# The efficacy of topical thiocolchicoside (Muscoril®) in the treatment of acute cervical myofascial pain syndrome: a single-blind, randomized, prospective, phase IV clinical study

## *Servikal miyofasiyal ağrı sendromunun tedavisinde topikal tiyokolşikosid'in (Muscoril®) etkinliği: Tek-kör, randomize, prospektif, faz IV klinik çalışma*

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**Summary**

**Objectives:** Myofascial pain syndrome is a disorder characterized by hypersensitive sites called trigger points at one or more muscles and/or connective tissue, leading to pain, muscle spasm, sensitivity, rigor, limitation of movement, weakness, and rarely, autonomic dysfunction. Various treatment methods have been used in the treatment of myofascial pain syndrome. Among these, stretch and spray technique, trigger point injection, dry needling, pharmacological agents, and physical therapy modalities have been proven effective.

**Methods:** Sixty-five patients with acute myofascial pain syndrome were recruited into the study. Patients were randomized into three groups. The first group received thiocolchicoside ointment onto the trigger points, the second group received 8 mg thiocolchicoside intramuscular injection to the trigger points, and the third group received both treatments. Treatment was applied for 5 consecutive days. Algometric and goniometric measurements and pain severity assessments with visual analog scale (VAS) were repeated on the first, third, and fifth days of the treatment.

**Results:** Pain severity measured with VAS significantly improved after the first day in the mono-therapy groups and after the third day in all groups. While significant improvement was observed in all three groups in right lateral flexion measurements, no significant changes were observed in the combined treatment group in left lateral flexion measurements.

**Conclusion:** Thiocolchicoside can be used in the treatment of myofascial pain syndrome. The ointment form may be a good alternative, particularly in patients who cannot receive injections.

Key words: Local injection; medical treatment; muscle relaxant; myofascial pain syndrome; trigger point.

***Özet***

***Amaç:*** *Miyofasiyal ağrı sendromu, bir veya birkaç kas ve/veya bağ dokusunda bulunan ve tetik nokta denilen hipersensitif bölgelerle kendini gösteren; ağrı, kas spazmı, hassasiyet, sertlik, hareket kısıtlılığı, güçsüzlük ve nadiren otonomik disfonksiyon yapabilen bir rahatsızlıktır. Miyofasiyal ağrı sendromunun tedavisinde çeşitli tedavi yöntemleri kullanılmıştır. Bu tedaviler arasında germe ve sprey tekniği, tetik nokta enjeksiyonu, kuru iğneleme, çeşitli ilaç tedavileri ve fizik tedavi yöntemlerinin etkinliği gösterilmiştir.*

***Gereç ve Yöntem:*** *Çalışmaya akut miyofasiyal ağrı sendromulu 65 hasta alındı. Hastalar üç gruba randomize edildi. İlk gruba tetik noktalar üzerine tiyokolşikosid merhem, ikinci gruba tetik noktalar üzerine tiyokolşikosid ampul intramuskuler, üçüncü gruba ikisi birlikte uygulandı. Tedaviler beş gün boyunca yapıldı. Algometrik ve goniometrik ölçümler, vizüel analog skala (VAS) ile ağrı şiddeti değerlendirimi birinci, üçüncü ve beşinci günde yapıldı.*

***Bulgular:*** *VAS ile ölçülen ağrı şiddeti birinci günden itibaren monoterapi gruplarında, üçüncü günden itibaren tüm gruplarda anlamlı oranda düştü. Her üç grupta da sağa lateral fleksiyonda anlamlı düzelme gözlenirken, kombine tedavi grubunda sola lateral fleksiyonda anlamlı düzelme saptanmadı.*

***Sonuç:*** *Tiyokolşikosid, miyofasiyal ağrı sendromu tedavisinde kullanılabilir ve merhem formu özellikle enjeksiyon uygulanamayan hastalar için iyi bir alternatif oluşturabilir.*

Anahtar sözcükler: Lokal enjeksiyon; medikal tedavi; kas gevşetici; miyofasiyal ağrı sendromu; tetik nokta.

