INAPPROPRIATE USE OF ASPIRIN AND ITS CONCOMITANT USE WITH NONSTEROIDAL ANTIINFLAMMATORY DRUGS

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ABSTRACT

Background*: Our aim was to investigate the aspirin usage patterns of patients and to determine if patients are taking medication regularly and appropriately caring with the interaction with nonsteroidal anti-inflammatory drugs (NSAIDs).*

Methods*: This study was performed between March-July 2014 in primary health care clinics. Six different cities from different geographic regions of our country (Eskişehir, Kütahya, Ankara, Karaman, Rize, Sakarya) were randomly selected. Patients taking aspirin for at least one year period were included in the study on a voluntary basis. Our questionnaire was containing questions about indication, regular use of aspirin (at least three times a week for the last 3 months from the date of interview for any condition at any dose; taking aspirin or aspirin-containing products), concomitant use of NSAIDs and gastro-protective agents, duration of aspirin therapy and daily use of other drugs was asked to participants.*

Results*: Five hundred and ninety two subjects (268 females, 324 males) were included in the study. Mean age was 65.9±28.0 years. In our study population, 85.3% were taking aspirin regularly. The most commonly used daily dose of aspirin was 100 mg (79.6%). Among all aspirin-receiving participants, 45.2% were also taking an NSAID. Three hundred one patients were 65 years and older, and 49.8% of them were using aspirin concomitant with NSAIDs.*

Conclusions*: It was found that usage of NSAIDs concomitant with aspirin was high in our study population. Such finding can be the reason for recurrent cardiovascular diseases and also aspirin resistance. Patients should be informed about risks, and they should be advised not to use even any over-the-counter medications or dietary supplements without consulting to the healthcare team first*

Key words*: Aspirin, Nonsteroidal Antiinflammatory Drugs, concomitant use.*

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Introduction

As the cardiovascular diseases are the leading causes of morbidity and mortality worldwide, Aspirin is used for primary and secondary prevention and produces significant and meaningful reductions in cardiovascular events. Benefits of aspirin treatment may be achieved with doses in the range of 75 to 100 mg daily[1,2].

Forty-one percentage of adults that were 40 years and older use regular aspirin. Aspirin intake is more frequent in the female population, and 55.8% of aspirin users are women[3]. Aspirin resistance that attenuates the protective effect of aspirin was found to be high in Turkish population[4].

If expected benefit is significant, aspirin use is recommended for the prevention of MI in men between 45 to 79, for the prevention of stroke in women between 55 to 79. USPSTF (United States Preventive Services Task Force) concludes that the current evidence is insufficient to assess use of aspirin to decrease MI and stroke in men and

women 80 years or older, therefore does not recommend aspirin use in this population. The long-term use of aspirin also increases the risk of hemorrhagic stroke in men but does not appear to increase this risk in women. Side effects of aspirin (1/1000 persons-year) prevent aspirin use in low-risk patients[5].

Food and Drug Administration (FDA) stated that evidence does not support the general use of aspirin for primary prevention of a heart attack or stroke. It should be used for preventing further heart attack or stroke in patients who have already had a heart attack or stroke, or have other evidence of coronary artery disease, such as angina or a history of a coronary bypass operation or coronary angioplasty[6,7]. Although it has side effects of major bleeding events, its beneficial role in secondary prevention including cardiovascular death, myocardial infarction and stroke makes it an indispensable drug.

Patients using aspirin can take other pain relief medication such as non-steroidal anti-inflammatory drugs (NSAIDs). FDA also made some warnings about the concomitant use of NSAIDs and aspirin. According to FDA reports, NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events and administration of ibuprofen and potentially other nonselective NSAIDs, may attenuate aspirin's cardioprotective effect[8]. Concomitant use of aspirin with NSAIDs increases the risk of serious gastrointestinal adverse effect 3-4 times greater[5].

In this study, we aimed to investigate the aspirin usage patterns of patients and to determine if patients are taking medication regularly and appropriately caring with the interaction with NSAIDs.

Materials and methods

This study was performed between March-July 2014 in primary health care clinics. Six different cities from different geographic regions of our country (Eskişehir, Kütahya, Ankara, Karaman, Rize, Sakarya) were randomly selected. Patients taking aspirin for at least one year period were included in the study on a voluntary basis. Sociodemographic data including sex, age, and education were noted.

Inclusion criteria: The participants of this study were volunteering individuals that receive any form of aspirin in the last one year and with ages of 18 years and older were included. The participants were informed about the purpose of the study and voluntarily took part. We do not have any exclusion criteria in this retrospective study.

