

Aspirin improves the cognitive functions in patients with inflammatory status and asymptomatic peripheral artery disease

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Rezumat

Proteina C reactivă este un factor independent de predicție pentru AVCm sindromul coronarian acut și boala arterială periferică, toate manifestări secundare aterosclerozei. Se presupune ca în aproape toate tipurile de demență sunt de fapt demențe mixte, în care componenta vasculară nu poate fi neglijată. Indivizii cu boală arterială periferică și status inflamator prezintă un risc crescut de a prezenta deficit cognitiv.

Scopul acestei lucrări este de a dovedi posibila influență a tratamentului cu aspirină asupra statusului cognitiv la pacienții cu nivel ridicat de PCR și boală arterială periferică.

Abstract:

C reactive protein (CRP) is an independent predictor for stroke, acute coronary syndromes (ACS) and peripheral arterial disease (PAD), linked to atherogenesis. Now is suggested that almost all types of dementia are mixed dementia. Patients with PAD and inflammatory status have a higher risk to develop cognitive impairment.

The purpose of this research paper is to study if there is an improvement in the cognitive functions in subjects with inflammatory status and asymptomatic PAD that are following aspirin treatment as primary cardiovascular protection.

BACKGROUND

C-reactive protein (CRP) is a biomarker of inflammation, and elevated levels are recognized as an important mediator of cardiovascular disease (CVD) risk. Many observational studies have shown the predictive value of elevated

CRP for cerebral, coronary, and peripheral vascular diseases.

The use of aspirin as an antiplatelet agent in the primary and secondary prevention of cardiovascular events is well established. In contrast, the anti-inflammatory effects of low-dose aspirin (75-325 mg), including its effect on CRP levels, are less clear. Among several small clinical trials that evaluated the effect of aspirin on CRP levels, results have varied. In the large Physicians' Health Study, however, low-dose aspirin was shown to reduce the risk of a first myocardial infarction (MI), particularly among men with elevated baseline CRP levels.

Low doses of aspirin that markedly inhibit platelet COX-1 activity, as manifested by a profound decline in platelet-derived serum Tx B₂ concentrations, have no detectable effect on serum CRP levels in healthy men and women.

Recently it has been proposed that inflammation plays an important role in the pathogenesis of atherosclerotic cardiovascular diseases. Furthermore, elevated serum concentrations of C-reactive protein (CRP), a marker of inflammation, portend an increased subsequent risk of myocardial infarction

(MI), stroke and symptomatic peripheral vascular disease in healthy men and women. In men, low-dose aspirin (ASA) therapy appears to have its greatest protective effect against MI when serum CRP levels are relatively high.

Two recent prospective studies have examined whether low-dose ASA treatment reduces serum CRP levels. When administered 300 mg ASA per day for three weeks or placebo to 40 men with coronary artery disease the serum CRP levels were significantly lower after ASA therapy than they were after placebo.

CRP, a member of the pentraxin family, is the prototypic marker of inflammation. In addition to being a risk marker for atherosclerosis, it promotes tissue factor release from monocytes, phagocytosis and shedding of cell adhesion molecules. Furthermore, CRP co-localizes with complement in the atherosclerotic lesion. C-reactive protein is one of many proteins produced by the liver in response to cellular injury due to trauma, infarction or infection. Release of CRP from the liver into the circulation after cell injury is stimulated by the proinflammatory cytokine interleukin-6 (IL-6). Obesity is also associated with elevated IL-6 and CRP levels. Thus, CRP is a possible link between obesity and atherosclerotic vascular disease. They were in their gender-matched younger counterparts, this was probably related to other factors, such as BMI, than it was to age per se.

The effects of aspirin are complex. First it should be discussed the suppression of prostaglandins and thromboxanes. Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of the cyclooxygenase (COX) enzyme. Cyclooxygenase is required for prostaglandin and thromboxane synthesis. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the COX enzyme. This makes aspirin different from other NSAIDs (such as diclofenac and ibuprofen), which are reversible inhibitors.

