injection, and one month after the second injection. Additionally, the therapeutic effects of the co-injection were evaluated using internationally recognized KOOS, ICOAP questionnaires, and TUG tests. The study results revealed that the co-injection of PRP and ozone significantly improved mobility, gait, and reduced pain in patients with OA. In line with our findings, Sanchez, et al. conducted a similar study, injecting PRP and low molecular weight hyaluronic acid three times at weekly intervals, which resulted in better OARSI scores for the PRP and ozone gas group 24 weeks after injection [18]. Additionally, Pat and colleagues compared the therapeutic efficiency of normal saline with PRP injection, and they reported a significant improvement in WOMAC test scores six months after PRP injection compared to the normal saline group [19]. Feng, et al. also validated the effectiveness of ozone therapy, combined with anti-inflammatory drugs, in reducing osteoarthritis pain and complications compared to treatment with medication alone [20]. Similarly, Ghasroldasht, et al. demonstrated that intra-articular PRP injections alleviated pain, reduced stiffness, and improved the quality of life in knee osteoarthritis patients through the promotion of IGF-1 expression [21].

PRP and ozone gas have emerged as suitable treatment materials for osteoarthritis due to their ability to counteract pro-inflammatory mediators and catabolic enzymes. Intra-articular injection of PRP and ozone gas has been utilized to treat various musculoskeletal disorders [22]. Despite the increasing demand for PRP and ozone gas injections to treat osteoarthritis, the underlying mechanism of their action remains undiscovered [23]. It is hypothesized that cartilage destruction leads to inflammation, and inflammatory components, such as interleukins, play an essential role in the development and progression of osteoarthritis. Interleukins act as catabolic cytokines in the knee joints of osteoarthritis patients, enhancing metalloproteinase and elastase activity in synovial cells and chondrocytes [24]. Another contributing factor to osteoarthritis is epigenetic changes in chondrocytes, leading to genetic disorders that enhance the expression of cartilage-destroying protease genes and inflammatory activating factors [25]. Enzymes responsible for breaking down the joint extracellular matrix may further exacerbate osteoarthritis and hinder tissue regeneration during cartilage repair. The co-injection of PRP and ozone gas is believed to influence molecular pathways, ultimately impacting inflammatory and catabolic conditions in osteoarthritis joints, which contributes to its therapeutic effects [26].

Numerous studies have investigated the use of PRP in the treatment of knee osteoarthritis [11]. However, the number of PRP injections and the intervals between injections have been subject to variation across different studies, leading to a lack of consensus on the standard approach. For instance, some studies employed three PRP injections at three-week intervals [17], while others suggested two, three, or four injections, making the selection of the optimal number and interval of injections highly complex [6]. The interval between injections has also varied, ranging from one to four weeks [19]. Raeissadat, et al. found that two PRP injections at regular intervals were ore effective and stable in treating OA [27]. Despite this variation, there

is no evidence indicating that the number of injections and intervals significantly impact the study outcomes. In light of this, and based on previous studies with plasma-based products and to optimize treatment costs, we opted for two injections at one-month intervals.

Previous research has shown that the expression of IGF-1, HIF-1α, and BMP2 genes increased after the first and second injections in individuals with knee osteoarthritis, compared to gene expression before the injections [21]. Although the expression of these genes slightly decreased one month after the second injection compared to one month after the first injection, it remained higher than the expression observed before the injections. Real-time PCR analysis by Yuduh, et al. demonstrated higher HIF-1α transcription in degraded cartilage compared to healthy cartilage, confirming its presence and influence on factors crucial for cartilage formation in individuals with osteoarthritis [28]. Additionally, insulin-like growth factor (IGF-1) plays a pivotal role in regulating cartilage matrix biosynthesis, being crucial in prenatal development and body growth. IGF-1 also contributes to enhancing the innate and acquired immune system through its effect on lymphocyte proliferation, increased Tumor Necrosis Factor (TNFα) production, and enhanced NK-cell activity [29]. Moreover, BMP-2, produced at the injury site, plays an important role in protecting cartilage from destruction and stimulating regeneration during inflammation. BMPs play a significant role in cartilage regeneration by activating various intracellular signaling pathways upon binding to different receptor compounds, with their impact varying across different cell types [30]. The activity of BMPs is regulated by several inhibitors at different levels, including extracellular and intracellular inhibition [31]. Excessive BMP increase can promote chondrocyte differentiation, while inhibiting BMP activity can reduce proteoglycan levels, thus affecting the capacity for intrinsic cartilage repair during damage [30]. Hypoxic stress and catabolic joint chondrocytes induce the transcription of HIF-1α, which in turn, regulates cellular adaptation in a low-oxygen environment. As a key molecule in adapting cellular and tissue responses to low oxygen levels, HIF-1α increases the expression of erythropoietin, glucose transporters, glycolytic enzymes, pre-angiogenic factors, and other important molecules involved in apoptosis and cell proliferation [15].

IGF-1, a polypeptide containing 70 amino acids and sharing up to 50% similarity with insulin, plays a crucial role in regulating cartilage matrix biosynthesis. Studies have shown that higher IGF-1 expression leads to increased cell retention during the first week after cartilage damage, significantly enhancing collagen expression in the adjacent cartilage layer. While IGF-1 does not directly affect SOX9 expression, it exerts its effects by modulating the biological activity of surviving cells during the early stages of cartilage destruction, rather than generating new chondrocytes through SOX9 [32]. The study results revealed a significant increase in the expression of IGF-1, HIF-1α, and BMP2 genes after the first and second injections compared to before the injections in patients with knee osteoarthritis. Additionally, serum IGF-1 levels were significantly increased one month after the first PRP/ozone co-injection compared to pre-injection levels in patients with OA.

Conclusion

The results described in this manuscript indicated that co-injection of PRP and ozone gas causes a significant decrease in pain, stiffness, and a great increase in knee function efficiency one month after the first injection and one month after the second injection in patients with knee osteoarthritis through the upregulation of IGF-1, HIF-1α and BMP2 genes. Although the level of upregulation of gene expression decreases after the second injection than the first injection, a comparison of KOOS, ICOAP questionaries, and TUG test between the first/second injection and before injection indicates that the therapeutic effect of gene expression increases maintains for the at least two months. However, determining the mechanism of action of the co-injection of PRP/Ozone on cartilage regeneration needs further research.

Conflict of Interests

The authors declare that there is no conflict of interests.

Author Contributions

MMG designed the experiments. AM participated in the disease diagnosis and injections. FD and FA participated in the sample collections and carried out the experiments. FD and MMG participated in the data analysis and drafted the manuscript. All authors read and approved the final manuscript.

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