ORIGINAL ARTICLE
82

J Turk Spinal Surg 2023;34(2):82-6
DOI: 10.4274/jtss.galenos.2023.02996

CONSERVATIVE TREATMENT OF ACUTE LOW BACK PAIN: ACETAMINOPHEN COMBINED WITH ETODOLAC OR DICLOFENAC A COMPARATIVE STUDY OF 67 PATIENTS

Celaleddin Bildik[1], Tuna Pehlivanoğlu[2,3]

[1]Ataşehir Florence Nightingale Hospital, Department of Orthopedic Surgery and Traumatology, İstanbul, Turkey
[2]Liv Hospital Ulus, Department of Orthopedic Surgery and Traumatology, İstanbul, Turkey
[3]İstinye University Faculty of Medicine, Department of Orthopaedic Surgery and Traumatology, İstanbul, Turkey

ABSTRACT

Objective: Acute low back pain (LBP) is the leading cause of disability worldwide, whereas the ideal initial treatment protocol is still under debate. The aim of this study was to question, whether acetaminophen combined with etodolac or diclofenac could provide efficient ease of symptoms in patients with acute LBP and to assess whether one combination could be superior compared to the other in terms of clinical and functional outcomes, with health-related quality of life.

Materials and Methods: A retrospective, comparative study of 67 patients with acute, non-radicular, and non-traumatic LBP was undertaken. Patients were assessed in two groups, whereas daily, group one [34 patients, mean age of 47.1 (range 24-56)] received 4x500 mg acetaminophen combined with 2x400 mg etololac and the group two [33 patients, mean age of 44.8 (range 26-53)] received 4x500 mg acetaminophen combined with 2x75 mg diclofenac, for one week. Patients' pre-treatment and post-treatment visual analog scale (VAS), Oswestry Disability Index (ODI), and Roland-Morris Disability Questionnaire (RMDQ) scores were recorded and compared.

Results: Group 1-2 had a pre-treatment mean VAS back score of 7.4-7.1, ODI score of 76.2-75.8 and RMDQ score of 18.2-19.4 improved to 1.4-1.3, 16.1-16.4, and 5.8-6.2 at the end of 1st week (p<0.001 for all), which further improved to 1.1-1.2, 15.8-15.3, and 3.3-3.2 (p<0.001 for all) at the end of 12th week. Intergroup comparison yielded no statistically significant data (p>0.05 for all).

Conclusion: Daily 2000 mg acetaminophen combined with 800 mg etodolac or 150 mg diclofenac could provide effective and sustained pain relief, with significant clinical and functional amelioration resulting in significant improvements in health-related quality of life, if applied under strict indication criteria to patients with acute non-traumatic and non-radicular LBP.

Keywords: Acute low back pain, acetaminophen, non-steroidal anti-inflammatory drugs, etodolac, diclofenac, health-related quality of life, visual analog scale, Oswestry Disability Index, Roland Morris Disability Questionnaire

INTRODUCTION

Low back pain (LBP) is on the most prevalent global health problem[1,2], with a global point prevalence ranging between 18 to 33%[3,4]. It was reported, that over 80% of the population had at least one episode of acute LBP in their lifetime. Even with proper management, LBP was reported to cause a tremendous economical burden, while over 50 billion United States Dollars was reported as the estimated total costs associated with LBP in the United States[5] and 3.5 billion Euros in the Netherlands[6]. Acute LBP was defined as pain originating between the lower border of the scapula and upper gluteal folds and lasting shorter than 12 weeks frequently attributed to non-specific causes without any certain etiology[7,8]. Patients with acute, new - onset LBP were reported to have a favorable prognosis with complete resolution of pain in 80% of patients, while up to 20% of patients might experience moderate to severe pain 3 months later and 30% of them were noted to have LBP-related functional impairment[9,10].

Current guidelines recommend acetaminophen as the first line of analgesic treatment[11,12], while it was neither based on strong evidence[3,13], nor on its analgesic efficacy in patients with acute LBP, but on a relatively superior safety profile compared to other non-steroidal anti-inflammatory drugs (NSAIDs)[8]. However, because of the lack of symptomatic efficacy as monotherapy, acetaminophen was recommended to be used along with other NSAIDs[14,15].