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## Background

Myofascial pain syndrome (MPS) is a disorder characterized by hypersensitive sites called trigger points (TPs) at one or more muscles and/or connective tissue, leading to pain, muscle spasm, sensitivity, rigor, limitation of movement, weakness, and rarely, autonomic dysfunction.[1]

According to the Nuprin report, 53% of the American population complains about muscle pain. Among these, 33% and 10% experience pain for more than 11 and 100 days, respectively.[2,3] In one study, out of 172 patients admitted, 54 of them complained about pain and 30% of these were diagnosed with MPS. The frequency of MPS is 85% in patients admitting to chronic pain centers.[2,4,5] Over 44 million Americans are estimated to have this condition, at a cost of US $47 billion per year.[6] The most common causes of MPS are traumatization of myofascial structures and acute straining of the muscles. Following acute injuries, painful muscle spasms called TPs can be observed in some individuals.[1]

TPs can be classified as active or latent. An active TP is painful upon palpation and leads to pain, numbness, and/or prickling sensation reflecting to the defined region, whereas a latent TP can be palpated but is not painful.[2,4]

After injuries, TPs often remain latent within the muscle. When another injury or stress related to the same segment is added to the existing injury, the latent TP exacerbates. Due to these conditions, an unrecognized event may initiate various responses such as very severe pain, long-lasting edema, loss in the range of motion (ROM), and retarded healing. Latent TPs may also be activated by extreme hot or cold or prolonged vibration. Another etiological factor is the micro-traumas caused by daily activities or repetitive motions.[1]

Various theories have been suggested for the pathogenesis of MPS, including ischemic muscle spasm, hyperactivity of muscle fiber, hyperactivity of motor end plate, peripheral sensitization, central sensitization, and secondary hyperalgesia.[7]

According to the ischemic muscle spasm theory, a physical trauma such as injury or chronic strain results in continuous release of intracellular calcium and abnormal contraction of the localized part of the muscle. This spasm leads to reflex spasm, pain and damage by the release of serotonin, prostaglandin, and other inflammatory mediators.[1,4,7-9] Consequently, the resulting inflammation leads to localized fibrosis. The pathological findings of TP biopsies are compatible with this "energy crisis model" and explain the tension in the tensile ligaments in the absence of motor activity.[7] Other reports also support the theories of increased intramuscular motor activity and formation of muscle spasm.

Various treatment methods have been used in MPS. Among these, stretch and spray technique, TP injection, dry needling, pharmacological agents, massage, ultrasound, exercise, electrical stimulation, transcutaneous electrical nerve stimulation (TENS), and biofeedback methods have been proven effective.[2,4,8,10]

TP injection is one of the most effective methods in MPS treatment.[2] Several mechanisms have been proposed for the inactivation of TP.[2,4] Nevertheless, the primary objective of the injection treatment is to localize and damage the TP via the needle. The local anesthetic used not only reduces the pain sensation during the procedure, but also disturbs the self-stimulating cycle of many TPs.[10]

The medications used for treatment include nonsteroidal anti-inflammatory agents, steroids, analgesics, and antidepressants.[4] The efficacy of myorelaxants in the treatment of TP pain is controversial. It was suggested that when used at muscle relaxing doses, they could increase the load on the TPs by relaxing the muscles with protective corset function.[4] Botox injection to the TPs, which aims to reduce muscle activity, has become the most studied treatment in recent years.[11-14]

Thiocolchicoside (TCC) is a semi-synthetic derivative of colchicoside, a natural glycoside of Superba gloriosa. Its *in vitro* profile shows affinity for the inhibitory glycine and GABAA receptors. It has been shown previously that thiocolchicoside induces muscle relaxation without any subjective or objective sedative side effect.[15] In experimental models,

TCC was also found to possess analgesic and anti-inflammatory activities, and in a pharmaco-EEG study, TCC was also shown to be devoid of any sedation.[16] Clinical trials have demonstrated that the therapeutic efficacy of TCC is associated with a good level of safety with sedation rarely reported. [15,17-19]

The objective of this study was to evaluate the efficacy of TCC ointment applied over the TP regions compared to TP injection and to determine whether the efficacy increased when the ointment was applied together with the injection in pain control in patients with acute MPS in the cervical region.

