Ibuprofen plus paracetamol versus ibuprofen in acute low back pain: a randomized open label multicenter clinical study

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ABSTRACT

Objective: To estimate whether combination of ibuprofen and paracetamol is more effective than ibuprofen in monotherapy, in the treatment of acute low back pain.
Methods: 80 adult patients with acute low back pain were randomized into two subgroups. In the first subgroup, 40 patients were treated with ibuprofen 400mg three times a day (TID), whilst patients in the second subgroup (n=40) were treated with a fixed-dose combination tablet of ibuprofen 200mg plus paracetamol 325mg TID, for three consecutive days. Patients were followed for another 7 days. Efficacy and tolerability of both treatment options was assessed.
Results: A statistically significant decrease in pain intensity, assessed using a visual analogue scale ($p<0.001$), as well as the 5-point Likert scale, was noticed in both subgroups of patients. However, intensity of pain on Day 4 was significantly lower in patients treated with combined therapy ($t=2.05$, $p=0.045$). Considerable improvement in mobility of the lumbar spine was noticed in both subgroups of patients ($p<0.001$), but at the end of the follow up period, finger-to-floor distance was lower in patients on combined therapy (4.7cm vs. 8.3cm, $t=2.27$, $p=0.03$). Improvement of functional ability on Day 4 and Day 10 was significant, regardless of treatment ($p<0.001$). One patient on combined therapy and two patients on ibuprofen monotherapy reported minor gastric intolerability.
Conclusion: Compared to ibuprofen monotherapy, combination of ibuprofen and paracetamol may provide faster and longer analgesia in patients with acute low back pain, with equally favorable effect on mobility and functional ability and similar tolerability.

Keywords: Analgesics; Acute low back pain; Multicenter clinical study

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INTRODUCTION

Low back pain is one of the most common health problems, with an estimated global lifetime prevalence of 38.9%[1]. It is more prevalent in countries with high-income economies, where 60-80% of the population report back pain at some point in their life[1,2], compared to countries with low- or medium-income economies[3,4]. Low back pain is more common among females and persons ages 40–80 years[1]. Back pain is one of the main reasons for work loss and a major cost for the society[5]. Depending on duration of symptoms, one can differentiate acute and chronic low back pain. Although most of patients with acute low back pain recover after 6 weeks at the latest, chronic back pain is defined as pain, which occurs for more than 3 months. According to pathophysiologic mechanisms, pain may be classified as nociceptive or neuropathic. Whilst neuropathic pain is more common in chronic lumbar syndrome, acute low back pain is mainly nociceptive. Nociceptive pain may be caused by mechanical or inflammatory stimuli. Mechanical nociceptive pain is usual in spondylosis, facet syndrome, spinal disc herniation, spondylolisthesis, vertebral fracture, kyphosis or scoliosis. Inflammatory nociceptive pain is present in spondyloarthritis, including ankylosing spondylitis, psoriatic arthritis, Reiter's disease and entheropatic arthritis[6].

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for treatment of low back pain. By inhibiting cyclooxygenase-2 (COX-2), the key enzyme re-

quired for synthesis of prostaglandin E_2 (PgE_2) in peripheral tissues, as well as in the central nervous system, NSAIDs exert their analgesic effect through peripheral and central mechanism of action. In comparison to selective COX-2 inhibitors (etoricoxib, celecoxib), non-selective NSAIDs (i.e. ibuprofen, diclofenac, naproxen etc.) equally inhibit COX-1 and COX-2 izoenzyme. By inhibiting COX-1, NSAIDs may cause more frequently side effects on the gastrointestinal tract, predominantly dyspepsia, gastric ulcers and bleedings. For these reasons, NSAIDs are contraindicated or cannot be used in therapeutic doses in patients with increased risk for upper gastrointestinal bleeding (patients older than 60 years, patients with symptoms of dyspepsia or previous gastric ulcers or erosive gastritis, patients treated with corticosteroids or anticoagulant drugs).

Mechanism of action of paracetamol is still not completely clarified. Paracetamol easily permeates the blood–brain barrier and decreases prostaglandin synthesis in the brain, by inhibiting COX-3, an alternate slice variant of COX-1, showing significant analgesic and antipyretic, but not anti-inflammatory effect[7]. On the other hand, compared to NSAIDs, paracetamol has a significantly better safety profile.