The aim of this study was to question, whether acetaminophen combined with etodolac or diclofenac could provide efficient ease of symptoms in patients with acute LBP and to assess whether one combination could be superior compared to the other by comparing the pre- and post-treatment results of

Address for Correspondence: Tuna Pehlivanoğlu, Liv Hospital Ulus, Department of Orthopedic Surgery and Traumatology, İstanbul, Turkey
Phone: +90 533 393 66 00 **E-mail:** dr.tuna@hotmail.com **Received:** 13.01.2023 **Accepted:** 03.04.2023
ORCID ID: orcid.org/0000-0001-8886-7538

Roland-Morris Disability Questionnaire (RMDQ), Oswestry Disability Index (ODI), and visual analog scale (VAS) back scores.

MATERIALS AND METHODS

After obtaining institutional review board approval (Florence Nightingale Hospital, FNG-A 710), a retrospective, comparative study was performed on assessing consecutive patients in 2022 (January to November), who received conservative treatment with acute LBP. One hundred forty three consecutive patients were identified. The following inclusion criteria were applied: (1) having a new episode of LBP (defined as pain between the 12th rib and gluteal crease), (2) having LBP of less than 6 weeks of duration preceded by a painless period for at least 1 month, (3) being 18-60 years old, (4) having been treated with acetaminophen combined with etodolac or diclofenac, and (5) being willing to participate in the study. The following exclusion criteria were applied: (1) having radicular pain, (2) having a history of trauma, malignancy or metabolic bone disease, (3) having a diagnosis of spinal infection, fracture or neoplasm, (4) having a history of spinal surgery, (5) using any type of analgesic drug before the initiation of the current treatment regimen, (6) using any type of psychotropic drug currently, (7) having applied conservative treatment other than acetaminophen combined with etodolac or diclofenac due to any reason (allergy, contraindication, physician's preference), (8) being younger than 18, older than 60 years of age, and (9) being unwilling to participate in the study (Table 1). Because of the aforementioned criteria, 76 patients were excluded (16: radicular pain, 14: history of trauma, malignancy or metabolic bone disease, 12: having an age >60, 11: diagnosis of spinal infection, fracture or neoplasm, 9: usage of analgesic drug(s) before the initiation of the treatment, 7: having applied other drug(s) combination as conservative treatment, 4: being unwilling to participate, 3: usage of psychotropic drug(s) before the initiation of the treatment) (Table 2). The remaining 67 patients were included in the study.

The study was approved by the Demiroğlu Bilim University Ethics Committee (decision no: 24345, date: 17.01.2023).

Treatment Protocol

All patients were prescribed a daily dosage of 4x500 mg acetaminophen combined with 2x400 mg etodolac or 2x75 mg diclofenac taken orally in addition to advice and reassurance regarding the course of the acute LBP underlining remaining active, avoiding bed rest and resuming normal movement as soon as possible.

Clinical Outcome Parameters (COP)

As the patient reported outcome questionnaires ODI scores, VAS back scores were applied to evaluate the clinical and functional outcomes. RMDQ, which is 24 point-scale, was applied to evaluate LBP and related functional impairment in terms of disability. The aforementioned scores were applied before the initiation of the treatment and at 1st, 2nd, 4th, 6th, 8th and 12th week after the initiation of the medical treatment.

Information of Informed Consent

All patients were taken informed consent, so that their pre-, intra-, and post-operative data could be used for publication by hiding their identity.

