

Original Article

Efficacy of the Combination of Indomethacin and Methocarbamol versus Indomethacin Alone in Patients with Acute Low Back Pain: A Double-Blind, Randomized Placebo-Controlled Clinical Trial

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INTRODUCTION

Low back pain is a prevalent disorder that many people experience throughout their lives. Statistics indicate that 85% of people refer to a physician at least once in their lifetime due to low back pain.^[1] This disorder can involve muscles, nerves, or bones in the lower back. Low back pain can be divided based on the duration of pain into acute back pain (<6 weeks), subacute back pain (6–12 weeks), and chronic back pain (more than 12 weeks).^[2]

The pathophysiology of acute low back pain is often related to spasms of the muscles in the lower back and

ABSTRACT

Objective: Acute low back pain is a common ailment and causes pain and disability. Physicians often prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) to treat acute low back pain; however, due attention has recently been drawn to muscle relaxants to reduce the severity of patients' daily physical dysfunction. Therefore, this study aimed to evaluate the therapeutic effect of the administration of indomethacin alone compared with methocarbamol as a muscle relaxant and indomethacin as an NSAID on the treatment of acute low back pain.

Methods: The present double-blind clinical trial was performed on 64 patients with acute low back pain. The patients were categorized into two groups and received the treatments as follows. Indomethacin capsules of 25 mg every 8 h and placebo tablets every 8 h were administered in the first group (Group I). Indomethacin capsules of 25 mg every 8 h and methocarbamol tablets of 500 mg every 8 h were administered in the second group (Group I + M). Patient pain intensity and physical function based on Back Pain Function Scale (BPFS) were recorded before and 1 week after the intervention. **Findings:** The present study results revealed that the mean pain reduction of patients in Group I + M was significantly higher than that of Group I (3.66 ± 3.17 vs. 1.84 ± 1.53 ; $P < 0.001$). Moreover, the mean BPFS increase in Group I + M was significantly higher than that of Group I (19.44 ± 8.66 vs. 4.75 ± 4.35 ; $P < 0.001$). **Conclusion:** According to the results of the present study, concomitant administration of indomethacin and methocarbamol can be more effective in reducing pain intensity and improving the patient's physical function (or performance).

KEYWORDS: Acute low back pain, Indomethacin, Methocarbamol

around the vertebrae. The severity of the symptoms usually decreases over time and resolves without any medical treatments in many cases. The severity of symptoms in the 1st days can cause serious dysfunction of the patient and lead to absenteeism from school or work, resulting in many social and economic

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consequences at the community scale. Therefore, the application of effective therapies in the early days of symptom presentation that can return patients to their normal routine by reducing their pain and increasing their function is a significant issue.^[3]

Drug therapies include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants such as methocarbamol, analgesics, opium, and tricyclic antidepressants. However, the preference of any of the mentioned drugs over the other has not yet been definitively determined.^[4] Many previous studies have considered NSAIDs such as ibuprofen, diclofenac, naproxen, indomethacin, etc., to treat both acute and chronic low back pain. NSAIDs have also been revealed to effectively reduce pain in the first 3 weeks and reduce disability in acute low back pain.^[5-7]

Regarding the effect of indomethacin on the acute and chronic phase of pain, it has been reported that indomethacin inhibits the production of prostaglandins by inhibiting the cyclooxygenase enzyme.^[8]

Considering the proven analgesic and anti-inflammatory effects of indomethacin in long-term periods and the effectiveness of muscle relaxants in short-term periods, it seems that it is better to employ therapies that have rapid effectiveness in acute pains, such as acute low back pain. Hence, some studies have evaluated the effectiveness of using drugs such as muscle relaxants alone or in combination with nonsteroidal medications. For instance, a study has found that NSAIDs combined with muscle relaxants are effective in relieving acute low back pain.^[4,9] Emrich *et al.* also indicated that methocarbamol compared to placebo can be considered an effective and tolerable treatment for patients with low back pain.^[10]

However, there are still disagreements in prescribing any of the mentioned therapeutic drugs, and the necessity for conducting more studies to achieve appropriate treatment for these patients becomes more apparent considering the side effects of using NSAIDs.^[11,12] Therefore, the very aim of the present study was to evaluate the effectiveness of indomethacin alone and in combination with methocarbamol in patients with acute low back pain.