## Materials and Methods

Patients who admitted to the outpatient clinic between April 2005 and December 2005 with complaints of neck pain, upper back pain, difficulty in sleeping at night, inability to move the neck, and pain during movement during the last one week were included in the study. Patients, 18-50 years old, diagnosed with MPS by the establishment of active TPs in the trapezium and/or interscapular region according to the Simons and Travel criteria, and with 1-8 active TPs, were referred to our clinic. The study was explained to the patients and they were invited to participate. Those that provided written consent for participation were included in the study. Symptoms of significant cervical discopathy and osteoarthritis, hemorrhagic diathesis that would impede injection, use of anticoagulants, any known malignancies, use of steroids, immunosuppressive diseases, drug usage, pregnancy, and any known allergic reactions to thiocolchicoside were the exclusion criteria of the study. The study was approved by the ethical committee of Istanbul Medical Faculty (no: 2005153).

Sixty-five patients were recruited into the study. Patients were randomized into three groups. The first group received TCC ointment onto the TPs twice a day, the second group received 8 mg TCC intramuscular injection to the TPs once a day (with a black pointed needle), and the third group received both treatments. Evaluation of the patients and application of the treatments were performed by different physicians. Treatment was applied for 5 consecutive days and patients were evaluated according to the below-mentioned criteria.

At the beginning of the treatment, patients were evaluated by physical examination, laboratory findings, and measurement of the following: severity of pain upon movement and mean pain felt in the last 24 hours using visual analog scale (VAS); cervical ROM using goniometer; and pain severity at TPs using algometer. Algometric and goniometric measurements and pain severity assessments with VAS were repeated on the first, third, and fifth days of the treatment. Patient and physician satisfaction was evaluated using the Likert scale at the end of the treatment.

Since performing only manual palpation to measure TP sensitivity was not quite sufficient as an objective criteria for the MPS assessment, the Pressure Threshold Measurement (algometer) device was developed in order to determine the point where the greatest sensitivity and pain were felt both in clinical practice and experimentally. The ratio and sensitivity of the indicator ensure the measurement of both deep and superficial TPs.[1,2,20]

Therefore, VAS assessment of pain severity upon movement and daily mean pain severity was chosen as the evaluation criteria.[21] Restriction in ROM and pain upon movement are the most significant complaints of MPS patients. Cervical lateral flexions and rotations were measured with the goniometer. Patients were asked to perform lateral flexions and rotations three times and the mean values of these measurements were evaluated.

Assuming that a difference in the mean decrease in the algometer score upon treatment ranging from 1 to 5 between one group and the other groups would be clinically significant, the study was designed for 60 patients with 20 in each group. Mean drop out ratio was presumed as 10% and thus, 65 patients were recruited into the study.

The results were evaluated using the SPSS 10.0 software. Spearman correlation, Kruskal-Wallis test, Friedman test, and Intent to Treat (ITT) analysis were used for the evaluation.

**Table 1.** Improvement in pain evaluation in all three groups

| | Ointment | | Injection | | Ointment + Injection | |
|---|---|---|---|---|---|---|
| | T | p | T | p | T | p |
| VAS mean 1-VAS mean 2 | 3.078 | 0.006 | 2.017 | 0.057 | 1.634 | 0.117 |
| VAS mean 1-VAS mean 3 | 5.699 | 0.000 | 4.776 | 0.000 | 3.104 | 0.005 |
| VAS mean 1-VAS mean 4 | 5.293 | 0.000 | 6.858 | 0.000 | 5.083 | 0.000 |
| VAS mov 1-VAS mov 2 | 2.226 | 0.039 | 3.520 | 0.002 | 3.012 | 0.007 |
| VAS mov 1-VAS mov 3 | 4.316 | 0.000 | 5.698 | 0.000 | 5.272 | 0.000 |
| VAS mov 1-VAS mov 4 | 4.935 | 0.000 | 7.910 | 0.000 | 6.903 | 0.000 |

VAS mov: Pain severity upon movement;
VAS mean: Mean pain severity felt in the last 24 hours;
1. Initial, 2. First day, 3. Third day, 4. Final control.