Statistical Analysis

For the statistical analysis, SPSS software (Version 22.0; SPSS Inc, Chicago, IL, USA) was used. Data are expressed as mean +/- standard deviation. The chi-square test and Fisher's exact

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Having a new episode of LBP (defined as pain between the 12th rib and gluteal crease)	Having radicular pain
Having LBP of less than 6 weeks of duration preceded by a painless period for at least 1 month	Having a history of trauma, malignancy, or metabolic bone disease
Being 18-60 years old, (4) having been treated with acetaminophen combined with etodolac (2x400 mg) or diclofenac (2x75 mg)	Having a diagnosis of spinal infection, fracture or neoplasm
Having been treated with acetaminophen combined with etodolac or ketorolac	Having a history of spinal surgery
Being willing to participate in the study	Using any type of analgesic drug before the initiation of the current treatment regimen
-	Using any type of psychotropic drug currently
-	Having applied conservative treatment other than acetaminophen combined with etodolac or diclofenac due to any reason (allergy, contraindication, physician's preference)
-	Being younger than 18, older than 60 years of age
-	Being unwilling to participate in the study

LBP: Low back pain

test were used for the analysis of categorical variables and to compare different time points where appropriate. One-way analysis of variance (ANOVA) was used to determine a significant difference at various time points. A p-value less than 0.05 was considered as statistically significant.

RESULTS

Sixty seven consecutive patients (52 females, 15 males) with acute LBP, which was treated with a daily dosage of 4x500 mg acetaminophen combined with 2x400 mg etodolac or 2x75 mg diclofenac taken orally for one week were enrolled. Patients were divided into two groups, which were comparable in terms of their demographic values and pre-treatment clinical and functional scores Table 3. Group 1 was applied 4x500 mg acetaminophen combined with 2x400 mg etodolac for one week. It comprised 34 patients with a mean age of 47.1 (range 24-56). Group 1 had a pre-treatment mean VAS back score of 7.4 (range 5-9), ODI score of 76.2 (range 72-81), and mean RMDQ score of 18.2 (range 14-23). At the 1st week follow-up, group 1 had a mean VAS back score of 1.4 (range 0-2), ODI score of 16.1 (range 15-21), and mean RMDQ score of 5.8 (range 0-13) ($p<0.001$ for all). At the 12th week follow-up, group 1 had a mean VAS back score of 1.1 (range 0-2), ODI score of 15.8 (range 15-18), mean RMDQ score of 3.3 (range 0-9) ($p<0.001$ for all). It was detected, that the treatment protocol was yielding remarkable improvements regarding the clinical and functional outcomes with high statistical significance from pre-treatment to the 1st week post-treatment, and from 1st week post-treatment to 12th week post-treatment. Group 2 was applied 4x500 mg acetaminophen combined with 2x75 mg diclofenac for one week. It comprised 33 patients with a mean age of 44.8 (range 26-53). Group 2 had a pre-treatment mean VAS back score of 7.1 (range 5-9), ODI score of 75.8 (range 71-80), and mean RMDQ score of 19.4 (range 13-22). At the 1st week follow-up, group 2 had a mean VAS back score of 1.3 (range 0-2), ODI score of 16.4 (range 15-21), and mean RMDQ score of 6.2 (range 2-15)

