Standardised tomato extract as an alternative to acetylsalicylic acid in patients with primary hypertension and high cardiovascular risk – a randomised, controlled trial

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Abstract

Introduction: Cardiovascular (CV) diseases remain a leading global cause of death. It has been proven that the use of acetylsalicylic acid (ASA) in secondary prevention reduces the CV risk, while the benefits of ASA in primary prevention have recently been debated. The aim of the study was to compare the antiplatelet effect of standardised tomato extract (STE) and ASA in hypertensive patients with high CV risk.

Material and methods: The study involved high-risk patients with arterial hypertension (AH) randomly assigned to one of two groups: group 1 included 33 patients receiving ASA and group 2 included 32 patients receiving STE. The platelet aggregation was determined using the VerifyNow analyser.

Results: After 4 weeks of ASA treatment in group 1, a statistically significant reduction in aspirin reaction units (ARU) was observed (p < 0.001). However, the obese subgroup using ASA (n = 18) did not reveal a significant decrease in ARU (p > 0.05). After 4 weeks of STE treatment in the obese subgroup (n = 14), significant declines in ARU by 8.6% (95% CI: –19.5 to –1.7%; p < 0.05) and in P2Y12 reaction units (PRU) by 7.5% (95% CI: –17.6 to 1.8%; p < 0.05) were observed.

Conclusions: The antiplatelet effect of STE in hypertensive patients may be weight dependent. The group with AH and obesity might have potentially benefitted from STE treatment.

Key words: anti-aggregation, arterial hypertension, high cardiovascular risk, obesity, diet supplement, standardised tomato extract.

Introduction

Reducing the process of platelet aggregation significantly decreases the risk of myocardial infarction and the total number of cardiovascular (CV) events [1, 2]. In patients with cardiovascular disease (CVD), antiplatelet
therapy reduces the risk of serious vascular events. Side effects, such as bleeding, are relatively small, so they are exceeded by the benefits of antiplatelet therapy in secondary prevention [3]. According to the 2013 ESH/ESC guidelines for the management of arterial hypertension, in patients with high and very high total CV risk, acetylsalicylic acid (ASA) administration should be considered in the treatment to reduce this CV risk [4]. It has already been well proven that the use of ASA in secondary prevention reduces the risk of major cardiovascular events, while the benefits of ASA in primary prevention have recently been debated [4]. According to the 2016 European Guidelines on CV prevention in clinical practice, ASA prophylaxis is not recommended in individuals who do not suffer from CVD, due to the increased risk of major bleeding [5]. Hence, it is important to look for alternative antiplatelet therapy in subjects with CV risk factors [6]. One of these alternative compounds could be a standardised extract of tomato. Standardised tomato extract (STE) has a strong multifactorial impact on platelet function: it affects the inhibition of ADP-mediated aggregation, thromboxane, collagen, von Willebrand factor, thrombin and inflammatory mediators. The effect of STE is reversible and it maintains a platelet activity level that allows aggregation in the case of vascular injury and does not cause side effects [7–15]. The available data support the thesis of the beneficial effect of the Mediterranean diet with a high content of vegetables (rich in tomatoes) and fruit due to its antiplatelet activity, which results in CV risk reduction [16–18]. It seems worthwhile to conduct a comparison of the less common STE with clinically recognised ASA. The aim of this study was to compare the antiplatelet effect of STE and ASA in hypertensive patients with high CV risk.

Material and methods

Study design

The study included 82 high-risk hypertensive patients (44 men and 38 women), aged 28–74 years, and it was conducted between July 2015 and February 2017 in the Department of Hypertension at the University of Medical Sciences in Poznan. Seventeen patients withdrew their consent during the study. The study was approved by the Local Bioethical Committee of Poznan University of Medical Sciences (permission no. 377/15) and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients undersigned written consent forms. The study was listed in the Registration and Results System and obtained the following ClinicalTrials.gov ID: NCT03206944. Patients with primary AH and high and very high total CV risk were randomised in a blinded fashion (the sealed envelope method) to one of two groups (4). Group 1 ASA included 33 patients who received ASA at a dose of 75 mg in the morning. Group 2 STE included 32 patients receiving STE (ZAAX, Sequia, Poland) at a dose of 213 mg orally in the morning. The patients had two visits, a baseline one and after...
4 weeks of treatment, according to the scheme presented in Figure 1. There were no changes in the concomitant treatment (lipid-lowering, anti-hypertensive and antidiabetic) and no non-steroidal anti-inflammatory drugs (NSAID) were taken during the study.