## Results

In total, 59 patients completed the study. One of the patients receiving TCC ointment did not attend the last follow-up; three patients in the ointment group plus one patient from each of the other groups were excluded after the first evaluation because they showed complete recovery on their third-day follow-up.

There were no significant differences between the groups at the beginning of the treatment (p>0.05). Although there was no significant difference between the groups in the pressure algometer evaluation performed on the third day of treatment, a statistically significant difference was found between the groups in the pain severity upon movement in the last 24 hours (f: 4.196, p: 0.020). This difference was also significant at the last evaluation on Day 5 (f: 3.342, p: 0.04). In groups including injection treatment, a statistically significant, faster improvement was determined in the pain severity upon movement, compared to the ointment-only group. Pain severity measured with VAS was significantly improved after the first day in the monotherapy groups and after the third day in all groups (Table 1, Fig. 1). However, when the evaluation was repeated using the ITT analysis, no significant differences were observed between the groups in the pain severity upon movement (Day 3 f: 0.403, p: 0.670; Day 5 f: 1.317, p: 0.275). Nevertheless, significant improvements were observed in all groups after the first evaluation. In addition, although measurements performed with algometer revealed no statistically significant difference between the

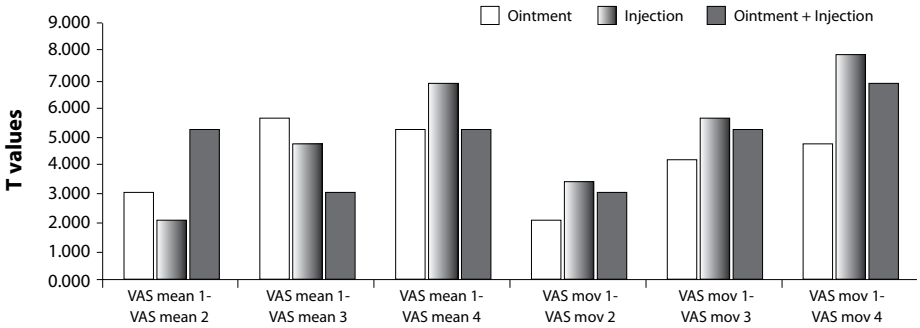


**Fig. 1.** Improvement in pain evaluation in all three groups.

**Table 2.** Mean TP pain thresholds measured with algometer according to groups

| Group | Control | Mean | Median | SD | Minimum | Maximum |
|---|---|---|---|---|---|---|
| | Initial | 3.40 | 3.00 | 1.30 | 1.90 | 7.60 |
| Ointment | Day 1 | 3.50 | 3.10 | 0.90 | 2.30 | 5.20 |
| | Day 3 | 3.60 | 3.20 | 1.60 | 1.50 | 7.80 |
| | Day 5 | 3.70 | 3.40 | 1.10 | 1.80 | 6.40 |
| | Initial | 3.60 | 3.40 | 0.90 | 2.30 | 5.20 |
| Injection | Day 1 | 3.70 | 3.30 | 1.70 | 1.70 | 7.80 |
| | Day 3 | 4.00 | 3.50 | 1.70 | 1.30 | 8.50 |
| | Day 5 | 3.70 | 3.30 | 1.10 | 2.50 | 6.40 |
| | Initial | 3.60 | 3.40 | 1.40 | 1.70 | 7.00 |
| Ointment+ | Day 1 | 4.40 | 4.00 | 1.70 | 2.70 | 9.90 |
| Injection | Day 3 | 4.10 | 3.70 | 1.00 | 2.70 | 6.20 |
| | Day 5 | 3.90 | 3.60 | 1.40 | 1.70 | 7.20 |

| Test | Control | p |
|---|---|---|
| | Initial | 0.684 |
| Kruskal- | Day 1 | 0.889 |
| Wallis test | Day 3 | 0.624 |
| | Day 5 | 0.643 |

| Test | Group | p |
|---|---|---|
| | Ointment | <0.001 |
| Friedman | Injection | 0.001 |
| | Ointment+ Injection | <0.001 |