METHODS

The present study was a double-blind clinical trial. The study population was all patients with acute low back pain referred to the general clinic of Shariati Hospital in Isfahan in 2019. The sample size was estimated to be 64 patients (32 patients in each group) at the confidence interval of 95%, test power of 80%, and an error rate

of 0.7. The convenience random sampling technique was employed to select the sample of the present study from eligible patients. Inclusion criteria included patients within the age range of 18–65 years and with acute low back pain, no history of gastrointestinal bleeding, and no comorbidities such as kidney failure, mental illness, heart disease, liver disease, active peptic ulcer, hemorrhoids, etc. In addition, if patients had warning signs such as fever, tenderness, recent significant weight loss, pain extending to the legs, urinary incontinence, had not followed the prescribed medication correctly, or were not responding to further follow-ups, they were excluded from the study [Figure 1].

After obtaining the code of ethics from the Ethics Committee of Islamic Azad University, Najafabad Branch (IR.IAU.NAJAFABAD. REC.1398.081) and obtaining written consent from eligible patients, their demographic characteristics such as age, sex, and body mass index (BMI) were first recorded. Moreover, patients' pain score was recorded based on the Visual Analog Scale with a score range from 1 to 10. The Back Pain Function Scale (BPFS) was also used to evaluate the patient's function.^[13] The mentioned scale included 12 items about the severity of disability generated in the patient's daily physical function. The responses of this scale were based on a 6-point Likert scale as follows: 0 = unable to perform activity, 1 = extreme difficulty, 2 = quite a bit of difficulty, 3 = moderate difficulty, 4 = a little bit of difficulty and 5 = no difficulty. A minimum and maximum score of 0 and 60 could be obtained following the total score calculation. The higher the patients' score, the better their function will be.^[13]

Indomethacin capsules of 25 mg every 8 h and placebo tablets every 8 h were administered in the first group (Group I). Indomethacin capsules of 25 mg every 8 h and methocarbamol tablets of 500 mg every 8 h were administered in the second group (Group I + M).

It should be noted that placebo tablets have the same shape and color as methocarbamol tablets prepared by the pharmacist and were provided for the researcher to meet the blindness condition. Therefore, the patient and the researcher were not informed of the type of group therapy.

Attention to the physician's instructions and the condition of patients was checked on the telephone 1 week later. If the patients did not follow the physician's instructions well, they were excluded from the study; otherwise, the pain level, the BPFS status, and the possible side effects of the drug were evaluated and recorded.

Finally, the collected information was entered into SPSS software (version 25; SPSS Inc., Chicago, Ill.,

USA). Data were presented as frequency (%) and/or means \pm standard deviation. According to Kolmogorov–Smirnov test results indicating the normal distribution of data, independent samples *t*-test, paired sample *t*-test, and Chi-square test were used. The significance level of <0.05 was considered in all analyses.

RESULTS

In the present study, ten females (31.3%) and 22 males (68.7%) with a mean age of 42.69 ± 8.89 years were in the indomethacin alone group (I group). In addition, 16 females (50%) and 16 males (50%) with the mean age of 39.22 ± 11.37 years were in the indomethacin + methocarbamol group (I + M group) ($P > 0.05$) [Table 1].

In addition, patients' pain scores did not differ significantly between the two groups and by sex before the intervention ($P > 0.05$). Although there was a significant improvement in the pain score of patients in each of the two groups after the intervention as compared to before the intervention ($P < 0.001$), the pain score of patients in Group I + M with the mean of 3.84 ± 2.19 was not significantly different from that of Group I with the mean of 4.90 ± 2.13 ($P = 0.053$). Moreover, comparisons made between sexes revealed that pain reduction was higher in males as compared with females; however, there was still no significant difference between the two groups in terms of the pain score after the intervention ($P > 0.05$) [Table 2]. In addition, the level of pain reduction in Group I + M with a mean of 3.66 ± 3.17 was significantly higher than that of Group I with a mean of 1.84 ± 1.53 ($P < 0.001$) [Figure 2].

Moreover, the mean score of BPFS before the intervention was not significantly different between the two groups and by sex ($P > 0.05$). In contrast, the BPFS score of patients in Group I + M with a mean of 46.81 ± 10.48 was higher than that of Group I with a mean of 39.25 ± 8.37 ($P < 0.05$). Furthermore, comparisons made between sexes revealed that the increase in BPFS of male patients after the intervention in Group I + M with a mean of 49.87 ± 10.82 was significantly higher than that of male patients in Group I with a mean of 39.67 ± 8.89 ($P = 0.002$), although the mean BPFS score of female patients was not significantly different between the two groups ($P > 0.05$). In addition, there was a significant improvement in patients' function in both groups after the intervention as compared to before the intervention ($P < 0.001$); however, the increase in BPFS of Group I + M with a mean of 19.44 ± 8.66 was significantly higher than that of Group I with a mean of 4.75 ± 4.35 ($P < 0.001$) [Table 3 and Figure 2].

