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Research Article

Verification of the Effect of Oral intake of MgS-Containing E-type Chondroitin (GAGs®) in Alleviating Symptoms of Osteoarthritis and Lumbar Spinal Stenosis Pain

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Abstract

With the aging of society, musculoskeletal diseases, mainly osteoarthritis, are currently on the rise. The increase in musculoskeletal diseases may lead to frailty and aging-related diseases due to the inability to exercise. A particular problem is that the "pain" caused by osteoarthritis of the knee and lumbar spinal canal stenosis reduces movement. This can lead to a significant decline in movement and behavior, which limits daily life, resulting in a decline in QOL. At the same time, the decline in QOL can lead to a decline in healthy life expectancy, which can result in a difference from the average life expectancy. Therefore, in this study, a combination of E-type chondroitin sulfate and magnesium disalicylate, a natural ingredient extracted from natural kelp (brown algae), was used to have patients with osteoarthritis and lumbar spinal canal stenosis take the drug for 8 weeks, and statistically significant improvement in pain was confirmed. Therefore, it can be said that sufficient effects were obtained in terms of pain relief. In this study, the drug was used on orthopedic patients, mainly with osteoarthritis, but it is also expected to be sufficient for pain relief after surgical procedures. We report this test substance because we believe that by using it as a type of complementary and alternative therapy, it can be used as a substance that can be expected to have a pain-relieving effect without experiencing the side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

Keywords: COX-2 inhibition; Healthy life expectancy; Musculoskeletal diseases; Pain relief; Surgical procedures

Introduction

As the population ages, the prevention and treatment of musculoskeletal diseases, such as osteoarthritis and lumbar spinal canal stenosis, is becoming increasingly important. These musculoskeletal diseases are the most common joint diseases in the elderly, and are characterized by pathological conditions such as deterioration, deformation, and inflammation of the bones and cartilage of the joints, causing symptoms such as pain and numbness. The pain and numbness limit walking, exercise, and daily activities, significantly reducing the patient's quality of life, and indirectly contributing to various lifestyle-related diseases such as dementia, leading to a shortened healthy lifespan [1]. Osteoarthritis was initially thought to be a cartilage wear disease, but in recent years it has been understood as an inflammatory disease accompanied by inflammatory mediators released from cartilage, bone, and synovium [2,3]. Many studies have demonstrated the beneficial effects of chondroitin sulfate as a treatment for osteoarthritis for many years [4-8].

Chondroitin is a major component of cartilage and has excellent water retention and elasticity, as well as anti-inflammatory effects, osteocalcin production, BMP (bone morphogenetic protein) production, and osteoblast proliferation. In other words, it is thought that the mechanisms that maintain the physical structure of articular cartilage and suppress inflammation that causes the disease to progress are working properly. However, some studies have stated that the effectiveness cannot be proven [9]. One factor that may explain the lack of therapeutic effect is that the quality (content, impurity contamination, origin) of chondroitin sulfate products on the market is not regulated, and the data may include quality variations and low-quality products [10]. In particular, the differences in quality and therapeutic effects due to the origin of chondroitin sulfate are noteworthy points. Chondroitin sulfate is classified into types A to E according to its origin and structure. Types A and C are generally distributed as health foods, but it is known that type E chondroitin sulfate is the most effective in suppressing inflammation, producing osteocalcin, producing BMP (bone morphogenetic protein), and promoting osteoblast proliferation [11,12].

MgS-containing E-type chondroitin sulfate (product name: GAGs) is a mixture of high-purity E-type chondroitin sulfate (60% all types, 40% E-type chondroitin sulfate) and magnesium disalicylate (Magdisalicylate®), a natural ingredient extracted from natural kelp (brown algae). A pilot study showed that it has a pain-relieving effect on osteoarthritis of the knee. Magnesium disalicylate (Magdisalicylate®) has a salicylic acid skeleton-like structure and is an ingredient with selective COX2 inhibitory properties. It is speculated that the effectiveness against osteoarthritis is due to the synergistic effects of the respective actions of E-type chondroitin sulfate and Magdisalicylate® [13]. Lumbar spinal stenosis is thought to be a pathology similar to osteoarthritis in that it involves bone and cartilage degeneration and inflammation [14]. Therefore, this study was planned with the aim of elucidating the effect of MgS-containing E-type chondroitin sulfate in alleviating the symptoms of pain and numbness in osteoarthritis and lumbar spinal stenosis, and contributing to the development of new treatment strategies.