groups, significant improvements were observed in all three groups at the same level (Table 2, Fig. 2). In the cervical ROM measurements, initial values were close to complete in rotation measurement. Only the changes in lateral flexions were considered in the evaluations. While significant improvement was observed in all three groups in right lateral flexion measurements, no significant changes were observed in the combined treatment group in left lateral flexion measurements (Tables 3, 4; Fig. 3, 4). Patient and physician satisfaction from the treatment was correlated particularly with the decrease in mean pain severity. The most commonly observed side effects were nausea and vomiting; however, there were no dropouts or dose adjustment requirements because of the side effects.

## Discussion

Since patients with MPS are generally young and actively working people, it is very important to rapidly control the pain in order to reduce the loss to the labor force and prevent the pain from becoming chronic. For this purpose, various physical treatment methods, stretch techniques, and injections using various medical agents are recommended.[22]

For the treatment, various local anesthetic TP injections and dry needling methods had been mostly used until 2000. Some of the studies have also investigated laser therapy, Botox application, and medical treatment methods. Since 2000, Botox applications and various physical therapy applications have

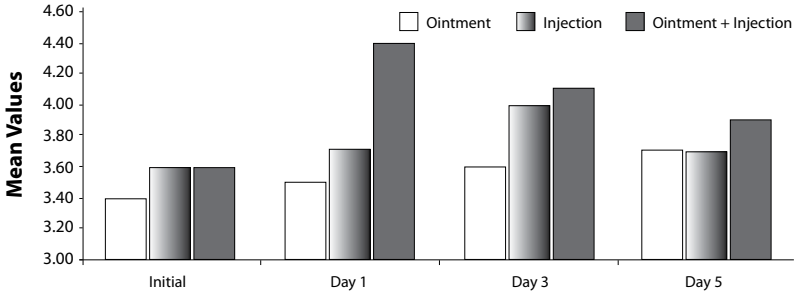


**Fig. 2.** Mean TP pain thresholds measured with algometer according to groups.

**Table 3.** Change in right lateral flexion measurements according to groups (all values are in degrees)

| Group | Control | Mean | Median | SD | Minimum | Maximum |
|---|---|---|---|---|---|---|
| | Initial | 39.20 | 40 | 9.6 | 25 | 70 |
| Ointment | Day 1 | 41.16 | 41 | 8.7 | 30 | 70 |
| | Day 3 | 42.68 | 42 | 8.7 | 30 | 70 |
| | Day 5 | 41.77 | 45 | 4.1 | 35 | 45 |
| | Initial | 41.91 | 45 | 5.7 | 20 | 45 |
| Injection | Day 1 | 43.59 | 45 | 5.6 | 35 | 64 |
| | Day 3 | 42.90 | 45 | 3.9 | 30 | 45 |
| | Day 5 | 43.67 | 45 | 4.3 | 30 | 52 |
| | Initial | 40.23 | 42 | 6.1 | 20 | 45 |
| Ointment+ | Day 1 | 41.32 | 44 | 5.0 | 25 | 45 |
| Injection | Day 3 | 41.36 | 42 | 4.5 | 27 | 45 |
| | Day 5 | 42.09 | 45 | 4.3 | 30 | 45 |

| Test | Control | p |
|---|---|---|
| | Initial | 0.051 |
| Kruskal- | Day 1 | 0.147 |
| Wallis test | Day 3 | 0.335 |
| | Day 5 | 0.335 |

| Test | Group | p |
|---|---|---|
| | Ointment | <0.001 |
| Friedman | Injection | 0.019 |
| | Ointment+ Injection | 0.009 |

been the most often investigated for treatment purposes. The efficacy of local medical treatment was reported in the studies of Dalpiaz. The investigator reported that lidocaine patch was well-tolerated by the patients and was also effective in pain control. [23,24] Since the studies about local medical treatment applications onto the TPs are limited, we decided to conduct this study in order to provide an alternative treatment method for the patients who experienced difficulties with the injections or could not admit for physical therapy.