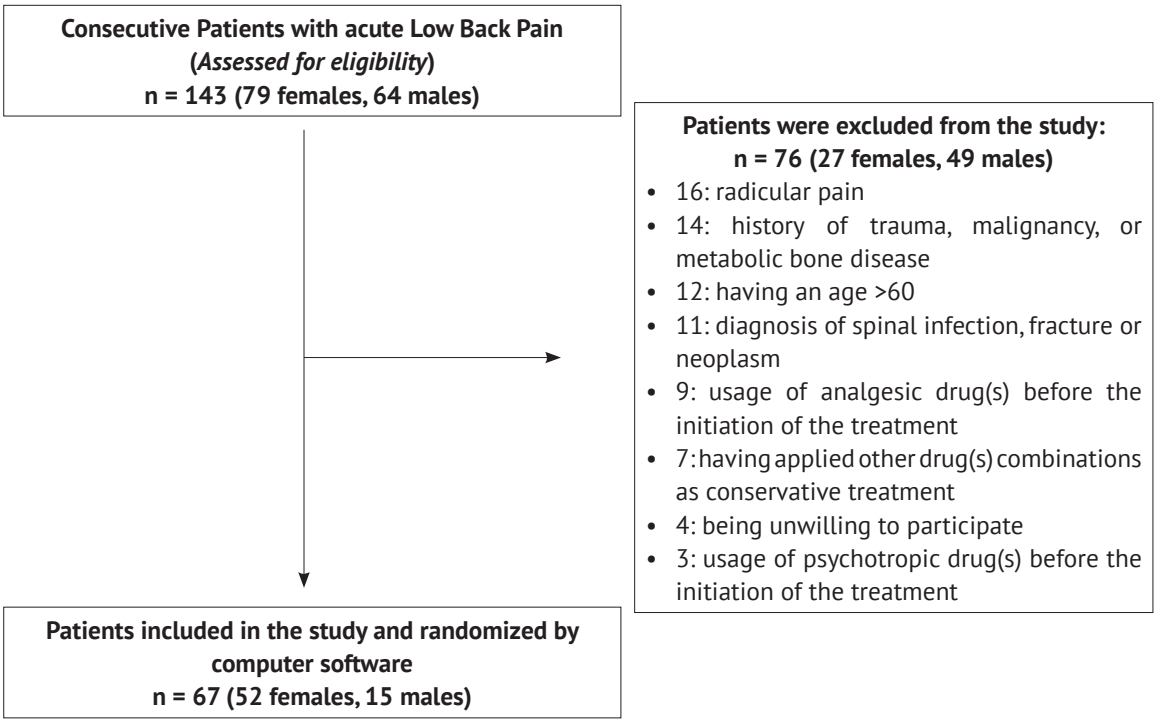

Table 2. Flowchart of the study population

Table 3. Demographic data, pre-treatment clinical and functional scores

	Group 1	Group 2	p-value
Number	34	33	0.34
Age	47.1 (range 24-56)	44.8 (range 26-53)	0.47
Treatment protocol	4x500 mg acetaminophen + 2x400 mg etodolac	4x500 mg acetaminophen + 2x75 mg diclofenac	N/A
Mean VAS back score	7.4 (range 5-9)	7.1 (range 6-9)	0.24
Mean ODI score	76.2 (range 72-81)	75.8 (range 71-80)	0.39
Mean RMDQ	18.2 (range 14-23)	19.4 (range 13-22)	0.27

VAS: Visual analogue scale, ODI: Oswestry Disability Index, RMDQ: Roland-Morris Disability Questionnaire

Table 4. Comparison of Post-treatment clinical and functional scores

	Group 1	Group 2	p-value
Post-treatment 1st week			
Mean VAS back score	1.4 (range 0-2)	1.3 (range 0-2)	0.41
Mean ODI score	16.1 (range 15-21)	16.4 (range 15-21)	0.24
Mean RMDQ	5.8 (range 0-13)	6.2 (range 2-15)	0.27
Post-treatment 12th week			
Mean VAS back score	1.1 (range 0-2)	1.2 (range 0-2)	0.39
Mean ODI score	15.8 (range 15-18)	15.3.(range 15-20)	0.27
Mean RMDQ	3.3 (range 0-9)	3.2 (range 0-11)	0.34

VAS: Visual analogue scale, ODI: Oswestry Disability Index, RMDQ: Roland-Morris Disability Questionnaire

(p<0.001 for all). At the 12th week follow-up, group 2 had a mean VAS back score of 1.2 (range 0-2), ODI score of 15.3 (range 15-20), and mean RMDQ score of 3.2 (range 0-11) (p<0.001 for all). It was detected, that the treatment protocol was yielding remarkable improvements regarding the clinical and functional outcomes with high statistical significance from pre-treatment to the 1st week post-treatment, and from 1st week post-treatment to 12th week post-treatment similar to the results of group 1. Intergroup comparison of clinical-functional outcomes recorded in post-treatment periods yielded no statistical significance (p>0.05 for VAS, ODI and RMDQ scores at all times) attributed to equal treatment efficacy and success of both treatment combinations Table 4. In groups 1 and 2 following adverse events were reported: Gastrointestinal problems including diarrhea (2-1) (p=0.26) and dizziness (1-2) (p=0.34). Patients in both groups were detected to have relatively low rates of complications, underlining the safety of the treatment protocols.