Material and Methods

Fifteen subjects were asked to take MgS-containing E-type chondroitin sulfate (GAGs®), provided free of charge by HYDROX Inc., one packet (total 1g) per day before going to bed for a total of 56 days (8 weeks). All subjects were interviewed using the Numerical Rating Scale (NRS) before the start of intake, 14 days after intake, 42 days after intake (one month was left between intakes to consider the burden on the subjects), and for the 56 days. This NRS is a subjective evaluation on a 10-point scale, with 10 being the initial pain felt, and is an index to check how much pain has been alleviated from that point. The lower the number, the more the person's pain has been alleviated. In addition, the period was set to 56 days to avoid pain reduction due to the placebo effect. Each was quantified, and statistical processing was performed using IBM SPSS Statistics (Ver.25) with a significance level of $p<0.05$. Statistical processing was performed using the NRS, and all values before intake were 10, so normal distribution could not be confirmed. Furthermore, in order to perform the test using the pre-intake group as the control group, statistical analysis was performed using the Wilcoxon signed rank test after the Friedman test. This study was also approved by the International Society of Geriatrics and Gerontology Ethics Committee. (Ethics review number: ISGN_NI10032024)

Selection of Study Subjects

Eligibility Criteria

- Those diagnosed with osteoarthritis or lumbar spinal canal stenosis
- Those who fully understand the study plan and are able to give consent

Exclusion Criteria

- Those with obvious underlying diseases and unstable medical conditions
- Others who the clinical research physician judges to be inappropriate

Discontinuation Criteria

- If an allergy occurs to the study material
- If consent is withdrawn
- Others who the clinical research director judges to be appropriate for discontinuation due to health hazards or ethical considerations

Results

Changes Over Time in Pain Relief

Table 1 shows the pain relief for each subject. Table 2 shows the average and SD. Figure 1 also shows the changes over time in intake.

Subject No.	Affected area	Age	Before intervention	2weeks After	6weeks After	8weeks After	Improved results after 8 weeks
1	Lower back	50s male	10	8	8	8	8
2	Neck	50s female	10	7	7	6	6
3	Hip joint	60s male	10	7	6	5	5
4	Knee	80s female	10	10	Cancelled	Cancelled	10
5	Knee	70s female	10	0	0	0	0
6	Shoulder	50s female	10	8	7	3	3
7	Knee	80s male	10	5	5	5	5
8	Lower back	70s male	10	5	5	Unanswered	5
9	Knee (OP eligible)	80s female	10	8	Unanswered	1	1
10	Knee	70s female	10	0	0	0	0
11	Knee	90s female	10	9	9	9	9
12	Lower back	80s female	10	6	2	0	0
13	Knee	70s male	10	Unanswered	Unanswered	1	1
14	Knee	70s female	10	7	7	7	7
15	Lower back	70s male	10	9	8	7	7

Table 1: Subjective effects over time in improving pain.

	Before intervention	4weeks After	6weeks After	8weeks After
Average	10	6.36	5.33	4
SD	0	3.05	3.08	3.32

Table 2: Mean and SD for each item.

As shown above, looking at the average values, it can be seen that the overall pain relief decreased with continued intake. Table 3 also shows the rankings using SPSS.

	Rank
Before intervention	4
2weeks After	2.41
6weeks After	2.05
8weeks After	1.55

Table 3: Ranking of changes over time.

As shown above, the values decreased over time, and there was a tendency for pain to improve.Furthermore, when shown in a graph, it can be seen that the pain was further reduced, as shown below (Figure 1).