Exclusion criteria for the study were as follows: secondary hypertension, white coat hypertension, coronary artery disease, myocardial infarction, re-vascularisation, stroke, transient ischaemic attack (TIA), peripheral arterial disease (PAD), congestive heart failure, chronic kidney disease (glomerular filtration rate (GFR) < 30 ml/min), addiction to alcohol and psychotropic substances, active cancer, congenital or acquired haemostatic disorder, and use of ASA, STE, or other antiplatelet agents within 14 days prior to the study. Additional exclusion criteria for group 2 were hypersensitivity to acetylsalicylic acid and active gastric or duodenal ulcers.

Blood pressure measurements

In all the patients, during each visit, clinical blood pressure (BP) measurements were performed three times at rest, in a supine position, in standard conditions, and using an upper-arm blood pressure monitor (Omron 705IT). Ambulatory 24-hour blood pressure measurements (ABPM) were carried out using an A&D 24-hour ambulatory peripheral blood pressure monitor. The frequency of measurements was every 15 min between 7:00 and 22:00, and every 30 min between 22:00 and 7:00.

VerifyNow test procedure

Whole blood samples were collected at 1–4 h from a peripheral vein using a 21-gauge needle in a partial fill 3.2% citrate vacuum collection tube, after the ingestion of a morning dose of ASA or STE.

The VerifyNow System is a point-of-care turbidimetry-based optical detection system that measures platelet-induced aggregation (Accumetrics Inc., USA). In the study, two types of VerifyNow test kits were used: VerifyNow Aspirin Test and VerifyNow P2Y12. Platelet function was measured in ABPM were significantly higher after 4 weeks of therapy. At baseline, the BP values measured in ABPM were significantly higher than in the ASA group (Table I).

Statistical analysis

Statistical analyses were performed with Statistica, version 12.5. (StatSoft, USA). Since the tested data did not meet the assumption of Gaussian distribution (evaluated with the Shapiro-Wilk method), non-parametric methods were applied. The Wilcoxon signed-rank test was used for evaluation of the differences between the initial values and the values obtained after the treatment for factors of body weight composition, blood pressure, and platelet aggregation. To evaluate the differences and correlations between the two independent groups the Mann-Whitney U test and Spearman’s rank correlation coefficient (Rs) were used respectively. The data presented in the figures and tables included median and interquartile ranges. A p-value < 0.05 was considered significant.

Results

The detailed demographic data of the studied groups are presented in Table I. There were no statistically significant differences (p > 0.05) between these groups for age and body mass index (BMI) (Table I). The baseline blood and lipid profile parameters in both groups did not show statistically significant differences (p > 0.05), except for a higher triglyceride (TG) concentration in the STE group (Table II; p < 0.05). No changes in these parameters in either of the groups were observed after 4 weeks of therapy. At baseline, the BP values measured in ABPM were significantly (p < 0.05) higher in the STE group than in the ASA group (Table I).

After 4 weeks of treatment in the ASA group, there was a statistically significant reduction in ARU values measured by the VerifyNow Aspirin test (p < 0.001; Figure 2). Sex and age had no significant impact on ARU values (p > 0.05). In the STE group, there were no statistically significant differences
in ARU values between baseline and after 4 weeks of STE treatment ($p > 0.05$; Figure 2). However, it was found that the use of STE in obese patients significantly ($p < 0.05$) decreased the ARU values by 8.6% on average (95% CI: –19.5 to –1.7%) (Figure 3). The STE group was further analysed using the VerifyNow P2Y12 test at the start and after 4 weeks of treatment. In the STE group, there was no statistically significant effect of the extract intake on PRU values. The median PRU values at the start and end of the study were 228 (range: 149–309) and 232 (range: 141–290), respectively. However, after 4 weeks of STE treatment in the obese subgroup, a significant decrease ($p < 0.05$) in the PRU values by 7.5% on average (95% CI: –17.6 to 1.8%) was observed (Figure 4).

