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EVALUATION OF PROHYPERTENSIVE EFFECT OF MELOXICAM ON THE BLOOD PRESSURE INDICATORS

Abstract

The objective of the study is to assess the influence of meloxicam on the blood pressure level among patients with hypertension, as well as among patients without cardiovascular system diseases, in relation to its prohypertensive effect. **Materials and methods.** The *retrospective* study involved 60 patients who regularly took meloxicam in a dose of 7.5 mg/day. There were patients without cardiovascular disorder in the first group. The second group consisted of patients with hypertension, taking antihypertensive drugs. Retrospectively, the level of blood pressure, measured by the Korotkov's method, was analyzed by medical histories, before and after 3 months of taking meloxicam in both groups. The total cardiovascular risk was estimated according to the SCORE scale. **Results.** It was determined that long-term administration of meloxicam led to an increase of blood pressure levels, both in patients without diagnosed cardiovascular diseases, and in patients with hypertension and medium SCORE risk, who regularly takes antihypertensive agents to achieve target blood pressure level.

Key words: *meloxicam, NSAIDs, blood pressure, hypertension, prohypertensive effect, hypotensive therapy*

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BP — blood pressure, BAB+TD — β-blocker in combination with thiazide diuretic, DBP — diastolic blood pressure, dCCB+TD — dihydropyridine calcium channel blocker in combination with thiazide diuretic, ACEI+TD — angiotensin converting enzyme inhibitor in combination with thiazide diuretic, NSAID — non-steroidal anti-inflammatory drugs, SBP — systolic blood pressure

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the leading groups of drugs used to treat musculoskeletal diseases, particularly pain syndrome [1]. However, long-term administration of drugs of this class results in higher risk of developing adverse gastroenterological effects and cardiovascular side effects [2]. Safety issues are most relevant when selecting non-steroidal anti-inflammatory therapy. Creating a new class of COX-2 selective inhibitors helped to reduce incidence of gastropathy, but the issue of their negative impact on blood pressure and effect on antihypertensive therapy is still unresolved [3]. Safety of meloxicam with respect to negative cardiovascular effects is understudied [1]. Foreign research findings showed that this drug increased the risk of myocardial infarction by 38 % [4]. Furthermore, it is known that NSAIDs reduce the efficacy of antihypertensive therapy and aggravate the course of hypertension [5]. The most extensive randomized controlled studies are too short-term to reveal a significant difference in incidence of cardiovascular complications between meloxicam and comparators [1].

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The objective of the study was to examine the effect of meloxicam on the blood pressure level in patients with hypertension, as well as in patients without any cardiovascular diseases with respect to its prohypertensive action.

Materials and Methods

A retrospective study was carried out in the Department of Outpatient Therapy of the N. N. Burdenko Voronezh State Medical University, as well as at the Voronezh Region State-Funded Health Institution "Voronezh Municipal Outpatient Clinic No. 4". The study included 60 patients who regularly took meloxicam 7.5 mg/day. Mean age of the study subjects was 52.7±1.2 years; there were 23 males and 37 females. All the patients were divided into 2 groups. The first group included patients without any cardiovascular pathology, with medium SCORE risk (15 subjects). The second group was comprised of patients with hypertension who achieved the target BP, regularly took antihypertensive therapy for at least 3 years, with medium SCORE risk (45 subjects). Pharmacotherapy was analyzed retrospectively based on outpatient medical records. Depending on the drugs administered, patients with hypertension were divided into three subgroups. Subgroup 1 included patients receiving ACEI+TD (17 subjects), subgroup 2 — BAB+TD (16 subjects), subgroup 3 — dCCB+TD (12 subjects). Based on outpatient medical records, we performed a retrospective analysis of blood pressure level in both groups measured according to Korotkov's method using a blood pressure gauge as per clinical guidelines [6], before and after 3 months of administration of meloxicam 7.5 mg/day. Measurements were made by a primary care physician during a visit. Average blood pressure was used for the study. Cardiovascular risk was estimated as per the SCORE scale. Statistics was calculated using Microsoft Office Excel 2016 and Statistica 6.0 software. The Wilcoxon T-test was used to compare mean quantitative features from two dependent samples (before and after meloxicam therapy). Statistical significance between the groups was assessed using the Kruskal-Wallis H-test. Differences between the parameters examined were deemed statistically significant at $p < 0.05$.

Results

Blood pressure was assessed in both study groups (Fig. 1, 2).

After 3 months of meloxicam administration, increase in BP was reported in 60 % of patients in group I, in 64.7 % of group II patients receiving ACEI+TD, and in 62.5 % of patients receiving BAB+TD.

