

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND HYPERTENSION – DOES AN EXEPTION CHANGE THE RULE?

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The aim of the study was to estimate the influence of nonsteroidal anti-inflammatory drugs (NSAIDs) on blood pressure, as well as the effects of these drugs on changing the response to applied antihypertensive treatment.

The study included 661 patients, with elevated blood pressure, on regular antihypertensive treatment, of both sexes (51.1% female, 48.9% male) aged 30-89 years (65.86±13.5 years); 191 patients did not use NSAIDs (first group) and 470 patients regularly used these drugs (second group): (290 patients used acetylsalicylic acid (ASA) 100 mg per day, 108 patients used ASA in combination with acetic acid derivatives (AAD) 75-100mg per day or propionic acid derivatives (PAD) 400-800mg per day, and 72 patients AAD or PAD in the above doses). From the mean values of systolic blood pressure (SBP) and diastolic blood pressure (DBP), measured in one month intervals, during the 12 months, mean arterial pressure (MAP) was calculated.

The mean values of blood pressure were 142.84±17.23mmHg for SBP, 85.08±11.16mmHg for DBP and 104.34±11.64mmHg for MAP. Value of SBP was not significantly different between the groups (I: 142.2±16.24mmHg; vs. II: 143.1±17.63mmHg, $t=0.61$, $p>0.05$), as well as MAP (I: 105.57±11.59mmHg; vs. II: 103.83±11.62mmHg, $t=1.74$, $p>0.05$). The value of diastolic blood pressure was significantly lower in patients who used NSAIDs (I: 87.25±11.3mmHg; vs. II: 84.19±11.0mmHg; $t=3.22$, $p<0.05$). There were no significant differences in the values of SBP, DBP, and MAP in relation to used type of NSAIDs ($p>0.05$).

Mean values of systolic blood pressure and mean arterial pressure in observed patients were above the target value, with no significant differences between the groups, while the diastolic blood pressure was in the normal range, but with considerably lower values in patients, who regularly used NSAIDs. Efficacy of antihypertensive treatment was independent of the applied type of NSAID. *Acta Medica Medianae* 2014;53(3):25-31.

Key words: hypertension, nonsteroidal anti-inflammatory drugs, blood pressure

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Aim

Bearing all this in mind, we have set a goal to assess the impact of use of nonsteroidal anti-inflammatory drugs on blood pressure in patients with arterial hypertension, and to assess the effects of these drugs on changing the response to applied antihypertensive treatment.

Subjects and methods

The study was conducted over a period from January to December 2013 in the General Medical Service of Health Center in Žitorađa. The study included 661 patients of both sexes, aged from 30 to 89 years, with a confirmed diagnosis of primary hypertension. All patients were on regular antihypertensive treatment, with two or three drugs (calcium channel blockers, ACE inhibitors, diuretics) for over the three years. Under the provisions of the Helsinki Declaration, they signed consent to participate in the study. The questionnaire was filled in, in addition to anamnestic and clinical management of patients, which aimed to provide information about risk factors for primary disease.

Introduction

It is considered that a long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) may be a risk factor for the onset and progression of hypertension (1). It is often the reason for the inadequate response of patients with hypertension to applied therapy.

If the number of patients with hypertension is increasing, and statistical data point to the increasing use of these drugs on the principle of "self-healing", this leads to a very important question - how to balance the treatment of these patients?

Patients were divided into two groups, based on the data if they regularly used NSAIDs or not. The first group of 191 patients did not use NSAIDs, and the second, with 470 respondents, were regularly taking these drugs. Second group of patients were divided into three subgroups, depending on the type of NSAIDs they used. In the first group, there were 290 patients that only used acetyl salicylic acid (ASA) in a dose of 100 mg per day, preferably as an antiplatelet therapy. In the second subgroup, there were 108 patients who regularly used other NSAID from the group of acetic acid derivatives (AAD) (Diclofenac) in a daily dose 75-100mg or propionic acid derivatives (PAD) (Naproxen and Ibuprofen) in a dose 400-800 mg per day, in addition to ASA. The third subset of 72 subjects used AAD or PAD in the above mentioned doses. Patients were taking nonsteroidal anti-inflammatory drugs for at least 12 months.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured during the regular monthly visits to a doctor, by sphygmomanometer Spirit CK112, after a 10-minute rest. Blood pressure values were presented as mean values of blood pressure measured monthly for a year from clinical and anamnestic processing. The mean arterial pressure was calculated from the obtained values of systolic and diastolic blood pressure by the formula:

$$MAP = (2 \times DBP + SBP) / 3.$$

Mean values of blood pressure less or equal than 139/89 mmHg were taken for well-regulated blood pressure. Blood pressure values equal or higher than 140/90 mmHg represented inadequately regulated blood pressure (2).

Data are presented in tables and graphs, structured by gender, age and type of used NSAIDs.

For data analysis we used the software package MS Excel 2007, the difference was tested by Pearson's and Student's t test.

Results

Study processed 661 patients with arterial hypertension, of whom 338 (51.1%) were female and 323 (48.9%) were male. Gender distribution of patients in groups was approximately equal; 191 patients of the first group: 101 (52.88%) female, 90 (47.12%) male, 470 patients of the second group: 237 (50.43%) female, 233 (49.57%) male, (Table 1).

Table 1. The structure of both groups of patients by gender

Gender	First group	Second group	Total
Male	90 (47.12%)	233 (49.57%)	323 (48.9%)
Female	101 (52.88%)	237 (50.43%)	338 (51.1%)
Total	191 (100%)	470 (100%)	661 (100%)

The average age of the patients was 65.86 ±13.5 years; the largest percentage of patients - 258 (37.52%) belonged to the age group of 70-79 years, and the lowest 30 (4.54%) in the group from 30 to 39 years. The number of the first group patients showed a trend of decline with age, and the number of patients of the second group increased in relation to the compared risk factor (Figure 1).

Comparison of certain NSAIDs use in subgroups, with the age of patients, showed that the majority of the first subgroup patients was between 60 and 69 years (64.33±2.75), whereas most of second and third subgroup patients was significantly older (70-89 years; 76.51±4.82), (Figure 2).

If we compare the use of certain NSAIDs in relation to gender, female patients more used drugs from the group of AAD and PAD, while the use of ASA was more prevalent in males (Figure 3).

Mean values of systolic blood pressure (142.84±17.23 mmHg), and mean arterial pressure (104.34±11.64 mmHg) in both study groups were above the recommended target values, while the value of the diastolic blood pressure was in the normal range (85.08±11.16 mmHg).