DISCUSSION

This study reported that 2000 mg acetaminophen combined with either 800 mg etodolac or 150 mg diclofenac could provide effective clinical and functional recovery together with successful pain relief in the short term in patients with acute non-traumatic, non-radicular LBP. However, no clinically significant difference regarding the clinical and functional outcomes between the two two treatment protocols were detected. The literature is highly conflicting regarding the ideal treatment of acute LBP. Recent clinical guidelines prepared for the initial treatment of acute LBP recommend the use of acetaminophen as the first line of medical treatment and NSIADs as the second line of treatment, which could be added to acetaminophen in addition to general recommendations including staying active, avoiding rest, and returning to daily activities as soon as possible[1,11]. The PACE study, as a double-blind randomized study regarding the efficacy of acetaminophen for acute LBP, reported, that neither regular, nor as-needed usage of acetaminophen as a standalone treatment for acute LBP provided improved recovery, as compared to placebo[8]. In addition, they also noted, that acetaminophen as a standalone treatment for acute LBP had no effect on function, pain, quality of life, disability, sleep, and global symptom change[8]. In conjunction with the aforementioned study, we seldom prescribe acetaminophen as the initial standalone treatment for patients with acute LBP. However, acetaminophen was reported to be ineffective if used as the standalone treatment[14]. Therefore, NSAIDs were recommended to be added to acetaminophen to provide superior pain management for patients with acute LBP[10,15]. Plapler et al.[16] reported in their double-blind, randomized study, that ketorolac could provide faster pain relief compared with naproxen in patients with acute LBP. Irizarry et al.[15] reported in their randomized controlled trial conducted to compare the efficacy of ibuprofen versus ketorolac versus diclofenac, that ketorolac resulted in better pain relief and less gastric irritation compared with ibuprofen. However, there is a lack of data in the current literature regarding the efficacy of etodolac versus diclofenac combined with acetaminophen for acute LBP. This is why we also preferred to compare etodolac or diclofenac combined with acetaminophen to assess the efficacy of pain management, which was equally successful in both groups. The ideal treatment combination of LBP still constitutes a controversy. Acetaminophen was determined to have a safer profile in terms of adverse effects, as compared to NSAIDs, leading to the recommendation of it as the first -line treatment[10,17]. We similarly reported rates of adverse effects in both groups of patients, while non of them necessitated any change in the treatment protocol. Opposed to our findings, Friedman et al.[10] reported, that when combined with an NSAID, acetaminophen had no additional benefit in acute LBP. Another double blind-randomized study, conducted by Ridderikhof et al.[17] reported that 50 mg diclofenac combined with 1000 mg acetaminophen was not superior compared to diclofenac alone, while similar to our study, both treatments provided efficient pain relief after 3 days. A Cochrane review concluded that, NSAIDs were marginally better than placebo for acute LBP, whereas a combination with acetaminophen was not assessed[18].

Study Limitations

This study has some limitations. First, it is a retrospective study with a limited number of patients, which is owed to strict

inclusion criteria to have less biased data with homogenous patient groups. Another limitation is having no placebo group because of the retrospective nature of the study. Another limitation is, that despite the fact, that patients were strictly advised to stick to the drugs, that were prescribed by their physician, they might still take additional analgesics and did not inform their physician about that confounding the data provided for the study.

This study also possesses some strength. First, it is best to our knowledge the first study in the literature comparing the treatment efficacy of etodolac versus diclofenac combined with paracetamol in a highly selective group of patients with acute, non-traumatic, and non-radicular LBP, which is the leading cause of disability worldwide with no clear guideline for ideal treatment[19]. Another strength is, that it is a comparative study providing concrete data with good evidence.

CONCLUSION

This study concluded, that daily 2000 mg acetaminophen combined with 800 mg etodolac or 150 mg diclofenac could provide effective and sustained pain relief, with significant clinical and functional amelioration resulting in significant improvements in health-related quality of life, if applied under strict indication criteria to patients with acute non-traumatic and non-radicular LBP.