To compare the findings, the Kruskal-Wallis analysis of variance was used for several independent groups. There were statistical differences in BP level between the groups of patients ($H=98.12$ at $p=0.01$). Statistically significant differences ($p < 0.01$)were found as a result of the comparative analysis of BP before and after administration of meloxicam in groups I and II (ACEI+TD; BAB+TD). In group II of patients receiving dCCB+TD, BP increase after 3 months of meloxicam administration was statistically insignificant.

Based on the data obtained, in group I, SBP increased on average by 7.7±1.2 mm Hg, DBP — by 7.2±0.9 mm Hg ($p < 0.01$). In group II of patients receiving ACEI+TD, SBP increased on average by 10.4±1.4 mm Hg, DBP — by 8.6±0.9 mm Hg ($p < 0.01$). In group II of patients receiving BAB+TD, SBP increased on average by 9.5±0.9 mm Hg, DBP — by 8.5±1.3 mm Hg ($p < 0.01$). Blood pressure increase in both groups was explained by the administration of meloxicam, which required its replacement with a drug with a wider cardiovascular safety profile (celecoxib).

The findings are partially supported by data from other studies. I. A. Zolotovskaya et al. carried out sub-analysis of PANDA cohort study, which described the renal-associated escape phenomenon of antihypertensive therapy during administration of non-steroidal anti-inflammatory drugs, including meloxicam [7]. However, a number of literary sources contain data on its high safety [8], as well as low risk of cardiovascular complications [9]. According to some studies, it was found that meloxicam had no significant pro-hypertensive effect as compared to other NSAIDs [10].

In analyzing the data from scientific literature, it has been established that there is a discussion of several potential pathogenetic mechanisms, which explain the pro-hypertensive action of non-steroidal anti-inflammatory drugs: inhibited filtration,

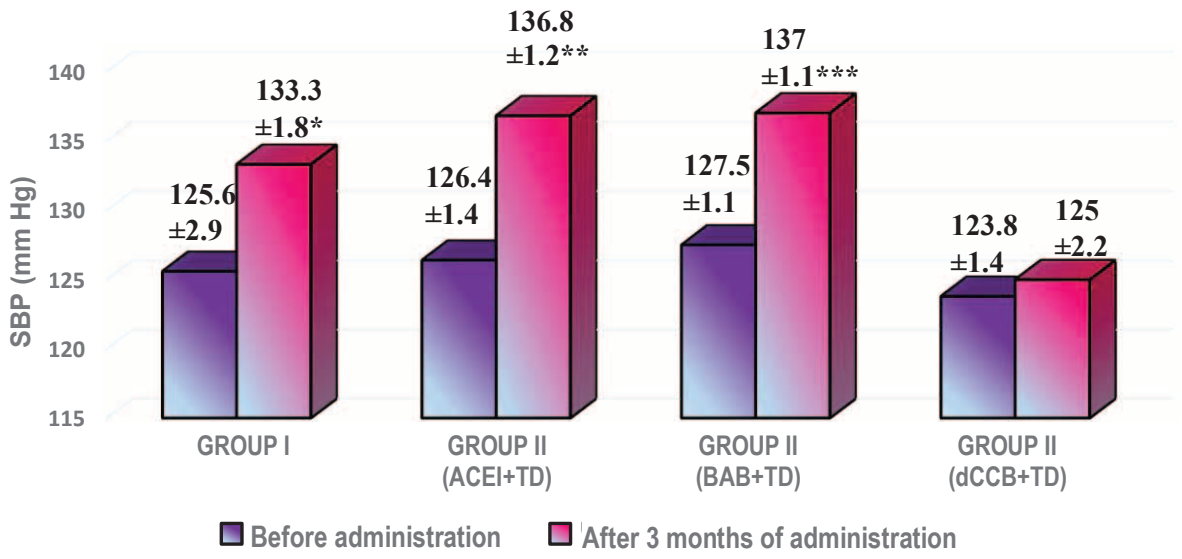

Figure 1. *Dynamics of mean systolic blood pressure (mm Hg) before and after 3 months of meloxicam administration*

*, **, *** — reliability of differences in BP level before and after meloxicam administration, p < 0.01