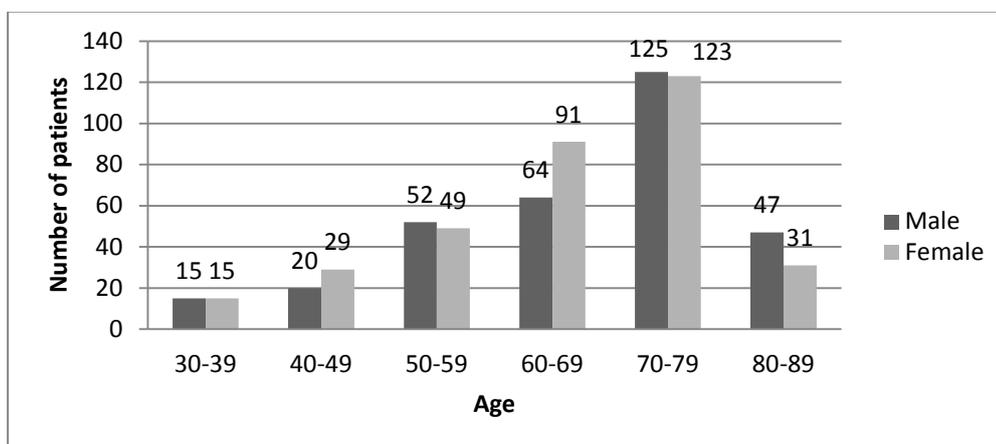


Figure 1. Age structure of patients of both genders with hypertension

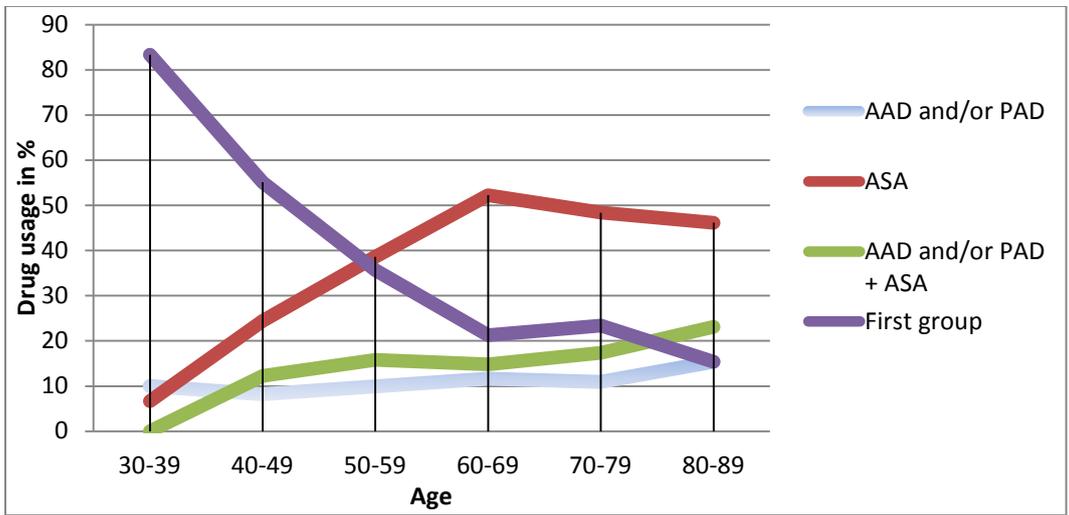


Figure 2. The ratio of the age structure of the patients of both groups and the use of NSAIDs

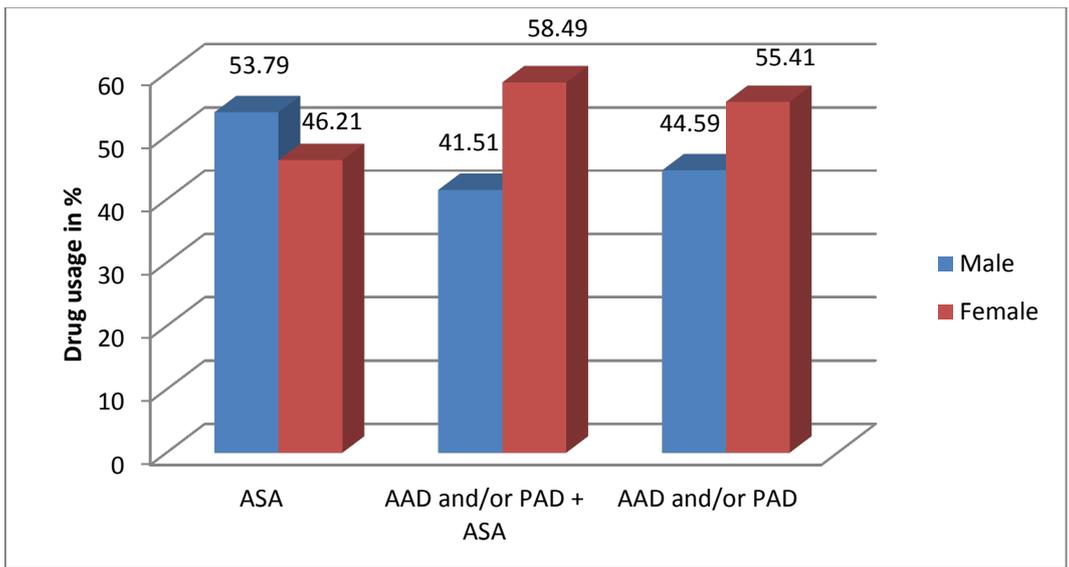


Figure 3. Use of particular classes of NSAIDs with respect to gender in percentage

