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Original Article

Anaesthesia Section

Therapeutic Efficacy of Ozone Injection into the Knee for the Osteoarthritis Patient along with Oral Celecoxib and Glucosamine

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ABSTRACT

Introduction: Suffering from osteoarthritis is prevalent among elderly patients so the use of intra-articular injection of medical ozone may well be the effective way to relieve their pain.

Aim: To evaluate the effect of intra-articular injection of medical ozone given into the knee of the osteoarthritis patients, and to compare it with taking celecoxib and glucosamine orally.

Materials and Methods: In the present study, 76 patients suffering from osteoarthritis were randomly assigned into two groups. In the ozone group, 20 ml ozone-oxygen mixture gas concentration of 20 μg/ml was injected into knee articular cavity and each patient took oral celecoxib and glucosamine hydrochloride. Patients in control group only took the celecoxib and glucosamine hydrochloride orally.

Pain score and Lysholm knee score were measured prior to the injection (pretreatment) and at one, three, six weeks after the beginning of the treatment (posttreatment).

Results: After the treatment, the pain intensity and function significantly improved in the two groups compared with the pretreatment ($p<0.05$). In the ozone group, three weeks after intervention, the pain score improved significantly when compared with the control group ($p<0.05$).

After the treatment, the lysholm scores increased significantly ($p<0.05$), but in the ozone group, it improved faster.

Conclusion: Intra-articular injection of ozone plus oral celecoxib and glucosamine could significantly decrease pain intensity in patients with mild to moderate Knee Osteoarthritis (KOA), and improve their functional status early than oral celecoxib and glucosamine only.

Keywords: Intra-articular, Medicine, Pain

INTRODUCTION

KOA is a common disabling and degenerative disease leading to painful joints, articular stiffness, and decreased function [1]. The accurate mechanism of pain and disability has not been well identified. Felson pointed out that the origin of pain was attributed to various body parts such as the articular capsule, ligaments, synovium bone, lateral part of the meniscus, extra-articular ligaments and tendons [2]. Heijink A et al., examined the available basic science, preclinical and clinical evidence regarding several unfavorable biomechanical conditions about the knee: malalignment, loss of meniscal tissue, cartilage defects and joint instability [3]. Above all, the chronic inflammation in the tissue around the knee could be the cause of knee pain for the patient with KOA. For the past few years, the therapy of several musculoskeletal disorders with ozone has raised concern gradually. It has an antinociceptive effect with several mechanisms. Ozone-selectively activates a subset of C-fibers by directly stimulating Transient Receptor Potential A1 (TRPA1) which is associated with the factors of inflammation [4]. After ozone exposure, suppression of Nerve Growth Factor (NGF) might reduce SP response and suppression of IL-1β may attenuate both NGF and Substance-P (SP) release. These inflammatory factors made contribution to the knee pain [5]. The elucidation of the mechanisms of action of ozone may encourage clinical scientists to evaluate ozone therapy in vascular diseases, such as peripheral arterial diseases and disk herniation [6,7]. Perhaps the mechanism of the ozone of relieving the pain and improving the knee function is through inhibiting the inflammation reaction in the KOA directly. Actually, the ozone intra-articular injection had been used to relieve the pain caused by KOA [8]. Since, the sample size in the research was small, the effect could not last long.

The experiment by Lin Q et al., suggests that ozone concentrations from 10 μg/ml to 80 μg/ml injected around peripheral nerve will not cause serious squeal or serious damage to the structure and function of peripheral nerve [9].

Pharmacokinetic studies have shown that glucosamine is easily absorbed, and has no major adverse events [10]. In the clinical practice guidelines, glucosamine sulfate 1500 mg once daily is therefore recommended. It could reach higher plasma and synovial fluid concentrations that are above the threshold for a pharmacologically relevant effect [11].

Celecoxib was shown to affect all structures involved in KOA pathogenesis: cartilage, bone, and synovium. Celecoxib modulates COX-2-independent signal transduction pathways [12]. Celecoxib had efficacy in reducing pain, stiffness, functional limitation and joint swelling after six months in patients with painful KOA, with a good safety profile [13]. By delaying cartilage degeneration and impairing the function of inflammatory mediators, celecoxib might repair and protect early osteoarthritis cartilage [14]. Diacerein and glucosamine are equally efficacious for symptom relief in KOA, but diacerein which is not a selective non-steroidal anti-inflammatory drug has more side effects [15]. So, the medicine we choose for the present study was celecoxib, a selective COX-2 inhibitors which could had less side effects.