Ethics

Ethics Committee Approval: The study was approved by the Demiroğlu Bilim University Ethics Committee (decision no: 24345, date: 17.01.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.B., T.P., Concept: C.B., T.P., Design: C.B., T.P., Data Collection or Processing: C.B., T.P., Analysis or Interpretation: C.B., T.P., Literature Search: C.B., T.P., Writing: C.B., T.P.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Miki K, Ikemoto T, Hayashi K, Arai YC, Sekiguchi M, Shi K, et al. Randomized open-label [corrected] non-inferiority trial of acetaminophen or loxoprofen for patients with acute low back pain. J Orthop Sci. 2018;23:483-7.
2. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. Lancet. 2012;379:482-91.
3. Schreijenberg M, Luijsterburg PA, Van Trier YD, Rizopoulos D, Koopmanschap MA, Voogt L, et al. Efficacy of paracetamol, diclofenac and advice for acute low back pain in general practice: design of a randomized controlled trial (PACE Plus). BMC Musculoskelet Disord. 2017;18:56.
4. Friedman BW, Irizarry E, Solorzano C, Zias E, Pearlman S, Wollowitz A, et al. A Randomized, Placebo-Controlled Trial of Ibuprofen Plus Metaxalone, Tizanidine, or Baclofen for Acute Low Back Pain. Ann Emerg Med. 2019;74:512-20.
5. Deyo RA. Low-back pain. Sci Am. 1998;279:48-53.
6. Lambeek LC, van Tulder MW, Swinkels IC, Koppes LL, Anema JR, van Mechelen W. The trend in total cost of back pain in The Netherlands in the period 2002 to 2007. Spine (Phila Pa 1976). 2011;36:1050-8.
7. McIntosh G, Hall H. Low back pain (acute). BMJ Clin Evid. 2011;2011:1102.
8. Williams CM, Maher CG, Latimer J, McLachlan AJ, Hancock MJ, Day RO, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. Lancet. 2014;384:1586-96.
9. Gottlieb M, Njie A. Comparison of naproxen with cyclobenzaprine, oxycodone-acetaminophen, and placebo for the treatment of acute low back pain. CJEM. 2016;18:491-4.
10. Friedman BW, Irizarry E, Chertoff A, Feliciano C, Solorzano C, Zias E, et al. Ibuprofen Plus Acetaminophen Versus Ibuprofen Alone for Acute Low Back Pain: An Emergency Department-based Randomized Study. Acad Emerg Med. 2020;27:229-35.
11. Koes BW, van Tulder M, Lin CW, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. Eur Spine J. 2010;19:2075-94.
12. Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147:478-91.
13. Davies RA, Maher CG, Hancock MJ. A systematic review of paracetamol for non-specific low back pain. Eur Spine J. 2008;17:1423-30.
14. Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Abdel Shaheed C, Maher CG. Paracetamol for low back pain. Cochrane Database Syst Rev. 2016;2016:CD012230.
15. Irizarry E, Restivo A, Salama M, Davitt M, Feliciano C, Cortijo-Brown A, et al. A randomized controlled trial of ibuprofen versus ketorolac versus diclofenac for acute, nonradicular low back pain. Acad Emerg Med. 2021;28:1228-35.
16. Plapler PG, Scheinberg MA, Ecclissato Cda C, Bocchi de Oliveira MF, Amazonas RB. Double-blind, randomized, double-dummy clinical trial comparing the efficacy of ketorolac trometamol and naproxen for acute low back pain. Drug Des Devel Ther. 2016;10:1987-93.
17. Ridderikhof ML, Lirk P, Goddijn H, Vandewalle E, Schinkel E, Van Dieren S, et al. Acetaminophen or Nonsteroidal Anti-Inflammatory Drugs in Acute Musculoskeletal Trauma: A Multicenter, Double-Blind, Randomized, Clinical Trial. Ann Emerg Med. 2018;71:357-68.
18. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Nonsteroidal anti-inflammatory drugs for low back pain: an updated Cochrane review. Spine (Phila Pa 1976). 2008;33:1766-74.
19. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163-96.