Another approach for the treatment of MPS is the combination of the treatments. For this purpose, injection and medical treatment or combinations of other treatment methods have been used. Edwards et al. reported that treatment of MPS was more successful in case of concomitant administration of injections in patients performing stretch exercises.[25]

Cummings reviewed 'Needling Therapies in the Management of Myofascial Trigger Point Pain' in 2001 and stated that "…although the present review does not provide proof of efficacy for any individual technique, it clearly shows that no difference exists between TP injections with different substances, or between dry and wet needling."[26]

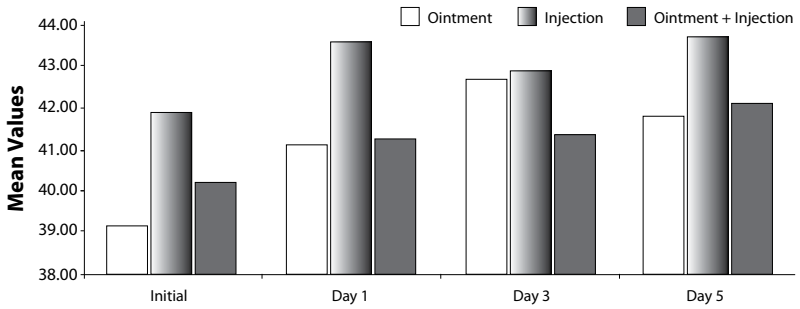


**Fig. 3.** Change in right lateral flexion measurements according to groups (all values are in degrees).

**Table 4.** Change in left lateral flexion measurements according to groups (all values are in degrees)

| Group | Control | Mean | Median | SD | Minimum | Maximum |
|---|---|---|---|---|---|---|
| | Initial | 40.20 | 40 | 8.3 | 25 | 62 |
| Ointment | Day 1 | 43.21 | 43 | 11.0 | 30 | 72 |
| | Day 3 | 44.74 | 45 | 10.4 | 30 | 74 |
| | Day 5 | 42.55 | 45 | 4.1 | 35 | 50 |
| | Initial | 42.22 | 45 | 3.9 | 32 | 45 |
| Injection | Day 1 | 42.95 | 45 | 3.2 | 35 | 45 |
| | Day 3 | 43.95 | 45 | 2.4 | 35 | 46 |
| | Day 5 | 44.38 | 45 | 2.3 | 35 | 46 |
| | Initial | 41.50 | 45 | 4.9 | 32 | 52 |
| Ointment+ | Day 1 | 41.91 | 45 | 3.5 | 35 | 46 |
| Injection | Day 3 | 41.59 | 42 | 3.8 | 32 | 45 |
| | Day 5 | 42.18 | 45 | 4.1 | 34 | 45 |

| Test | Control | p |
|---|---|---|
| | Initial | 0.418 |
| Kruskal- | Day 1 | 0.493 |
| Wallis test | Day 3 | 0.130 |
| | Day 5 | 0.073 |

| Test | Group | p |
|---|---|---|
| | Ointment | 0.001 |
| Friedman | Injection | <0.001 |
| | Ointment+ Injection | 0.117 |

In this study, we aimed to determine whether the ointment form of the muscle relaxant TCC could be an option particularly in patients with injection phobia, contraindications for injections, or with obstacles preventing presentation to the physician for physical therapy or to regular exercise programs. The effects of muscle relaxants have been investigated in previous studies; however, it has been reported that the negative impacts of side effects on daily life observed upon oral administration limit their usage. [27] Since TCC has a low degree of sedation side effect as well as a myorelaxant effect in addition to its anti-inflammatory effect, which was shown in animal studies, we decided to investigate this drug so that patients could benefit from both effects.[28,29]

Another route of administration of these drugs is injection. Although studies on the usage of various local anesthetics have been conducted since the beginning of the 1980s, the study of Frost in 1986 investigated the use of anti-inflammatory agents in injection form and compared their efficacy with lidocaine. When the investigator assessed the pain severity four hours after the injection, he stated that diclofenac group demonstrated a better improvement than the lidocaine group and he related this