Ozone (O_3) gas was discovered in the mid-nineteenth century. It is a molecule consisting of three atoms of oxygen in a dynamically unstable structure. Ozone was known for therapeutic effects because of the anti-inflammation effect, it had been demonstrated to work on cellular metabolism by accelerating the use of glucose, improving protein metabolism, converting unsaturated fatty acids into hydrosoluble compounds, and increasing erythrocyte activity [16]. Based on the anti-inflammation feature of the ozone, we studied the effects of ozone on the KOA through randomized intra-articular injection into the knee of patients with KOA.

MATERIALS AND METHODS

To ensure the comparison between the two groups is valid, A power analysis was performed ($\alpha=0.05$, $\beta=0.8$), indicating that at

least 61 patients should be recruited for the study. In the present randomized clinical trial, 76 patients with mild to moderate KOA (Kellgren-Lawrence Grade I and II), aged 50-78 years, from January 2015 to November 2015, were enrolled. All patients gave their written informed consent before the study. The trial was performed in compliance with the Helsinki Declaration and ICH-GCP. Ethical approval was obtained from the Ethics Committee of Xuzhou First People's Hospital.

The diagnosis of KOA hook on to clinical examination and antero-posterior standing radiography according to the diagnostic criteria made by the Chinese medical association of rheumatology [17]. The exclusion criteria included several underlying diseases such as diabetes, a candidate for knee joint replacement (Kellgren-Lawrence Grade III and IV), anticoagulant use (stroke), and previous intra-articular injection within the last year, infectious or inflammatory arthritis, daily use of opioid or nonopioid analgesic drugs.

Patients were randomly assigned into two groups according to the tables of random numbers: the ozone group and the control group. In the ozone group, before the intra-articular injection, 1% lidocaine was injected as a local anesthetic to the skin and underlying tissues at the inferomedial knee. A 20 ml ozone-oxygen mixture (the concentration of ozone was 20 μg/ml) was injected intra-articularly through the inferomedial approach and this therapy lasted for six weeks, twice a week for each patient. In addition to the injection, oral celecoxib and glucosamine hydrochloride had been recommended to be tried at a dose of 200 mg once a day (morning) and 240 mg three times (morning, noon and night) a day respectively for the pain relieve for six week. In the control group, the medicines were administrated orally for six week without the intra-articular injection.

The pain intensity was determined by using VAS. In this scale, 0 indicated no pain and 10 indicated the worst pain. Moreover, Lysholm knee score [18] standard was used to assess the functional ability of the knee, which varies between 0 and 100 points and in which lower scores indicate weaker knee status. All patients completed the Lysholm assessment. Pain intensity and functional ability were measured prior to the injection (pretreatment) and at one, three, six weeks after the beginning of the treatment.

STATISTICAL ANALYSIS

Statistical analysis was performed by using SAS statistical software Version.9.2. Numerical variables were expressed as mean±standard deviation. Mean tests were compared using independent t-test. The gender numbers of patients in the two groups were analysed by Chi-square test. The pain intensity score and the Lysholm assessment between the pretreatment and post-treatment were analysed by the ANOVA procedure for quantitative data. The level of significance was α=0.05.

RESULTS

The demographic characteristics of the patients were presented in [Table/Fig-1], which showed no statistically significant difference between the two groups. In the ozone group, 35 patients (15 males, 20 females) with the mean age of 64.57±6.74 years suffered the KOA for an average of 60.03±27.58 months. In the control group, 41 patients (18 males, 23 females) with the mean age of 62.29±7.55 years suffered the KOA for an average of 55.90±24.56 months.

Groups	Sex(n)		Age (years)	Course of KOA, (months)
The ozone group (n=35)	Male	15	64.57±6.74	60.03±27.58
	Female	20		
The control group (n=41)	Male	18	62.29±7.55	55.90±24.56
	Female	23		
p-value		0.9270	0.1727	0.4925

[Table/Fig-1]: Comparison of demographic findings between the two groups. Independent t-test and Chi-square test was used. Results represented as mean±SD and .*p<0.05 statistically significant.

Groups	Pretreatment	one week post-treatment	three week post-treatment	six week post-treatment	intragroup p-value
The ozone group (n=35)	7.89±1.08	5.25±1.74	3.97±1.15	3.46±1.04	<0.001
The control group (n=41)	8.34±1.04	5.83±2.07	4.95±1.56	3.83±1.26	<0.001
Intergroup p-value	0.0651	0.2008	0.0030	0.1694	

[Table/Fig-2]: Comparison of the VAS scores in each Group and between the two Groups. ANOVA test and Independent t-test was used. Results represented as mean±SD.
p<0.05 statistically significant.