Our questionnaire was containing questions about indication, regular use of aspirin (at least three times a week for the last 3 months from the date of interview for any condition at any dose; taking aspirin or aspirin-containing products), concomitant use of NSAIDs and gastro-protective agents, duration of aspirin therapy and daily use of other drugs was filled[6]. Statistical Package for the Social Sciences (SPSS) 21.0 was used for statistical analysis. IBM Corporation released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corporation. Ethical approval was taken from University of Recep Tayyip Erdoğan University Ethics Committee for Clinical Research (Approval date/number: 03. 12,2014/45).

Results

Our study was an observational and cross-sectional study. All data were collected in 6 different centers (Ankara, Eskişehir, Kütahya, Rize, Karaman, Sakarya) which are located in different geographical regions of Turkey. The socioeconomic levels of these cities were considered as average for Turkey. The participants were informed about the purpose of the study and voluntarily took part.

A total of 592 subjects (268 females, 324 males) were included in the study. Mean age was 65.9±28.0 years. Fifty-seven (9.6%) patients were 80 years and older. Mean aspirin usage time was 5.4 ± 4.8 years. Mean total numbers of drug use were 5,0 ± 2,7.

In our study population, 85.3% were taking aspirin regularly. The most commonly used daily dose of aspirin was 100 mg (79.6%), and this was followed by 300 mg (11.5%) and 150 mg (7.8%).

The proportion of time of taking receiving aspirin in the day was found as 65.9% in the morning, 11.7% in the afternoon, 11.3% in the evening, 4.7% at night and 5.6% randomly at any time of day. Use of anticoagulant or antithrombotics beside aspirin were seen in 9.8% of patients (58 patients). Among these patients 70.7% were receiving an antithrombotic (clopidogrel or dipyridamole), 29.3% were receiving warfarin as an anticoagulant.

Ratios of indications for aspirin use were found as coronary artery disease (42.9%) (by-pass surgery, coronary stent application, post-myocardial infarc-

tion (MI) were included), hypertension (33.1%) with no cardiovascular event history, vascular thrombosis (3.5%), diabetes mellitus (DM) (3.4%) with no cardiovascular disease history and other reasons (16.3%) (heart failure, expansion of varicose veins of lower extremity, arrhythmia, valvular heart disease). Percentage of patients receiving aspirin without any reason was 0.08%. Diabetes Mellitus and hyperlipidemia like co-morbid disorders were observed in 134 (68.4%) of 196 patients receiving aspirin because of hypertension. Among all aspirin-receiving participants, 45.2% were also taking an NSAID. Three hundred one patients were 65 years and older,, and 49.8% of such users were using aspirin concomitant with NSAIDs. Relations between NSAID and aspirin receiving time were as 40.2% at any time, 34.8% with aspirin, 19.1% two hours after aspirin, 4.7% two hours before aspirin and 1.2% leaving more than 8 hours of aspirin and NSAID use.

Patients were usually taking aspirin after meals (96.1%). Among all the participants, 49.5% were regularly receiving gastro-protective agents. In patients receiving anticoagulant or antithrombotic agents along with aspirin 39.7%, those receiving NSAID along with aspirin 37.3% were not using any gastro-protective agents.

According to the analysis made by Man-Whitney U test, there was no significant relation between regular use of aspirin and education, number of diagnoses, sex, diagnosis and age and compliance to aspirin therapy. We also found increased compliance to aspirin therapy with increasing number of received drugs ($p < 0.001$) and according to power analysis; Power was found as 0.942. Statistics of regular and irregular use of aspirin were shown in Table 1 and Percentages of regular and irregular aspirin use according to sex, education status, and indications were shown in Table 2.

	Mean ± Standard Deviation Median (Q1 – Q3)		p
	Irregular Use of Aspirin	Regular Use of Aspirin	
Age	63.28 ± 10.23 63.00 (56.00-71.00)	66.32 ±30.04 65.00 (58.00-73.00)	0.127
Number of Co-morbidities	2.70 ±1.31 2.00 (2.00-4.00)	2.93 ±1.41 3.00 (2.00-4.00)	0.166
Year of aspirin usage	5.80 ±5.08 4.00 (2.00-9.00)	5.31 ±4.78 4.00 (2.00-8.00)	0.431
Number of medication	4.23 ±2.86 4.00 (2.00-6.00)	5.19 ±2.66 5.00 (3.00-7.00)	**<0.001*** **

Table 1: Statistics of regular and irregular use of aspirin.
** Mann-Whitney U test*

	Total	Irregular Use of Aspirin	Regular Use of Aspirin
Sex			
Men	268	35 (%13.1)	233 (%86.9)
Women	324	52 (%16.0)	272 (%84.0)
Education status			
≤ High school	544	82 (%14.1)	462 (%84.9)
≥ University Degree	47	5 (%10.6)	42 (%89.4)
Indications			
Hypertension	196	30 (%15.3)	166 (%84.7)
Diabetes Mellitus	20	6 (%30.0)	4 (%70.0)
Coronary Artery Disease	254	33 (%13.0)	221 (%87.0)
Thrombosis	21	4 (%19.0)	17 (%81.0)
Other	101	14 (%13.9)	87 (%86.1)

Table 2: Percentages of regular and irregular aspirin use according to sex, education status, and indications.