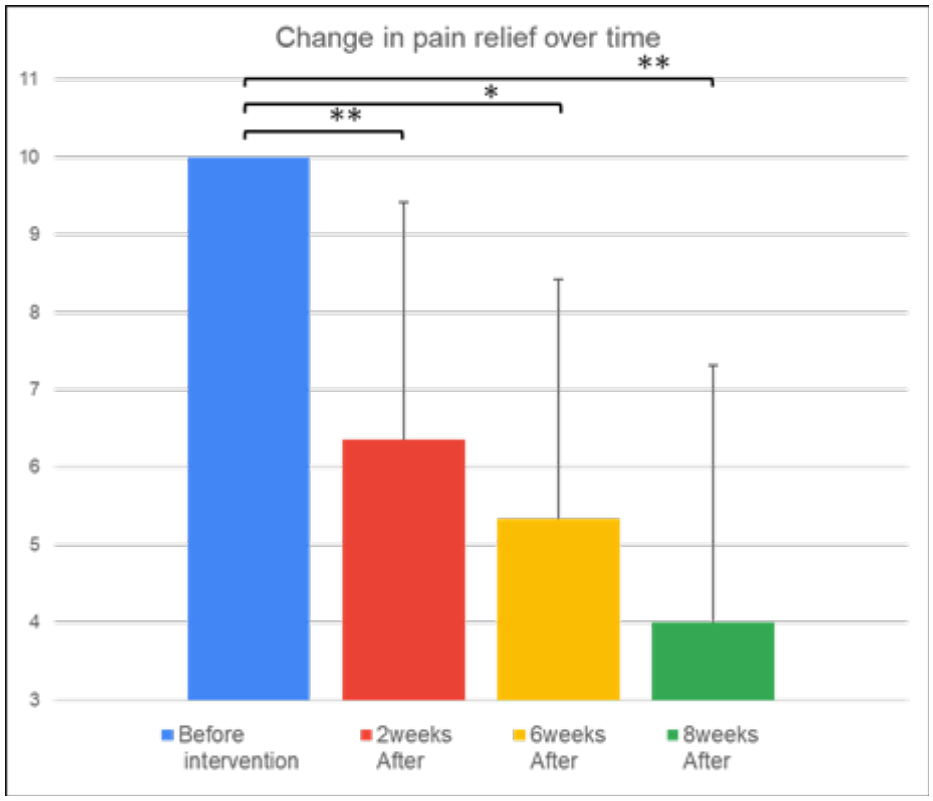

Figure 1: Changes in pain relief over time using Wilcoxon signed rank test ($P < 0.05$).

Final results in pain relief

In this study, we looked at changes over time, taking the average values after 2 to 8 weeks, and comparing them to before intake to examine the pain relief. The changes are shown in Table 4 and Figure 2 below.

	Before intervention	Improved results after 8 weeks
Average	10	4.47
SD	0	3.44

Table 4: Average pain relief final result.

When the above was statistically analyzed using the Student-t test, the result was P<0.05, confirming a significant difference.

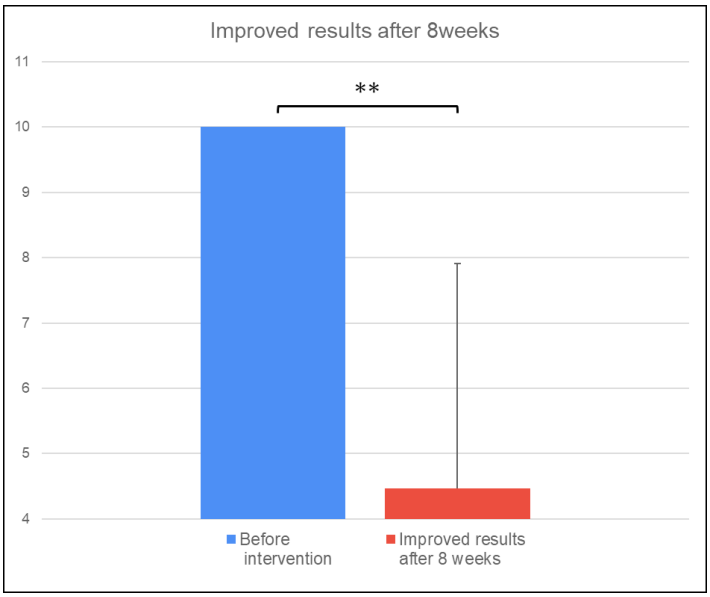

Figure 2: Difference in the average value between before and after 8 weeks of intake in student-t test.

As shown in Figure 1 and Figure 2, the reduction in pain was confirmed over time and in the end. It was suggested that the use of this test substance reduces pain, suggesting that it is effective against pain after surgical procedures and pain caused by orthopedic diseases.

Discussin

With the aging of society, locomotive syndromes, mainly osteoarthritis and osteoporosis, are becoming a problem [15]. Osteoarthritis and lumbar spinal stenosis cause pain, which can significantly reduce quality of life and lead to a decrease in healthy life expectancy [16]. Currently, the gap between average life expectancy and healthy life expectancy is a major problem, and there are concerns about the increase in medical expenses [17]. It is predicted that the issue of how to live a healthy life will be a future issue. In such a situation, osteoarthritis and lumbar spinal stenosis are caused in proportion to aging, and a causal relationship with obesity due to lifestyle habits has been pointed out [18]. Therefore, it is urgent to improve lifestyle habits, but it is predicted that it will be difficult to improve due to pain before changing lifestyle habits. In order to correct lifestyle habits, a balanced diet [19], sleep efficiency [20], and maintaining muscle strength through moderate exercise [21] are important, but it is thought that moderate exercise is difficult in such a situation. Currently, nonsteroidal anti-inflammatory drugs are often used to treat these pains [22], but since they do not always reduce the pain in the affected area, it is necessary to treat the affected area itself. However, osteoarthritis was previously thought to be a disease caused by wear of the cartilage, but recent reports have shown that it is an inflammatory disease that involves inflammatory mediators released from cartilage, bone, and synovium [23].