The concept of multimodal analgesia is often used in modern treatment of pain. It means the use of different classes of analgesics to provide superior pain relief (through additive or synergistic effects of drugs), with reduced analgesic-related side effects. For instance, it was shown that ibuprofen (200mg) plus paracetamol (500mg), is equally effective in pain relief after dental surgery compared to ibuprofen 400mg, but more effective compared to ibuprofen 200mg, or paracetamol 500mg, or paracetamol 1000mg[8].

The aim of the present study was to estimate whether combination of ibuprofen and paracetamol is more effective than ibuprofen in monotherapy, in the treatment of acute low back pain. Moreover, tolerability of two treatments was assessed and compared.

PATIENTS AND METHODS

Adult patients (n=80) with acute low back pain, or acute uncomplicated localized exacerbation of chronic low back pain, were included in this randomized, open-labeled, controlled, parallel-group, multicenter study. Subjects were recruited from 4 institutions specialized for treatment of patients suffering from musculoskeletal diseases (rheumatology and physical medicine and rehabilitation). In accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) consolidated guidelines, and the applicable local laws and regulatory requirements, copies of the protocol, amendments, and informed consent form (ICF) were reviewed and approved by independent ethics committees (IEC) for each investigational site. Written informed consent was obtained from all subjects prior to initiation of any procedures that were performed.

Subjects who were willing to follow all study procedures, and met all of the following criteria were eligible for the study: a) male or female aged ≥18 and ≤ 65 years, b) uncomplicated and localized acute low back pain or acute exacerbation of chronic low back pain (not radiating below the gluteal fold), c) moderate or severe pain (≥50 mm estimated on a visual analogue scale from 0 to 100 mm, 0 mm = no pain, 100 mm = worst possible pain) at least two days prior randomization without analgesics, d) aggravation of pain by movement and improvement by rest (mechanical pain). Exclusion criteria were history of hypersensitivity to aspirin or any other NSAIDs, suspicion of inflammatory, infective or neoplastic cause of pain, non-specific back symptoms related to abdominal, pelvic or thoracic pathology, sensory and/or motor deficits in lower extremities, prior surgery on the lumbar spine, history of gastroduodenal ulcer or bleeding, current anticoagulant therapy, current treatment with topical or systemic analgesics, corticosteroids, antidepressants, tranquilizers or muscle relaxants, local steroid injection for any reasons within previous 30 days, concomitant use of physical or alternative therapies to treat current episode of pain, alcohol or drug addiction or abuse, severe cardiac, hepatic or renal insufficiency, pregnancy and lactating.

Patients were randomized into two subgroups. In the first subgroup, 40 patients were treated with ibuprofen 400mg (produced by the same manufacturer) three times a day (TID), whilst patients in the second subgroup (n=40) were treated with a fixed-dose combination tablet of ibuprofen 200mg plus paracetamol 325mg (Metafex®) TID, for three consecutive days. Randomization was done using a systematic scheme, in which every other subject was assigned to the combined therapy.

ASSESSMENT OF EFFICACY

Efficacy of both treatment options was assessed by

measuring pain intensity (using a visual analogue scale –VAS and a 5-point Likert scale), mobility of lumbar spine (using the "finger to floor test") and functional ability (using the Quebec Back Pain Disability Score – QBPDS), before treatment (Day 1), on Day 4 and Day 10. The VAS is a horizontal 100 mm line, labeled with "no pain" on the left and "worst possible pain" on the right end. In order to indicate their actual intensity of pain, patients were asked to mark the line at the point, which correspond to her/his current pain. Pain intensity was obtained by measuring the distance between "no pain" and patient's mark in millimeters. Furthermore, patients assessed pain intensity on a 5-point Likert scale by answering the question "How much pain are you having now?" with "no pain", "mild pain", "moderate pain", "severe pain", or "very severe pain". The QBPDS is a self-rating scale that consists of 20 items, each graded on a 6-point scale. Scores for each question were summed to obtain the total functional disability score, ranging from no disability to total disability [9]. At the end of the follow up period (on Day 10) patients and investigators were asked to evaluate general efficacy of medication as "very satisfied", "satisfied", "reasonable", "slightly satisfied" or "not satisfied". Study design is showed in Figure 1.

RESCUE MEDICATION

Only rescue medication with up to 6 tablets of paracetamol 500mg per day was permitted, if further analgesic treatment was required from Day 4 to 10. If rescue therapy was needed during the treatment phase (Day 1-3), then rescue medication could be taken up to maximum 4 tablets of paracetamol of 500mg per day. Number of tablets and treatment period when rescue medication was taken was recorded, and compared between two subgroups of patients, as another indirect parameter of efficacy of study medications. No therapy for back-pain other than study medication was allowed during the study. No analgesics, muscle relaxant, topical preparation applied to the pain area, local injections or corticosteroids, as well as non-pharmacological procedures (i.e. physiotherapy, massage, bed rest) were allowed.