There was a statistically significant negative correlation ($R_s = 0.41$, $p < 0.05$) between the change in PRU values and BMI in the STE group (Figure 5). Side effects, such as bleeding, were not recorded in either of the groups. In the presented analysis, ASA resistance was confirmed in 24.2% of patients (8 from 33 patients), all characterised by BMI > 30 kg/m$^2$.

**Discussion**

At present, there is a tendency to reduce the role of ASA in primary prevention and to limit the application of ASA in patients with high CVD risk. This is primarily due to the increased risk of bleeding in patients taking ASA [3]. The role of platelets in the formation and progression of atherosclerotic lesions and the development of restenosis after endovascular procedures are well known and documented. The endothelial damage leads to exposure of collagen fibres and plaque adhesion initiating atherosogenesis [19]. A meta-analysis of many randomised clinical trials showed a 25% reduction in the risk of major vascular events with the use of

**Table I.** Demographic characteristics of patients treated with ASA or STE at visit 1 (median and interquartile range)

| Parameter                        | Group 1 (ASA) ($n = 33$) | Group 2 (STE) ($n = 32$) |
|----------------------------------|--------------------------|--------------------------|
| Female/male, n                   | 19/14                    | 8/24                     |
| Age [years]                      | 53 (44–63)               | 54.5 (45.0)              |
| BMI [kg/m$^2$]                   | 31.1 (27.4–36.3)         | 27.7 (25.3–33.4)         |
| BMI group, n:                    |                          |                          |
| Normal (18.5–24.9 kg/m$^2$)      | 5                        | 6                        |
| Overweigh (25.0–29.9 kg/m$^2$)   | 9                        | 11                       |
| Obesity (> 30.0 kg/m$^2$)        | 18                       | 14                       |
| Smokers, n                       | 4                        | 4                        |
| SBP24* [mm Hg]                   | 125.0 (120.0–137.0)      | 137.5 (122.0–143.0)      |
| DBP24* [mm Hg]                   | 74.0 (70.0–81.0)         | 80.5 (74.0–88.0)         |
| MAP24* [mm Hg]                   | 91.0 (87.0–99.0)         | 99.0 (91.0–107.0)        |
| HR24 [/min]                      | 70.0 (64.0–77.0)         | 71.0 (66.0–76.0)         |
| Concomitant lipid-lowering therapy, n | 29                       | 28                       |
| Concomitant antidiabetic therapy (metformin), n | 2                        | 2                        |
| Concomitant therapy (anti-hypertensive), n: | 2.9                      | 3.2                      |
| Diuretics/aldosterone antagonists | 25/8                     | 22/6                     |
| Angiotensin-converting enzyme inhibitors | 24                      | 23                       |
| Angiotensin II receptor antagonists | 15                      | 13                       |
| Calcium antagonists              | 11                       | 10                       |
| β-blockers                       | 17                       | 16                       |
| α-blockers                       | 1                        | 2                        |
| ARU                              | 574 (541–628)            | 582 (533–604)            |