One treatment method is to supplement with chondroitin sulfate [24]. It is said that chondroitin sulfate can delay the onset of osteoarthritis of the knee, regenerate cartilage, and alleviate pain [25]. There are three types of chondroitin sulfate: A type, C type, and E type, which was used in this study. E type chondroitin sulfate produces osteocalcin, a hormone in the blood that is essential for body formation [26]. Osteocalcin is also said to increase insulin production and sensitivity by increasing the proliferation of islet β cells [27]. Osteocalcin has also been shown to promote the expression of adiponectin [28]. Adiponectin is a hormone secreted from fat cells, and is known to be a beneficial hormone because it is said to promote glucose uptake without the involvement of insulin receptors [29]. It is also known to promote glucose and lipid metabolism [30]. It is also known to increase insulin receptor sensitivity by reducing intracellular fatty acids [31]. It is also known to be known to be a beneficial hormone because it is said to increase insulin sensitivity, inhibit arteriosclerosis, and have anti-inflammatory effects by activating AMPK [32]. In addition, this test substance contains high-purity E-type chondroitin and magnesium disalicylate, which can selectively inhibit COX2 [33]. The test substance used in this combination is also a patented ingredient.

COX2 stands for cyclooxygenase 2, an enzyme encoded by the PTGS2 gene in humans [34]. COX2 is one of two types of cyclooxygenases present in humans. The other is COX1, an enzyme that is widely distributed and expressed in tissues throughout the body [35]. COX1 activity is hardly suppressed by steroids. COX1 exists in cells at a constant level and can be induced by certain stimuli [36]. On the other hand, COX2 is constitutively expressed in the brain, kidney, thymus, etc., but is normally expressed at low levels in other tissues, and its expression is induced in inflamed tissues [37]. Unlike COX1, COX2 is mainly present in the nuclear membrane and its activity is strongly inhibited by steroids [38]. COX2 is involved in the conversion of arachidonic acid to prostaglandin H2 and is expressed during inflammation

[39]. It is also known that the expression of COX2 is induced by stimuli such as cytokines and growth factors [40]. During inflammation, the production of PGE2 and PGI2, etc., mediated by COX-2, is increased [41]. PGE2 is involved in increased vascular permeability, vasodilation, and pain [42], while PGI2 is involved in vasodilation and pain, and promotes the inflammatory response [43]. Therefore, in order to have an anti-inflammatory effect, it is necessary to inhibit COX-2. Cyclooxygenase inhibitors (NSAIDs) are generally available as medicines, but because they inhibit both COX1 and COX2, they can cause gastrointestinal and renal disorders as side effects [44]. Therefore, this test substance is thought to be able to reduce the occurrence of gastrointestinal and renal disorders by selectively inhibiting only COX2. Therefore, it is possible that it can be used for patients with gastrointestinal diseases. In this study, we used a substance that combines E-type chondroitin sulfate and magnesium disalicylate, and the following hypotheses can be considered.

- Suppression of inflammation through COX2 inhibition
- Relief of pain by inhibiting the arachidonic acid cascade
- Bone remodeling and cartilage tissue regeneration
- Prevention of various lifestyle-related diseases through adiponectin production

It is thought that this test substance can be approached from multiple angles. Although this test substance is classified as a health food, the data in this study suggest that it may be comparable to a medicine. In the future, we hope to further investigate this mechanism and find applications in extending healthy lifespan, increasing quality of life, and improving ADL, as well as for use as a substance to relieve pain after surgical procedures.

Conclusion

In this study, we used E-type chondroitin sulfate with high purity (60% all types of chondroitin sulfate, 40% E-type chondroitin sulfate) and MgS-containing E-type chondroitin sulfate (GAGs®), which contains magnesium disalicylate (magdisalicylate®), a natural ingredient extracted from natural kelp (brown algae), and found that it had a pain-relieving effect over time. Steroids and nonsteroidal anti-inflammatory drugs are generally used in the medical field to treat pain, so the fact that a health food has been shown to relieve pain in this way is of great significance. Although we are not denying this, steroids and nonsteroidal anti-inflammatory drugs often cause some kind of adverse event. However, no adverse events were observed with this test substance, even though it was administered continuously for 8 weeks. For this reason, it is thought to be very effective in relieving pain from osteoarthritis and lumbar spinal canal stenosis, and in relieving pain after surgical procedures. In this study, the supplement was administered to patients with osteoarthritis and lumbar spinal canal stenosis, but in the future we would like to examine whether the supplement is also effective in patients after surgical procedures.

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Conflict of Interest: Hydrox Inc. (Saitama, Japan) provided the test products for this study and conducted joint research, so there is no conflict of interest. Hydrox Inc. also cooperated in writing this paper.

Ethical Considerations: This study received ethical approval from the International Society of Geriatrics and Gerontology Ethics Committee. (Ethics review number: ISGN_NI10032024)

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