ASSESSMENT OF SAFETY

At each visit patients were asked about possible adverse events. Detailed information and investigators opinion on severity and probable relationship to the study medication was recorded. At the end of the follow up period (on Day 10) patients were asked to evaluate general tolerability of medication as "very satisfied", "satisfied", "reasonable", "slightly satisfied" or "not satisfied".

STATISTICAL METHODS

Student's T-test was used for parametric, and Mann-Whitney test for nonparametric data, to assess difference

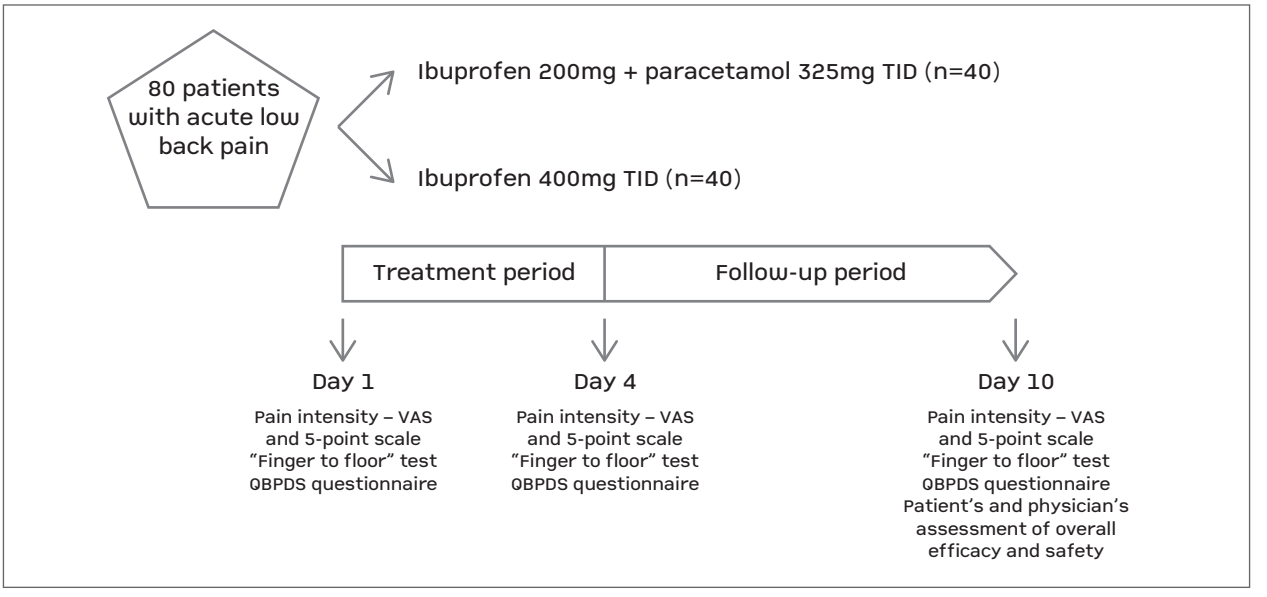

FIGURE 1. Study design.
TID – three times a day; VAS – visual analogue scale; QBPDS – Quebec Back Pain Disability Score

between mean values. Chi-squared test was applied to test difference between categories (contingency analysis). The pre-specified significance level was 0.05.

RESULTS

PATIENT CHARACTERISTICS AT BASELINE

Demographic and disease-related characteristics of patients in two subgroups at baseline are shown in Table I. Subgroups did not differ significantly in age, gender, height, weight, and body mass index, intensity of pain and mobility of the low back. Mean value of the QBPDS disability score at baseline was higher in subgroup of patients treated with ibuprofen compared to patients treated with combination of ibuprofen and paracetamol. The difference was statistically significant (p=0.04).

RESCUE MEDICATION USED IN TWO SUBGROUPS

During the treatment period (from Day 1 to Day 3), 8 patients treated with ibuprofen 400mg TID monotherapy, and 10 patients treated with ibuprofen 200mg + paracetamol 325mg TID needed and used rescue medication (z=0.54, p=0.59). There was no significant difference in number of paracetamol tablets taken in two subgroups of patients during this period (monotherapy vs. combined therapy = 39 vs. 47, X^2=0.57, p=0.57). During the follow-up period (from Day 4 until Day 10), 12 patients treated with ibuprofen, and 8 patients treated with ibuprofen+paracetamol used rescue medication (z=1.03, p=0.30). The number of additional tablets of paracetamol was significantly higher in patients treated with ibuprofen monotherapy (104 vs. 44, X^2=25.44, p<0.001).