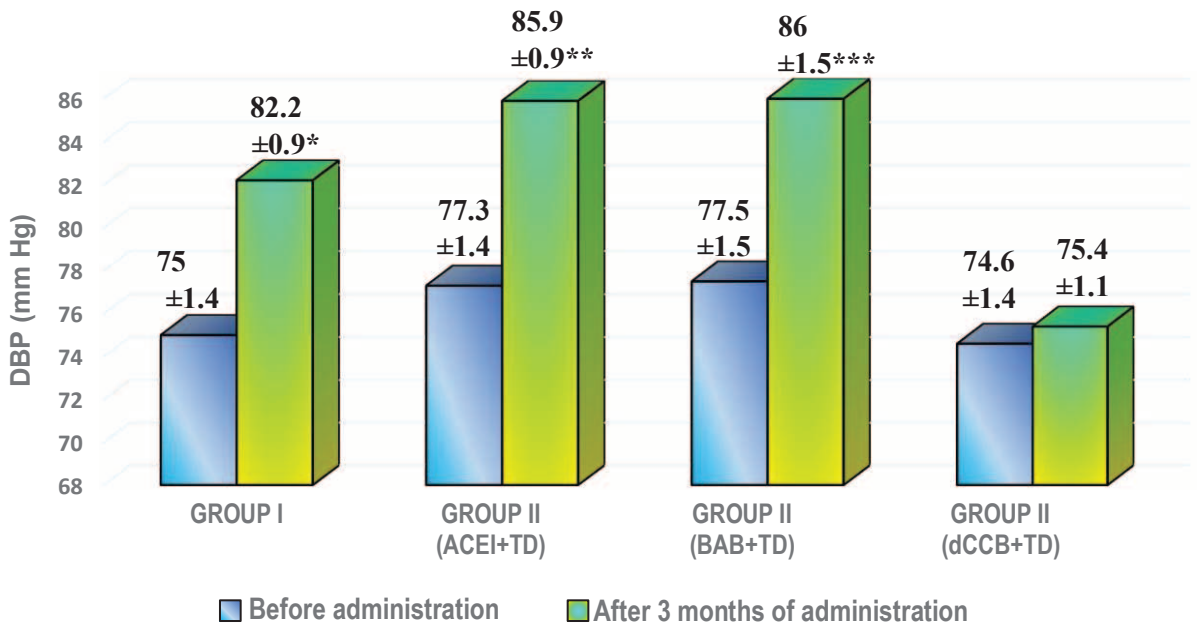

Figure 2. *Dynamics of mean diastolic blood pressure (mm Hg) before and after 3 months of meloxicam administration*

*, **, *** — reliability of differences in BP level before and after meloxicam administration, p < 0.01

enhanced tubular reabsorption and, as a consequence, reduced natriuresis; inhibited synthesis of prostaglandins (PGE2 and PGI2) with vasodilating effect, which results in increased resistance of extrarenal and intrarenal vessels, as well as enhanced release of noradrenaline from nerve terminals; higher vessel wall sensibilization to effects of circulating vasoconstrictive substances; supersecretion of endothelin I; and direct renal toxicity [11]. Considering probable differences of COX-2 inhibitors, it is important to take into account their effect on the endothelial function. In particular, celecoxib

improves NO bioavailability, endothelium-dependent vasodilatation, reduces synthesis of inflammatory cytokines, oxidative stress, thus demonstrating a positive effect [2]. Furthermore, according to foreign studies, naproxen has the lowest cardiovascular risk [12]. As per clinical guidelines, meloxicam is not an agent of choice in hypertensive patients receiving antihypertensive therapy, as well as in patients with medium SCORE risk.

Conclusions

1. Long-term administration of meloxicam resulted in increased blood pressure both in patients without proven cardiovascular diseases and in hypertensive patients who regularly received antihypertensive drugs and had achieved target BP level, with medium SCORE risk. In these cases, drugs having the minimum effect on blood pressure, such as naproxen and celecoxib (in the absence of coronary artery disease), are preferred.
2. Meloxicam reduced the efficacy of antihypertensive therapy with β-blocker in combination with thiazide diuretic, as well as combination of angiotensin converting enzyme inhibitor and thiazide diuretic, but had the least impact on antihypertensive therapy with dihydropyridine calcium channel inhibitor and thiazide diuretic. Consequently, dihydropyridine calcium channel inhibitors (particularly, amlodipine) should be deemed agents of choice to treat hypertension in patients requiring long-term non-steroidal anti-inflammatory therapy, as supported by clinical guidelines.
3. When selecting a non-steroidal anti-inflammatory drug, consideration must be given to the risk of cardiovascular and gastroenterological complications as described in clinical guidelines.
4. The safety concern of meloxicam with regard to its cardiovascular side effects requires further prospective research.

Conflict of interests

The authors declare no conflict of interests.

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