*Statistically significant difference between group 1 (ASA) and group 2 (STE) ($p < 0.05$, Mann-Whitney U test). SBP24 – 24h systolic blood pressure, DBP24 – 24-h diastolic blood pressure, MAP24 – 24-h mean blood pressure, HR24 – heart rate in 24 h, BMI – body mass index (kg/m$^2$), ARU – aspirin reaction units.
antiplatelet agents. This is the basis for the wide use of platelet aggregation inhibitors to lower the cardiovascular mortality rate [20]. In industrialised countries, cardiovascular mortality is lowest in the Mediterranean population because of their consumption of a proper diet [21–23]. In the literature, it is emphasised that the main components of this cardioprotective diet are tomatoes and their products with antiplatelet function [24–27]. The bioactivity of tomato extract has been confirmed in both *in vitro* and *ex vivo* models [10, 28–33]. The STE could be a beneficial food supplement for adults due to multiple actions, such as anti-aggregation, antihypertensive, antidiabetic, antioxidative, antiangiogenic, and protective endothelial effects [13]. Therefore, its use may be indicated in patients with high and very high cardiovascular risk, who are hypersensitive or resistant to ASA. It may also be recommended in subjects who have contraindications for the use of ASA or who have a high risk of complications after antiplatelet treatment (peptic ulcer, gastrointestinal bleeding, and use of medications that increase the risk of bleeding). The study emphasises that target populations, in which STE might be considered, are obese and hypertensive patients with complications or organ damage. The obese patients show results of many experiments show dose-dependent inhibition of platelet aggregation at 8–23% after administration of extract of tomato [10, 29].

Table II. Blood test parameters (median and interquartile range) for group 1 (ASA) and group 2 (STE) at baseline

| Parameter | Group 1 ASA | Group 2 STE |
|-----------|-------------|-------------|
| GLC [mmol/l] | 5.6 (5.1–6.3) | 5.8 (5.2–6.2) |
| TG [mmol/l] | 1.0 (0.8–1.4) | 1.6 (1.1–2.2) |
| LDL [mmol/l] | 2.8 (2.3–3.4) | 2.5 (2.1–3.3) |
| TC [mmol/l] | 4.9 (4.3–5.2) | 5.1 (4.0–5.6) |
| HDL [mmol/l] | 1.3 (1.1–1.7) | 1.2 (1.0–1.5) |
| Na [mmol/l] | 141 (139–143) | 142 (140–143) |
| K [mmol/l] | 4.3 (4.1–4.6) | 4.2 (3.9–4.6) |
| Serum creatinine [μmol/l] | 79.0 (70.9–87.9) | 92.1 (69.9–111.5) |
| Uric acid [μmol/l] | 271.0 (196.0–312.0) | 313.0 (251.0–348.6) |
| HGB [mmol/l] | 9.0 (8.7–9.4) | 9.3 (8.8–10.0) |
| HCT [l/l] | 0.4 (0.4) | 0.4 (0.4–0.5) |
| PLT [10–9/l] | 241.0 (189.0–276.0) | 223.0 (204.0–257.5) |

*Statistically significant difference between group 1 (ASA) and group 2 (STE) (p < 0.05, Mann-Whitney U test). GLC – glucose, TG – triglyceride, LDL – LDL cholesterol, TC – total cholesterol, HDL – HDL cholesterol, HGB – haemoglobin, HCT – haematocrit, PLT – platelets.

Figure 2. Aspirin reaction units (ARU) (median and interquartile range) in the ASA group and in the STE group at baseline and after 4 weeks of treatment. The decline in the ASA group was statistically significant according to the Wilcoxon signed-rank test. The ARU values differed significantly between ASA and STE groups according to the Mann-Whitney U test.

Figure 3. Aspirin reaction units (ARU) (median and interquartile range) in the ASA group (A) and the STE group (B) at baseline (white bars) and after 4 weeks of treatment (grey bars) depending on body mass index (BMI). Reported p-value for Wilcoxon signed-rank test. The ARU values did not differ significantly across BMI subgroups in both ASA and STE groups (p > 0.05 in both cases; Kruskal-Wallis test).
a decreased response to ASA. This may be due to a higher incidence of ASA resistance in this group. The study indicated that obese individuals might need a higher dose of ASA, administration of another antiplatelet agent, or one-time administration of statins to increase the effectiveness of ASA [34]. The above facts indicate that a decision to include ASA in the primary prevention is becoming more difficult and its use should be balanced. Consequently, this approach creates a therapeutic gap, which in many situations can be filled by other antiplatelet agents. This may be the basis for the search for new antiplatelet agents that will not have as many restrictions as ASA, such as STE.