Table 2. Mean values of blood pressure in the studied groups

Blood pressure	First group	Second group	t	p
SBP (mmHg)	142.2 ± 16.24	143.1±17.63	t=0.61	p>0.05
DBP (mmHg)	87.25 ± 11.3	84.19±11.0	t=3.22	p<0.05
MAP (mmHg)	105.57 ± 11.59	103.83 ± 11.62	t=1.74	p>0.05

Table 3. Observed parameters of blood pressure in relation to used NSAIDs

Blood pressure	First subgroup (I)	Second subgroup (II)	Third subgroup (III)		t	p
SBP (mmHg)	143.7±17.57	141.26±17.5	143.1±17.98	I vs. II	1.23	p>0.05
				I vs. III	0.26	p>0.05
				II vs. III	0.68	p>0.05
DBP (mmHg)	84.06±10.83	84.03±9.31	84.86±13.89	I vs. II	0.22	p>0.05
				I vs. III	0.43	p>0.05
				II vs. III	0.48	p>0.05
MAP (mmHg)	103.94±11.42	103.1±10.69	104.27±13.76	I vs. II	0.66	p>0.05
				I vs. III	0.21	p>0.05
				II vs. III	0.64	p>0.05

Table 4: The effect of therapeutic treatment of patients with hypertension depending on the use of NSAIDs

Target blood pressure values	First group (I)	Second group (II)	Total
Not reached	87 (45.55%)	211 (44.89%)	298 (45.08%)
Reached	104 (54.45%)	259 (55.11%)	363 (54.92%)
Total	191 (100%)	470 (100%)	661 (100%)

Table 5: The effect of used NSAID on the therapeutic treatment of patients with hypertension

Second group subgroups	Reached target blood pressure values	Not reached target blood pressure values	Total
First	159 (61.39%)	131 (62.09%)	290 (61.7%)
Second	64 (24.71%)	44 (20.85%)	108 (22.98%)
Third	36 (13.9%)	36 (17.06%)	72 (15.32%)
Total	259 (100%)	211 (100%)	470 (100%)

Comparison of certain NSAIDs use in subgroups, with the age of patients, showed that the majority of the first subgroup patients was between 60 and 69 years (64.33 ± 2.75), whereas most of second and third subgroup patients was significantly older (70-89 years; 76.51 ± 4.82), (Figure 2).

If we compare the use of certain NSAIDs in relation to gender, female patients more used drugs from the group of AAD and PAD, while the use of ASA was more prevalent in males, (Figure 3).

Mean values of systolic blood pressure (142.84 ± 17.23 mmHg), and mean arterial pressure (104.34 ± 11.64 mmHg) in both study groups were above the recommended target values, while the value of the diastolic blood pressure was in the normal range (85.08 ± 11.16 mmHg).

There was no significant difference in systolic blood pressure and mean arterial pressure between the first and the second group (SBP: 142.2 ± 16.24 mmHg; vs. 143.1 ± 17.63 mmHg, $t=0.61$, $p>0.05$; MAP: 105.57 ± 11.59 mmHg; vs. 103.83 ± 11.62 mmHg, $t=1.74$, $p>0.05$).

Diastolic blood pressure values were significantly lower in the second group (I: 87.25 ± 11.3 mmHg, vs. II: 84.19 ± 11.0 mmHg, $t=3.22$, $p<0.05$), (Table 2).

There were no significant differences in the values of SBP, DBP, and MAP in relation to used NSAIDs ($p>0.05$), (Table 3).

There was no significant difference between the number of patients in both groups, in relation to the achievement of target blood pressure values (140/90 mmHg); (I: 54.45%, vs. II 55.11%, $\chi^2 = 0.024$, $p>0.05$), (Table 4).

There was no significant difference in the number of patients with achieved target blood pressure compared to those who did not, within the subgroups, i.e. with a satisfactory antihypertensive effect of therapy depending on the used type of NSAIDs (I: 159 (61.39%) vs. 131 (62.09%), II: 64 (24.71%) vs. 44 (20.85%), III: 36 (13.9%) vs. 36 (17.06%), $\chi^2=1.52$, $p>0.05$), (Table 5).