Low-dose, long-term aspirin use irreversibly blocks the formation of thromboxane A₂ in platelets, producing an inhibitory effect on platelet aggregation. This anticoagulant property makes aspirin useful for reducing the incidence of heart attacks. 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A₂ release provoked acutely, with the prostaglandin I₂ synthesis being little affected; however, higher doses of aspirin are required to attain further inhibition. Prostaglandins are local hormones produced in the body and have diverse effects in the body, including the transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation. Thromboxanes are responsible for the aggregation of platelets that form blood clots. Heart attacks are primarily caused by blood clots, and low doses of aspirin are seen as an effective medical intervention for acute myocardial infarction. The major

side-effect of this is that because the ability of blood to clot is reduced, excessive bleeding may result from the use of aspirin.

On the other hand aspirin irreversibly inhibits COX-1 and modifies the enzymatic activity of COX-2. Normally COX-2 produces prostanoids, most of which are pro-inflammatory. Aspirin-modified COX-2 produces lipoxins, most of which are anti-inflammatory. Newer NSAID drugs called COX-2 selective inhibitors have been developed that inhibit only COX-2, with the intent to reduce the incidence of gastrointestinal side-effects. However, several of the new COX-2 selective inhibitors, have been withdrawn recently, after evidence emerged that COX-2 inhibitors increase the risk of heart attack. It is proposed that endothelial cells lining the microvasculature in the body express COX-2, and, by selectively inhibiting COX-2, prostaglandins (specifically PGI₂; prostacyclin) are downregulated with respect to thromboxane levels, as COX-1 in platelets is unaffected. Thus, the protective anti-coagulative effect of PGI₂ is decreased, increasing the risk of thrombus and associated heart attacks and other circulatory problems. Since platelets have no DNA, they are unable to synthesize new COX once aspirin has irreversibly inhibited the enzyme, an important difference with reversible inhibitors.

Also aspirin presents additional mechanisms at least three additional modes of action. It uncouples oxidative phosphorylation in cartilaginous (and

hepatic) mitochondria, by diffusing from the inner membrane space as a proton carrier back into the mitochondrial matrix, where it ionizes once again to release protons. In short, aspirin buffers and transports the protons. When high doses of aspirin are given, aspirin may actually cause fever due to the heat released from the electron transport chain, as opposed to the antipyretic action of aspirin seen with lower doses. Additionally, aspirin induces the formation of NO-radicals in the body, which have been shown in mice to have an independent mechanism of reducing inflammation. This reduced leukocyte adhesion, which is an important step in immune response to infection; however, there is currently insufficient evidence to show that aspirin helps to fight infection. More recent data also suggests that salicylic acid and its derivatives modulate signaling through NF- κ B. NF- κ B is a transcription factor complex that plays a central role in many biological processes, including inflammation.

Peripheral arterial disease (PAD) is a common result of atherosclerosis. Upon suspicion of PAD, the first-line study is the ankle brachial pressure index which is a measure of the fall in blood pressure in the arteries supplying the legs.

A reduced ankle brachial index (ABI) (less than 0.9) is consistent with PAD. Normal range for ABI is 0.9 - 1.3. Abnormal values range from values less than 0.9 for incipient PAD to $0.5 < \text{ABI} < 0.8$ for moderate PAD and $\text{ABI} < 0.5$ for severe PAD with covert signs and symptoms such as claudication. Also an $\text{ABI} > 1.3$ signifies a PAD in the arms.

There is good evidence that the presence of symptomatic cardiovascular disease, including myocardial infarction (MI) and stroke, as well as peripheral arterial disease (PAD), is associated with cognitive impairment in older age.

There is also some evidence that cardiovascular risk factors such as smoking, high cholesterol, and hypertension are associated with age-related cognitive impairment.

Whether this is a causal relationship, and whether addressing these risk factors leads to a reduction in cognitive decline, is unknown. However, many individuals with significant atherosclerotic disease remain symptomatic in terms of coronary or cerebrovascular events, but have cognitive impairment.

PURPOSE

The purpose of this study is to verify if there is an improvement in cognition in the patients with high CRP levels, asymptomatic PAD and mild cognitive impairment when ongoing low dose aspirin therapy (75-325mg/day) compared to thienopyridines antiplatelet therapy, as primary prevention for ACS, when associated to pramiracetmum 1200mg/day.

MATERIAL AND METHOD

There were included 67 subjects admitted in the ER of the Neurology Clinic of the Arad County Clinical Hospital during 2006 – 2009 fulfilling the following criteria: age over 60, CRP>1 mg/L, ABI<0.9, with mild cognitive impairment and no history of cardiovascular or cerebrovascular disease.