ASSESSMENT OF EFFICACY

Only patients who did not use rescue medication (30 patients on combined treatment and 28 patients on ibuprofen monotherapy) were analyzed to assess efficacy of two treatment options.

A statistically significant decrease in pain intensity, assessed using the VAS, was noticed in both subgroups of patients (p<0.001) (Figure 2). However, intensity of pain on Day 4 was significantly lower in patients treated with combined therapy, compared to patients treated with ibuprofen monotherapy (t=2.05, p=0.045). Intensity of pain did not differ significantly between two subgroup of patients on Day 10 (t=1.43, p=0.15). Using the 5-point Likert scale as measure for pain intensity, we have found that in comparison to patients on ibuprofen monotherapy, more patients treated with ibuprofen plus paracetamol reported "no pain" or "mild pain" on Day 4 (70% vs. 46.9%), but without statistical significance (p=0.065). However, on Day 10 the difference reached statistical significance (84.4% vs. 60.7%, p=0.039). These data are shown in Table II.

Impact of treatment on mobility of the lumbar spine is shown in Figure 3. At baseline patients assigned to combined therapy had lower finger-to-floor distance then patients treated with ibuprofen monotherapy, but the difference was not statistically significant (p=0.07). A significant decrease in finger-to-floor distance was noticed in both subgroups of patients (p<0.001). At the end of the follow up period, patients treated with combined therapy had a significantly lower mean value of finger-to-floor distance than patients treated with

TABLE I. DEMOGRAPHIC AND DISEASE-RELATED CHARACTERISTICS AT BASELINE

Parameter	Ibuprofen (n=40)	Ibuprofen + paracetamol (n=40)	p
Age (yrs)	46.2 ± 11.3	47.8 ± 12.4	t=0.61, p=0.54
Gender (F/M)	15/25	15/25	NS
Height (cm)	175.5 ± 11.7	173.5 ± 10.1	t=0.79, p=0.43
Weight (kg)	76.7 ± 20.2	74.7 ± 14.2	t=0.51, p=0.61
Body Mass Index	24.7 ± 5.3	24.7 ± 3.9	t=0.11, p=0.99
Pain intensity (VAS)	66.6 ± 9.7	66.1 ± 9.6	t=0.24, p=0.81
Finger-to-floor (cm)	32.1 ± 16.2	24.8 ± 18.5	t=1.88, p=0.06
QBPDS disability score	57.5 ± 15.4	49.8 ± 18.9	t=-2.00, p=0.04

Level of statistical significance p<0.05; QBPDS – Quebec Back Pain Disability Score; VAS – visual analogue scale