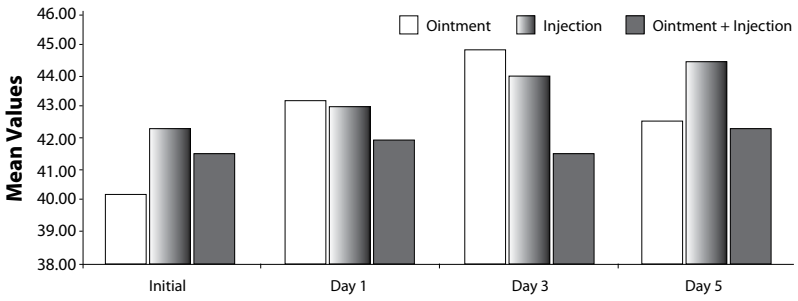


**Fig. 4.** Change in left lateral flexion measurements according to groups (all values are in degrees).

result to the effect of inflammation in the etiology of MPS.[30] Among the muscle relaxants, Botox is the one used in injection form and also the most extensively studied. Despite the controversial results on its efficacy, in the study of Göbel et al. in 2006, Dysport® application was found to be superior to placebo.[31]

Since the use of two different forms of the same drug was not previously reported in the literature, we also investigated whether the concomitant use of the ointment and injection forms of the same drug would provide more benefit than their single usage. In our study, patients were evaluated three hours after the administration of treatment, which is compatible with the literature.[23,32] The evaluation of the treatment results revealed that pain severity reduced significantly after the first day in all three groups. However, in the evaluation performed on Day 3, the decrease in the pain severity upon movement in the last 24 hours in the injection group was more than that of the ointment group. The faster reduction of the pain upon movement observed in the injection group was considered to be related to the direct effect of the needle on the TP.[33] However, when the patients who recovered completely and did not attend the follow-up on Day 5 were included in the statistical assessment, no significant difference was observed and the same rate of improvement in the patients in the ointment group was determined. This result suggests that the effect of TCC in MPS treatment is independent of the route of administration and that it provides a pain control as fast as that of the local injections.

One of the most important complaints in MPS is difficulty experienced upon movement. Therefore, cervical ROM measurements were also performed for the evaluation of treatment efficacy. Hou and Irnich also used ROM measurement as an evaluation criterion in their study and they showed that it increased after the treatment.[34,35] In the cervical ROM measurements in our study, there was significant improvement in the lateral flexions in all groups, particularly in right lateral flexion. This result is compatible with those of Hou et al.[34] The higher degree of improvement in right lateral flexion observed in our study was thought to be related to the higher incidence of MPS in the left-side postural muscles of right-handed individuals. It was suggested that right lateral flexion was more significantly improved after the relief of spasm in the muscles upon treatment.

Patient satisfaction with respect to treatment was mainly determined by the decrease in pain. While 6.5% of the patients evaluated the treatment outcome as perfect, 72.5% evaluated it as good and very good. When patient satisfaction was assessed according to groups, 94.7% of the ointment group, 95.2% of the injection group, and 50% of the combined treatment group evaluated the treatment outcomes as good and perfect. The physicians' satisfaction rates were calculated as 94.7%, 95.2%, and 59.1% in the ointment, injection, and combined treatment groups, respectively. Similar results were obtained in the study of Malanga et al., where they administered tizanidine; 89% of the patients and 78% of the investigators evaluated the outcomes as good and very good.[36] It is suggested that these results are associated with the fact that MPS is not considered a serious condition by most physicians, but it is indeed a pathology that worsens the quality of life and has a high chance of cure with appropriate treatment.

Side effects were observed in 31% of the patients. The most commonly observed side effect was mild nausea, which was observed mostly in the injection group. Dizziness was reported in only one patient. All side effects were well-tolerated and did not require quitting the treatment. This result is compatible with the study of Malanga et al., in which oral tizanidine was administered for the treatment of chronic MPS and no serious side effects upon five-week treatment were reported.[36]

In conclusion, the muscle relaxant TCC can be used in the treatment of MPS and the ointment form may be a good alternative, particularly in patients who cannot receive injections. However, the patients do not prefer the combined usage of ointment and injection forms. More extensive (multi-center, multi-drug) international studies are required on this topic.

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