Discussion

It is known that arterial hypertension is a medical condition whose incidence increases with

age, i.e. age is important risk factors for its occurrence. This also refers to the observed population with hypertension in our study, with the mean age of patients over 65 years, and more than a third of respondents in the eighth decade of life.

Allegations for the possible reasons for the high prevalence of hypertension in the elderly are increased rigidity of the blood vessels walls, endothelial dysfunction, decreased baroreceptor activity and pronounced sensitivity of this population to sodium (3,4).

Our results have shown that use of NSAIDs increased with aging, and the most commonly used drug of this group was acetylsalicylic acid. The use of other NSAIDs with mainly anti-rheumatic effect, also increased with age, but the increase was smaller compared with ASA, which corresponds to the data published by other authors (5).

However, when we compare the use of certain drugs from this group by gender of the respondents, it is evident that female patients more used NSAIDs with primary anti-rheumatic effect, alone or in combination with ASA, while the male patients predominantly used ASA. The justification for this attitude in use of NSAIDs may be related to a higher incidence of rheumatic diseases in women in older age, but also with the existence of a lower threshold for pain perception in women (6,7).

There are different opinions about use of NSAIDs and their effect on the change of blood pressure. A large number of studies showed that long-term use of these agents, increases blood pressure, especially in patients who already suffer from hypertension. It is considered that NSAIDs have a more pronounced effect on the increase in systolic blood pressure in comparison to the diastolic (8-10). This effect was not observed in the short-term use of nonsteroidal anti-inflammatory drugs.

A small number of studies denies that long-term use of NSAIDs has effects on blood pressure, as there are authors who claim that the effect of these drugs is strictly individual (11).

Recent studies have indicated that the use of low-dose ASA does not influence the level of systolic and mean arterial pressure, and lowers the diastolic pressure (12). However, the hypotensive effect of ASA does not only depend

on the applied dose and duration of administration, but also on the drug taking time. Administration of ASA in the evening lowers the normally high renin level, and at the same time lowers blood pressure, while the use of the same dose of medication in the morning does not lead to this effect (13).

In addition, it has been shown that ASA has direct effect on the blood vessel endothelial cells. Long-term administration of low-dose ASA leads to the improvement of endothelial function, increased release of nitric oxide (NO), vasodilatation, and therefore the reduction in blood pressure (14). However, the revision of large Hypertension Optimal Treatment (HOT) study, made just for the reason to assess the impact of low-dose ASA on the level of blood pressure, has not shown that a long-term use of ASA affect changes in blood pressure in patients with hypertension (15), which is found in our results.

It is known that drugs from the group of AAD and PAD decrease the synthesis of prostaglandins by inhibition of the enzyme, cyclooxygenase, thereby inhibiting their vasodilatory effects, and indirectly influence the reduction of glomerular filtration rate. On the other hand, they increase tubular reabsorption of salt and water and potentiate the activity of the renin-angiotensin-aldosterone system (16). Described mechanisms of action, of this group of drugs, are cited as the reason for the increase in SBP and DBP, not only in patients with hypertension, but also in healthy individuals.

It has been shown that drugs from this group show a more pronounced effect on the rise of blood pressure in elderly, because they primarily lead to increased retention of salt and water, to which are these individuals very sensitive. There are also opinions that extended use of NSAIDs in elderly leads to reactivation of renin system and to the occurrence of systolic hypertension. Our results showed no impact of NSAIDs on the increase in systolic and diastolic blood pressure, as well as dependence of blood pressure on the applied type of NSAIDs. However, it has been shown that diastolic blood pressure has lower values in the second group, which is consistent with the allegations of those

authors who claim that the effect of NSAIDs on the diastolic pressure is negligible. On the other hand, it should be taken into account that these were patients with primary systolic hypertension, who were using a low dose of NSAID once a day. The doses of NSAIDs in other studies were much higher (ibuprofen 1200 mg daily), and they were applied several times a day, thereby time of the drug action was prolonged (17, 18). The absence of the expected effect of these drugs on blood pressure in our patients can be explained by one-time application of the drug, as well as the relatively short time of their elimination half-life.