Table 1: Basic characteristics of the study patients

Characteristics	Group I (n=32), n (%)	Group I+M (n=32), n (%)	P
Sex			0.076*
Female	10 (31.3)	16 (50.0)	
Male	22 (68.7)	16 (50.0)	
Age (year)	42.69 \pm 8.89	39.22 \pm 11.37	0.179**
BMI (kg/m ²)	22.06 \pm 2.78	22.65 \pm 1.93	0.327**

*Chi-squared test, **Student's *t*-test. Group I=Indomethacintreatment, Group I + M = Indomethacin + methocarbamol treatment, BMI=Body mass index

Table 2: Determination and comparison of the mean pain score of patients between the two groups

Pain score	Group I (n=32)	Group I + M (n=32)	P ^a
Total			
Before the intervention	6.75 \pm 1.79	7.50 \pm 1.76	0.097
After the intervention	4.90 \pm 2.13	3.84 \pm 2.19	0.053
P ^b	<0.001	<0.001	
Male			
Before the intervention	6.54 \pm 1.79	7.25 \pm 1.61	0.100
After the intervention	4.71 \pm 2.14	3.31 \pm 2.55	0.069
P ^b	<0.001	<0.001	
Female			
Before the intervention	7.37 \pm 1.77	6.75 \pm 1.61	0.147
After the intervention	5.50 \pm 2.14	4.37 \pm 1.67	0.083
P ^b	<0.001	<0.001	

^aUse of independent samples *t*-test to compare the mean of pain score between the two groups, ^bUse of paired sample *t*-test to compare the mean of pain score after the intervention as compared to before the intervention in each of the two groups. Group I=Indomethacintreatment, Group I + M = Indomethacin + methocarbamol treatment

Table 3: Determination and comparison of the mean back pain function scale score of patients between the two groups

Function score	Group I (n=32)	Group I + M (n=32)	P ^a
Total			
Before the intervention	34.50 \pm 8.69	29.37 \pm 13.29	0.072
After the intervention	39.25 \pm 8.37	46.81 \pm 10.48	0.002
P ^b	<0.001	<0.001	
Male			
Before the intervention	30.67 \pm 8.29	24.75 \pm 14.27	0.105
After the intervention	39.67 \pm 8.89	49.87 \pm 10.82	0.002
P ^b	<0.001	<0.001	
Female			
Before the intervention	34.00 \pm 10.39	30.00 \pm 9.67	0.361
After the intervention	38.00 \pm 6.93	43.75 \pm 9.47	0.143
P ^b	<0.001	<0.001	

^aUse of independent samples *t*-test to compare the mean of BPFS score between the two groups, ^bUse of paired sample *t*-test to compare the mean of BPFS score after the intervention s compared to before the intervention in each of the two groups. Group I=Indomethacintreatment, Group I + M = Indomethacin+methocarbamol treatment, BPFS=Back pain function scale

Finally, four patients (12.5%) in Group I and two patients (6.25%) in Group I + M had gastrointestinal problems ($P > 0.05$).

DISCUSSION

In the present study, more than 60% of patients with acute low back pain were men. Although the percentage of male patients was expected to be higher due to more men in tough jobs requiring physical work, the two groups were similar in terms of age, sex, and BMI.

The present study results on the evaluation of patients' pain revealed that the therapeutic intervention in each of the two groups generally reduced the patients' pain. There was no significant difference between the two groups in terms of the patients' mean pain score after the intervention ($P > 0.05$); however, the changes in patients' pain relief in Group I + M were significantly more than those of Group I.

Consistent with the present study's findings, Itoh and Kawakita indicated that the injection of indomethacin could prevent the development of a region sensitive to pain.^[14]

It has also been well-established that prostaglandins, especially prostaglandins E and F, are responsible for

stimulating pain-sensitive receptors, and indomethacin indirectly inhibits the synthesis of prostaglandins E2 by inhibiting inflammatory pathways reduces pain.^[15] In previous studies, the effect of indomethacin administration as one of the inhibitors of prostaglandin synthesis on the acute and chronic phase of pain has been studied. The researchers stated that indomethacin's mechanism inhibits the production of prostaglandins by inhibiting the cyclooxygenase enzyme.^[16] The mentioned effect has been proven for indomethacin in the study conducted by Meamarbashi and Rajabi.^[17] Although the present study addressed acute back pain and differed from the mentioned studies in this respect, the mechanism of action of this drug can confirm its positive effect on reducing pain in patients.