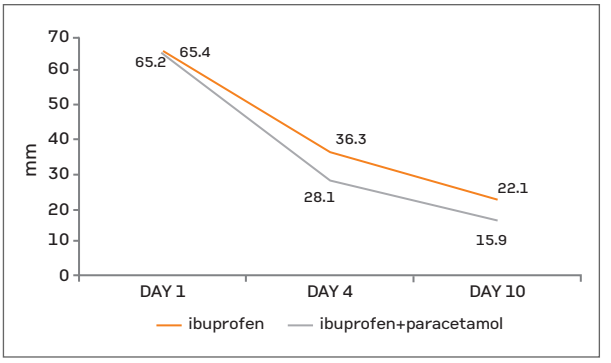

FIGURE 2. Change in pain intensity assessed using the VAS

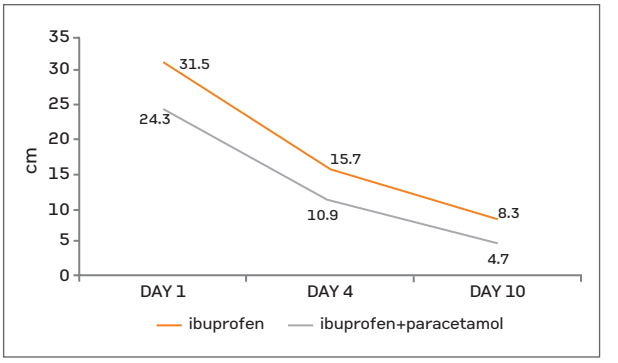

FIGURE 3. Change in finger-to-floor distance

TABLE II. PAIN INTENSITY ASSESSED BY PATIENTS IN TWO SUBGROUPS ON THE 5-POINT LIKERT SCALE

	Day 1		Day 4		Day 10	
	IBU n (%)	IBU+PARA n (%)	IBU n (%)	IBU+PARA n (%)	IBU n (%)	IBU+PARA n (%)
No or mild pain	0 (0)	1 (2.5)	15 (46.9)	21 (70)	17 (60.7)	27 (84.4)
Moderate, severe or very severe pain	40 (100)	39 (97.5)	17 (53.1)	9 (30)	11 (39.3)	5 (15.6)
Statistical analysis	NS *		X2=3.4 , p=0.065 **		X2=4.27, p=0.039**	

IBU – ibuprofen; PARA – paracetamol; NS – not significant. *Fisher's exact test; **Chi-square test, contingency table 2x2.

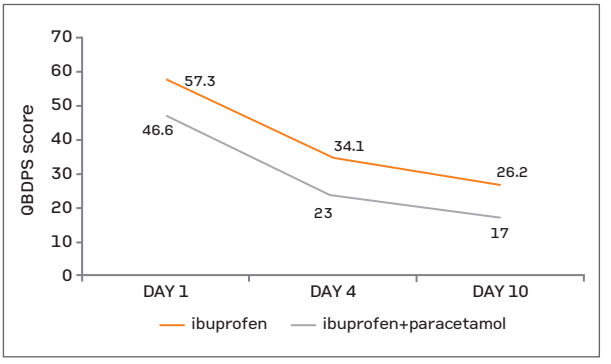

FIGURE 4. Mean Quebec Back Pain Disability Score (QBDPS) in two subgroups of patients

ibuprofen monotherapy (4.7cm vs. 8.3cm, t=2.27, p=0.03)

Decrease of QBPDS disability score on Day 4 and Day 10 was significant regardless of treatment (p<0.001). These data are shown in Figure 4. Due to considerable differences at baseline, results were not compared between two subgroups of patients.

A significant difference was noticed in patient's global efficacy assessment at Day 10 (p<0.001) - 90% of patients on combined therapy were "very satisfied" or "satisfied" with the treatment, compared to 60% of patients treated with ibuprofen monotherapy (p=0.001). Similar to patients, investigators were "very satisfied" or "satisfied" with treatment efficacy in 90% of patients on combined therapy, compared to 65% of patients on ibuprofen monotherapy (p=0.007).

ASSESSMENT OF SAFETY

The proportion of patients who valued the global treatment acceptability of ibuprofen+paracetamol with "very satisfied" or "satisfied" is greater, compared to ibuprofen monotherapy, but the difference was not statistically significant (92.5% vs. 80%, p=0.1). One patient on combined therapy and two patients on ibuprofen monotherapy reported adverse events during the follow up. All patients reported gastric intolerability (i.e. nausea, epigastric pain, heartburn). These side effects were considered as minor, but related to study medications.

DISCUSSION

Pain is generally the main complaint of individuals pre-

senting with low back disorders. One systematic review found that NSAIDs were effective for short-term relief of chronic low back pain[10]. Another Cochrane systematic review of 65 studies suggests that NSAIDs are effective for pain relief in patients with acute and chronic lumbar syndrome without sciatica. Furthermore, there does not seem to be a specific type of NSAID, which is clearly more effective than others[11]. Ibuprofen is a non-selective COX-inhibitor, developed in the 1960s and is used extensively for relief of pain and inflammation in both acute and chronic conditions. It is available over the counter in most countries, usually as 200 mg tablets. A major concern regarding the use of non-selective NSAIDs is bleeding from the upper gastrointestinal tract. Such complications are more likely to occur with chronic use[12], especially in the elderly, in patients who already have symptoms of dyspepsia, previous gastric ulcers or erosive gastritis, or concomitantly use corticosteroids or anticoagulant drugs. Moreover, there is a clear dose-dependent elevation in gastrointestinal risk in individuals taking NSAIDs[13].