Available data from the literature about the effects of NSAIDs on the blood pressure level are mainly related to patients with hypertension who used single antihypertensive drug, whereas in our patients, treatment included two or three drugs from this group (19). The combination of antihypertensive drugs could have a dominant hypotensive effect in comparison to the use of a single antihypertensive drug.

It is considered that the mechanism, by which a particular group of antihypertensive drugs regulate blood pressure, may affect the inhibition of the hypertensive effect of NSAIDs (20), which has been shown in a study, in which the patients were treated with calcium channel blockers (11). Calcium channel blockers were the most commonly used antihypertensive drugs in combination with low doses of diuretics, and/or ACE inhibitors in our respondents considering age structure and characteristics of their hypertension.

Conclusion

1. Application of nonsteroidal anti-inflammatory drugs in low doses, in patients with primary arterial hypertension on regular antihypertensive treatment, showed no effect on systolic and mean arterial pressure, while diastolic blood pressure were significantly lower.

2. Changes in blood pressure did not depend on the type of applied nonsteroidal anti-inflammatory drug.

3. The effectiveness of antihypertensive treatment did not depend on the applied nonsteroidal anti-inflammatory drugs.

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NESTEROIDNI ANTIINFLAMATORNI LEKOVI I ARTERIJSKA HIPERTENZIJA – DA LI IZUZETAK MENJA PRAVILO?

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Cilj rada bio je da se proceni uticaj nesteroidnih antiinflamatornih lekova (NSAIL) na vrednosti krvnog pritiska, kao i efekti ovih lekova na promenu odgovora na primenjeni antihipertenzivni tretman.

Istraživanje je obuhvatilo 661 bolesnika sa povišenim arterijskim pritiskom, na redovnom antihipertenzivnom tretmanu, oba pola (51,1% žena, 48,9% muškaraca), starosti 30-89 godina ($65,86 \pm 13,5$ godina), od kojih 191 nije koristio NSAIL (prva grupa), a 470 (druga grupa) redovno je upotrebljavalo ove lekove (290 bolesnika acetil salicilnu kiselinu (ASK) 100 mg dnevno, 108 bolesnika ASK u kombinaciji sa derivatima sirćetne kiseline (DSK) 75-100 mg dnevno ili derivatima propionske kiseline (DPK) 400-800 mg dnevno i 72 bolesnika DSK ili DPK u pomenutim dozama). Iz srednjih vrednosti sistolnog (SKP) i dijastolnog krvnog pritiska (DKP) merenog u jednomesečnim intervalima, u toku 12 meseci, izračunavan je srednji arterijski pritisak (SAP).

Srednja vrednost SKP kod bolesnika bila je $142,84 \pm 17,23$ mmHg, DKP $85,08 \pm 11,16$ mmHg i SAP $104,34 \pm 11,64$ mmHg. Vrednosti SKP nisu se bitno razlikovale između grupa (I: $142,2 \pm 16,24$ mmHg; vs. II: $143,1 \pm 17,63$ mmHg; $t=0,61$, $p>0,05$), kao ni SAP (I: $105,57 \pm 11,59$ mmHg; vs. II: $103,83 \pm 11,62$ mmHg; $t=1,74$, $p>0,05$). Vrednost dijastolnog pritiska bila je značajno niža u grupi ispitanika koji su koristili NSAIL (I: $87,25 \pm 11,3$ mmHg; vs. II: $84,19 \pm 11,0$ mmHg; $t=3,22$ $p<0,05$). Nije bilo značajne razlike u vrednostima SKP, DKP i SAP u odnosu na korišćeni NSAIL ($p>0,05$).

Kod ispitivanih bolesnika, prosečne vrednosti sistolnog krvnog pritiska i srednjeg arterijskog pritiska bile su iznad ciljnih vrednosti, bez značajnih razlika između grupa, dok je dijastolni krvni pritisak bio u granicama normale, ali sa značajno nižim vrednostima kod bolesnika koji su redovno koristili NSAIL. Efikasnost antihipertenzivnog tretmana nije zavisila od vrste primenjenog NSAIL. *Acta Medica Medianae 2014;53(3):25-31.*

Ključne reči: arterijska hipertenzija, nesteroidni antiinflamatorni lekovi, krvni pritisak