It can be stated that the pain transmission path is divided into three peripheral, spinal, and supraspinal pathways.^[18-20] NSAIDs inhibit pain in the early stages and the peripheral site by inhibiting eicosanoid production, such as prostaglandins.^[15] Prostaglandins are one of the most important mediators of inflammation, and the inhibition of their production by NSAIDs such as ibuprofen and indomethacin reduces inflammation.^[16,21] Researchers have paid attention to the mechanism of action and duration of action in

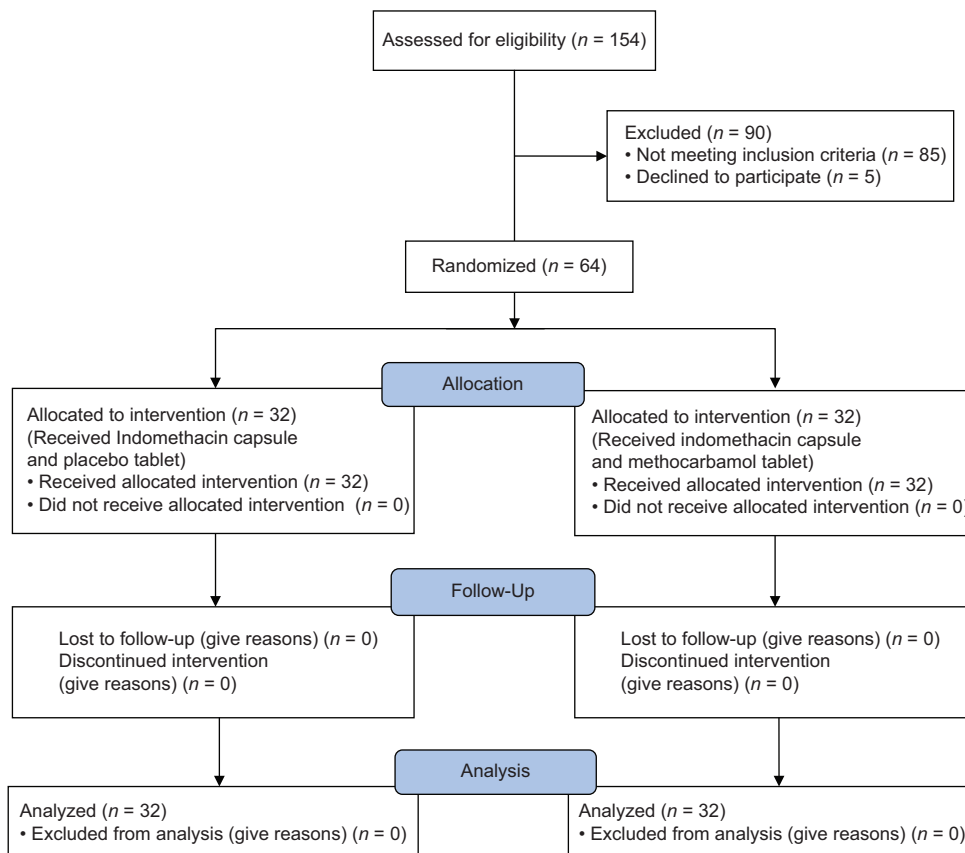


Figure 1: CONSORT diagram of the study

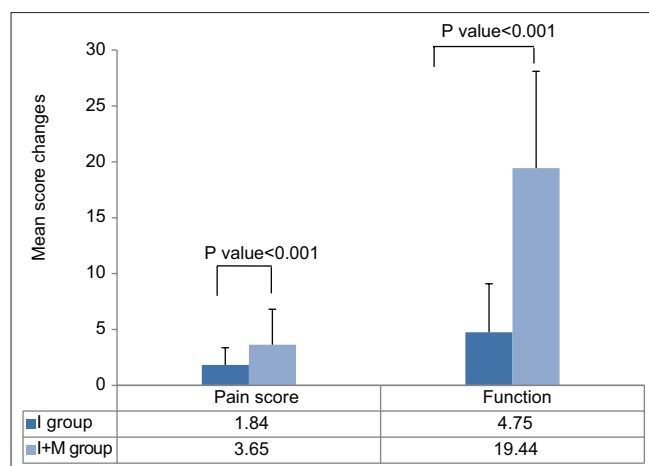


Figure 2: Comparison of the mean pain and Back Pain Function Scale score between two groups