The lack of significant anti-inflammatory activity of paracetamol implies a mode of action distinct from that of NSAIDs. A central analgesic effect of paracetamol is thought to be likely[7,14]. Gastrointestinal side effects are less common compared to NSAIDs, but when used in high doses, paracetamol has a recognized potential for hepatotoxicity[15]. Regarding efficacy of paracetamol in the treatment of low back pain, there are some contradictories in the literature. Guidelines recommend to use paracetamol as first line therapy in low back pain, because of relatively low risk of side effects with benefits comparable to other analgesics[10,16]. But a randomized controlled study showed that paracetamol does not affect recovery time (defined as pain score of 0 or 1 on a 0–10 pain scale sustained for 7 consecutive days) compared with placebo in low back pain[17]. Moreover, results of a recently published meta-analysis indicates that paracetamol is ineffective for reducing pain intensity and disability or improving quality of life in the short term in people with low back pain[18].

The concept of multimodal analgesia means the use of different classes of analgesics to provide superior pain relief, with reduced side effects. Combination of paracetamol and ibuprofen is an example of multimodal analgesia, since ibuprofen exerts analgesic effect through central and peripheral mode of action, whilst paracetamol is likely to be a central analgesic. A systematic review of 21 randomized controlled trials in patients with postoperative pain (n=1909) found that combination of paracetamol and NSAIDs provided superior analgesia than either agent administered alone. Seventeen of 20 studies that compared combined treatment with paracetamol alone found combined treatment to be more effective, whilst 9 of 14 studies that compared combined treatment with an NSAID alone found combined treatment to be more effective[19].

Aim of the present study was to determine efficacy and tolerability of a fixed-dose combination tablet of ibuprofen 200mg plus paracetamol 325mg (Metafex®), taken during three consecutive days, in the treatment of uncomplicated acute low back pain, compared to ibuprofen monotherapy. We have found that both treatment options are effective. However, pain reduction at the end of the treatment period (on Day 4) was larger in patients on combined therapy, then in patients treated with ibuprofen alone. But at the end of the follow-up period (on Day 10) pain relief was similar in both subgroups. This finding indicates a faster analgesic effect of the combined therapy. Moreover, a significantly higher number of rescue medications taken by patients treated with ibuprofen monotherapy during the follow-up period, suggests that analgesic effect of combined therapy lasts longer. Both treatment options improved significantly mobility of the lumbar spine. However, at the end of the follow-up, patients treated with combination ibuprofen+paracetamol had significantly lower "finger-to-floor distance" than patients treated with ibuprofen alone. Functional ability, measured using the Quebec Back Pain Disability Score, improved in both treatment groups. Finally, both patients and physicians were more satisfied with overall efficacy of combined therapy, compared to ibuprofen monotherapy.

Additive or synergistic effects of combined therapy with ibuprofen and paracetamol were shown by other authors in different diseases and conditions. For the treatment of fever in children, combination of paracetamol plus ibuprofen was superior to paracetamol or ibuprofen alone[20]. Combination of ibuprofen and paracetamol provides better analgesia than paracetamol alone after orthopedic[21] or oral surgery[8,22]. A recently published review indicated that ibuprofen plus paracetamol combinations provide better analgesia than either drug alone (at the same dose) in the treatment of postoperative pain, with a smaller chance of needing additional analgesia over about eight hours, and with a smaller chance of experiencing an adverse event[23]. On the other hand, superior analgesic effect of

combination ibuprofen plus paracetamol is less convincing in the treatment of chronic pain, for instance in chronic knee pain[24].

Overall tolerability and safety of two treatment options was similar, according to patients and physicians who participated in our study. No difference in adverse effects between combined ibuprofen + paracetamol and paracetamol or ibuprofen alone was noticed also in other studies[20-22]. A retrospective longitudinal cohort study found that the risk for upper gastrointestinal events, myocardial infarction, stroke, acute renal failure and congestive heart failure does not appear to be modified by concomitant use of ibuprofen and paracetamol compared with paracetamol or ibuprofen alone[25]. Better gastrointestinal tolerability of combined therapy probably should be expected if medications are used a longer period of time, for instance to treat a chronic painful condition. Further investigation is needed to confirm this speculation.

This study has some limitations. Since acute low back pain is a condition with very high prevalence and incidence, results on a sample of 80 patients, cannot be completely generalized to the whole population. Moreover, it was an open-labeled study, with a systematic assignment scheme, which may have impact on final results and their interpretation. However, our findings suggest that combination of ibuprofen and paracetamol may provide faster and longer analgesia in patients with acute low back pain, then ibuprofen monotherapy, with equally favorable effect on mobility and functional ability, and similar overall tolerability and safety. These findings provide good evidence, but need to be confirmed in a randomized clinical trial with a larger number of patients included.

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