The present study has revealed that the administration of ASA significantly decreases ARU values (21% reduction after 4 weeks of treatment). The use of STE only in the obese subgroup significantly decreased ARU values by 8.6%. The antiplatelet effect of the STE was also evaluated in the second method, assessed by the VerifyNow P2Y12 test. A significant decrease in the PRU values after 4 weeks of STE treatment in the obese subgroup was also observed. In the present study, only two pathways for platelet activation were studied using the VerifyNow Aspirin Test and VerifyNow P2Y12. It is known that STE affects multiple mechanisms of platelet aggregation (ADP, collagen, von Willebrand factor, thrombin, inflammatory mediators, P-selectin, and platelet factor 4) [7]. The verification of all possible routes of antiplatelet action of STE was beyond the scope of this analysis. It was shown that three hours after STE administration, there was a significant reduction of ADP-induced platelet aggregation in 97% of the studied patients in one randomised controlled trial of 90 patients (aged 45–70 years) [29]. This may support the idea that this extract, as a functional food or food supplement, due to its anti-aggregation and anticoagulant properties, could be helpful in the primary prevention of cardiovascular events in patients with high CV risk [13].

It has been demonstrated that the effect of STE on platelet activity is probably weight-dependent, but the study group was too small to draw definitive conclusions. The results may suggest the need for individualisation of antiplatelet therapy according to BMI. One reason for ASA ineffectiveness in patients with high BMI is the phenomenon of ASA resistance. According to various laboratory methods, the presence of ASA resistance in patients with stable coronary disease ranges from 4% to 60% [31].

In the present analysis, aspirin resistance was confirmed in 24% of patients (8 from 33 patients), everyone with BMI > 30 kg/m². Using multiple electrode aggregometry and VerifyNow Larsen et al. found that a high BMI was an independent determinant of increased platelet aggregation, which is consistent with the results found in healthy individuals, as well as in patients with ischaemic heart disease [31–33]. Obesity affects pharmacokinetics on the basis of changes in
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the volume of distribution, regional blood flow, and mechanisms of renal and liver elimination [35–37]. The evidence suggests that obesity, regardless of additional comorbidities, may be associated with decreased efficacy of antiplatelet agents [38]. This conclusion can be partially explained by the faster inactivation of ASA due to the modification of obesity-related pharmacokinetic mechanisms [39]. Elevated leptin levels in obesity may reduce the effectiveness of ASA by increasing pro-thrombotic effects [40]. In addition, the present study revealed a significant negative correlation between change in PRU values and BMI (Rs = –0.41, p < 0.05) in the STE group. This correlation indicates that the greater the weight of patients is, the greater is the receptor P2Y12 inhibition (Figure 5). The obtained results are different from those published by O’Kennedy et al., who reported no such correlation [13]. Different results show the need to verify the response to ASA in this group of patients and its dependence on BMI especially. Even though the findings of the study are promising, there are certain limitations that need to be recognised. Firstly, the conducted investigation was a single-centre study, including only a small population of hypertensive patients with high cardiovascular risk. Additionally, only two types of tests for assessing platelet function were used: the VerifyNow Aspirin Test and the VerifyNow P2Y12 Test. Verification of all possible routes of antiplatelet action of STE was beyond the scope of this analysis. A future randomised study with clinical end-points would be required to substantiate our findings.

In conclusion, the present data demonstrate that the effect of antiplatelet agents in patients with hypertension and with high cardiovascular risk is heterogeneous and may be weight dependent. Patients with AH and obesity constitute a group that could potentially benefit from STE treatment. STE, which contains cardioprotective components, could be a beneficial agent in the prevention of thrombosis and inflammation associated with plaque activation in hypertensive and obese patients. The present data suggest that STE may be appropriate for use as a dietary antiplatelet agent in the primary prevention of cardiovascular diseases.

Conflict of interest
The authors declare no conflict of interest.

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