comparing indomethacin with other NSAIDs. Due to the effect of indomethacin on cell membranes, indomethacin inhibits not only 4-series leukotrienes that cause severe inflammation but also the cyclooxygenase-2 and 5-lipoxygenase pathways, which cause the production of thromboxane and 2-series prostaglandin, respectively. Instead, indomethacin leads to thromboxane and 3-series prostaglandins from cyclooxygenase-2 and 5-series leukotriene from 5-lipoxygenase that have less anti-inflammatory properties than previous pathway products.^[13,16,17] Compared with chemical and mechanical stimuli, thromboxane and prostaglandins from the cyclooxygenase-2 pathway and leukotriene from the 5-lipoxygenase pathway reduce the pain perceived by the individual by increasing the pain threshold in afferent nerves VI and III.^[14,17,22] Therefore, it seems that the effect of indomethacin in reducing patients' pain is desirable because of its mechanism of action. However, as patients' daily physical function is disrupted due to acute low back pain and they need to return to their typical life process in the shortest possible time. The present study aimed at examining whether it is possible to reduce the severity of the patient's disability with minor side effects and in the shortest time following the simultaneous administration of methocarbamol as a muscle relaxant and indomethacin as an NSAID?

In this regard, the results of this study on BPFs improvement showed that the mean BPFs score of patients in Group I + M was significantly higher than that of Group I after the intervention ($P < 0.05$). Moreover, comparison between sexes revealed that the mean of BPFs increase in male patients in Group I + M was significantly higher than that of Group I after the intervention ($P < 0.05$); however, the mean BPFs score of female patients was not significantly different between the two groups ($P > 0.05$). It can be stated that

the effect of using methocarbamol in combination with indomethacin can be more effective in improving the patient's daily physical activity.

Najarzadeh *et al.* also mentioned the beneficial effects of indomethacin on preventing a decrease in the knee range of motion and possibly inflammation compared to the control group.^[23] In line with the mentioned study, the present study results also indicated the effectiveness of indomethacin alone in improving the patient's physical function, although this improvement was more remarkable in Group I + M.

Moreover, in line with the present study, two meta-analysis studies provided robust results indicating the effectiveness of muscle relaxant therapy in treating simple acute low back pain.^[9,24] For example, patients receiving Flexeril (cyclobenzaprine) were much more likely to report an improvement in low back pain symptoms than those who received a placebo.^[9] Muscle relaxants have maximum effectiveness within the 1st week or the first 2 weeks of treatment. There is evidence that adding muscle relaxants to NSAIDs has led to further improvements in low back pain.^[24,25] Muscle relaxants yield the maximum benefit in the 1st week or the first 2 weeks of treatment and can be considered to have similar effectiveness regardless of various types of muscle relaxants.^[24]

In addition, the results of another study revealed that the use of NSAIDs along with muscle relaxants was effective in relieving acute low back pain.^[4,9] Emrich *et al.* also showed that methocarbamol compared to placebo can be considered an effective and tolerable treatment for patients with low back pain.^[10]

In addition, in the present study, the effectiveness of the intervention in Group I + M compared with Group I was higher in males than females. The mentioned point can be considered as the strength of the present study due to the following reasons. First, no research has addressed the effect of these drugs in two sexes. Second, with the greater effectiveness of this therapeutic intervention on men, more satisfaction can be achieved in these patients because with a significant improvement in their daily physical function (along with pain relief), they can return to work faster and with less pain and suffering. In addition, the other strength of the present intervention was the lower number of gastrointestinal side effects, so it can not pose a severe risk to patients. Given that the weakness of the present study was the nonevaluation of the effect of methocarbamol alone and the lack of follow-ups in <1 week duration, it is suggested that future studies evaluate the effect of indomethacin and methocarbamol alone and in combination with other NSAIDs and other muscle relaxants.

According to the present study results, although both treatments of indomethacin alone and indomethacin with methocarbamol were effective in improving patients with acute low back pain, the administration of indomethacin with methocarbamol was significantly more effective in reducing pain and increasing performance (or physical function) than indomethacin alone.

AUTHORS' CONTRIBUTION

Shiva Samsamshariat, Mehdi Sharifi-Sade and Shafeajafar Zoofaghari have proposed the concept, designed the study and defined the intellectual content, Asieh Maghami Mehr collected the data and performed statistical analysis, Shafeajafar Zoofaghari and Ali Mohammad Sabzghabae prepared the manuscript and revised it and re-checked the statistical analysis of the data. All authors are responsible for the integrity of the study and correct reporting of the results.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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