Groups	Pretreatment	one week Post-treatment	three week Post-treatment	six week Post-treatment	Intragroup p-value
The ozone group (n=35)	47.97±13.98	72.83±14.16	82.51±9.35	88.66±9.07	<0.001
The control group (n=41)	45.73±16.12	55.32±13.09	75.37±14.84	85.41±9.92	<0.001
Intergroup p-value	0.5233	<0.001	0.0161	0.1438	

[Table/Fig-3]: Comparison of the Lysholm scores in each Group and between the two Groups.
ANOVA test and Independent t-test was used. Results represented as mean±SD.
p<0.05 statistically significant.

In addition, before the treatment, the pain intensity and Lysholm scores were the same between the two groups (p<0.05) [Table/Fig-2,3]. After the treatment, the pain intensity and Lysholm scores improved in the two groups compared with the pretreatment (p<0.001) [Table/Fig-2,3].

In the ozone group, the mean±Standard Deviation (SD) of pain score before intervention was 7.89±1.08. Three weeks after intervention, it was reduced to 3.97±1.15 (p<0.001) and improved significantly compared with the control group (4.95±1.56) (p<0.05) [Table/Fig-2].

The Lysholm scores before the intervention in the ozone group was 47.97±13.98 and showed significant increase at one, three, six weeks after the treatment (p<0.001) [Table/Fig-3]. But at one, three weeks after the treatment, the Lysholm scores in the ozone group increased significantly compared with the control group (p<0.05) [Table/Fig-3]. However, there was no statistically significant difference in pain and Lysholm scores at the last visit between the two groups (p<0.05) [Table/Fig-2,3].

DISCUSSION

The versatility of ozone therapy is due to the cascade of ozone-derived compounds acting on several targets resulting in a pathological state. Judicious application of ozone in chronic diseases has yielded striking results [19]. The present study showed that the injection of 20 μg/mL of ozone-oxygen mixture plus oral celecoxib and glucosamine hydrochloride can be effectively used in the non-operative management of patients with KOA. The pain scores and Lysholm scores in the ozone group patient improved faster than the control group.

Injection with ozone to treat the KOA was used widely. It probably had the same therapeutic effect as other methods. Injection with dextrose and with ozone repeated three times with 10-day intervals result in the same pain relief or functional improvement in patients with mild to moderate KOA [20].

Different from what they had done is that our experiment let the patients take celecoxib with glucosamine orally, and the course

of treatment spends more time treating osteoarthritis. The whole process lasted for six weeks. We found that injection with ozone plus oral celecoxib and glucosamine hydrochloride operated quickly. For most patients, oral medication is more likely to be accepted than taking dextrose injection.

Another experiment validates the pain killing effect of ozone-oxygen injection on osteoarthritis of the joints [21]. We added the celecoxib and glucosamine orally in the treatment, but we could not found better effect between the two groups.

The patients affected by osteoarthritis of the knee were intra-articularly injected with hyaluronic acid, oxygen ozone, and the combination of both. Analysis showed a significant effect on the groups for pain, symptoms, activities of daily living and quality of life. The combination of O_2O_3 and hyaluronic acid treatment led to a significantly better outcome compared to hyaluronic acid and O_2O_3 given separately to patients [22]. In the treatment of mild-moderate KOA, platelet-rich plasma was more successful than hyaluronic acid and ozone injections [23]. From the above, the material which was injected in the knee articular cavity was ozone, hyaluronic acid, platelet-rich plasma, but the intra-articular injection with the ozone plus oral celecoxib and glucosamine was studied in our experiment.

At the end of the six week, the pain score and the function of the knee between the two groups had no significant difference. But the function of the ozone therapy plus oral celecoxib and glucosamine hydrochloride improved more quickly. Perhaps the inflammation in the knee was inhibited by the injection of the ozone into the knee and the oral anti-inflammation medicines which have different mechanism of action. The effect of ozone injection plus oral celecoxib and glucosamine hydrochloride could not last longer perhaps attributed to short period of observation.

There were many other methods for the treatment of KOA considering clinical presentation underlying pathophysiology, stage of disease. The combination of pharmacological and non-pharmacological treatments is most effective in treating KOA [24]. Identification of patient profiles may lead to more personalized healthcare and understanding of patient data could help give more targeted care for osteoarthritis [25].

LIMITATION

The small sample size also limits the generalization of the findings. However, further research is needed to examine the effect of the ozone injection into the knee.

CONCLUSION

Intra-articular injection of ozone plus oral celecoxib and glucosamine could significantly decrease pain in patients with mild to moderate KOA, and improve their functional status early than oral celecoxib and glucosamine only.

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