Discussion

In comparison with other studies aspirin compliance in our study is quite high[9,10]. In our study, 33.1% of aspirin users were hypertensive patients and 3.5% of users were diabetic patients with no cardiovascular event history. Cardiovascular disease (CVD) is the major cause of morbidity and mortality worldwide. Although the benefits of aspirin therapy in relative risk reduction for myocardial infarction, stroke, and vascular death among patients with pre-existing cardiovascular disease known as secondary prevention are well established[11-13]. The role of aspirin in primary prevention is unclear. Meta-analyses of multiple randomized trials suggested that aspirin can reduce nonfatal myocardial infarction in men with no previous history of cardiovascular disease and ischemic stroke in women[14-16]. In contrast according to recent guidelines antiplatelet therapy is recommended only in hypertensive patients with previous cardiovascular events and no antiplatelet agents licensed for primary prevention[6, 7, 17]. However, aspirin also increases the risk of gastrointestinal bleeding; therefore, the net benefit of aspirin depends on the absolute cardiovascular risk of the patient under treatment. It was reported that patients at high cardiovascular risk might potentially derive a net benefit from aspirin while those at very low risk of cardiovascular disease could experience deleterious rather than beneficial effects[18]. American Diabetes Association (ADA) modified its guidelines

stating that aspirin therapy should not be initiated in diabetes patients with low CVD risk (10-year risk <5%) because bleeding likely offsets potential benefits[19]. As a result, aspirin is not recommended for primary prevention as benefits are considered against the increased risk of hemorrhage[20].

In our study population 9.6% of aspirin users were 80 years and older. Current evidence is not sufficient enough to assess the balance of benefits and harms of aspirin for cardiovascular disease prevention in men and women 80 years or older[21].

In patients receiving anticoagulant or antithrombotic agents along with aspirin 39.7%, those receiving NSAID along with aspirin 37.3% were not using any gastro-protective agents. Gastroprotective agents especially proton pump inhibitors (PPI) may weakly interact with clopidogrel, and, therefore, potential risk of the reduction in efficacy of clopidogrel should be weighed against the gastrointestinal (GI) benefit of PPI. However, PPIs use can be recommended in patients on aspirin and clopidogrel who are at high risk of gastrointestinal bleeding[17]. According to a meta-analysis by Lanas et al., low doses of aspirin increased the risk of GI bleeding with accompanying use of clopidogrel and anticoagulant therapies, but such risk was decreased in patients who took PPIs[22]. In addition, it was stated that all combinations of warfarin, aspirin, and clopidogrel are associated with increased risk of nonfatal and fatal bleeding[23].

Another concern with aspirin use is the concomitant use of other drugs worsening gastrointestinal side effects and bleeding such as non-steroidal anti-inflammatory drugs (NSAIDs). It was suggested that NSAIDs roughly doubled the risk of bleeding in patients under aspirin treatment[12]. Among all aspirin users, 45.2% were also taking an NSAID and relations between NSAID and aspirin receiving time were as 40.2% at Anytime, 34.8% with aspirin. According to FDA reports, NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events and administration of ibuprofen and potentially other nonselective NSAIDs, may attenuate aspirin's cardioprotective effect[6,7]. NSAIDs were accused of inhibiting the clinical benefits of aspirin when regularly used[24].

One of the interesting results of our study is increased appropriate use of aspirin with multiple drug use. This effect may be explained by patients' paying further attention to drug use due to increased risk of mortality and morbidity of various medications.

Limitations of our study is an observational, cross-sectional study, and it is subjected to the factors that are associated with irregular aspirin use. Any data on potentially harmful side effects from daily long-term use of aspirin were not evaluated.

In conclusion, an addition of gastro protective agents to treatment in Aspirin and NSAIDs using patients especially 65 years and older should be revised. To minimize the risk of bleeding, the lowest recommended dose of aspirin, which is 75 mg for thromboprophylaxis, should be used. It must be kept in mind that concomitant use of with NSAIDs decreases protective effects of Aspirin. Patients should be informed about risks, and they should be advised not to use even any over-the-counter medications or dietary supplements without consulting to the healthcare team first[24].

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