There were measured the plasma CRP levels, the ABI (Doppler measurement) and cognitive status (MMSE).

The study group was divided in two arms: aspirin and thienopyridines arm, as follows:

32 of the subjects were set on aspirin therapy (75-325mg/day)

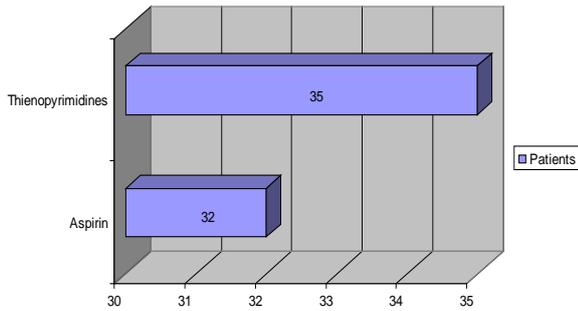
35 on thienopyridines, as they presented higher risk for ACS, or were aspirin intolerant.

Both arms were administered piracetamum 1200mg a day.

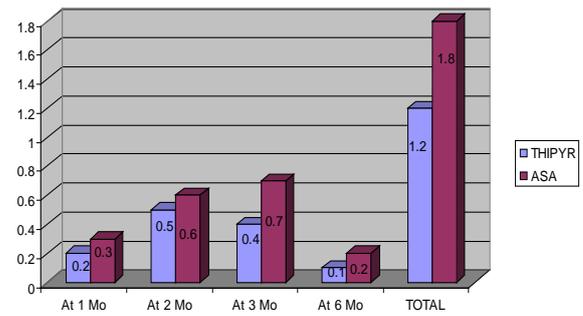
RESULTS

The average age of study group was 62.3 years. At admission, the MMSE mean value was 25.3 (n=67). The 32 subjects set on aspirin treatment had an initial MMSE median score of 25.2, while those on thienopyridines 24.7. After one month of evolution, the mean MMSE score improved by 0.3 points in aspirin group, and with 0.2 in the thienopyridines group. At two months of evolution, those in the aspirin arm had a mean MMSE score of 26.1, while the other arm 25.4. At three months, the aspirin arm had a MMSE median score of 26.9 and the thienopyridines arm 25.8. After six months of evolution, both arms showed a small increase in mean MMSE score, +0.2 in aspirin and +0.1 in thienopyridines arm in the last three months. On the whole there is an increase with +1.8 points on MMSE score for aspirin patients and +1.2 points gained for thienopyridines arm. The best improvement on the MMSE was during the third month for the aspirin arm, while both arms showed no significant improvement in the last three months of surveillance. These data are illustrated in the below graphs.

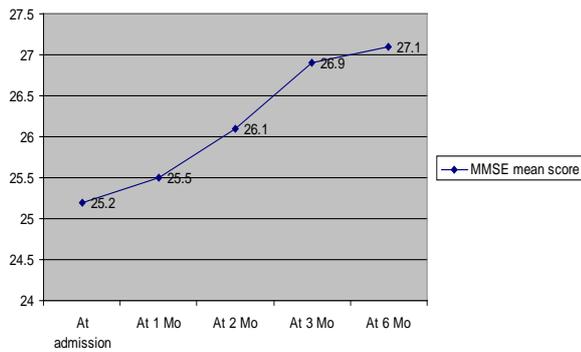
Study group's structure



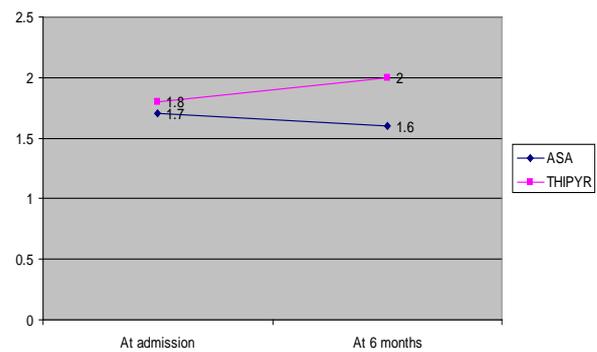
The compared evolution of the two arms (MMSE score mean increase)



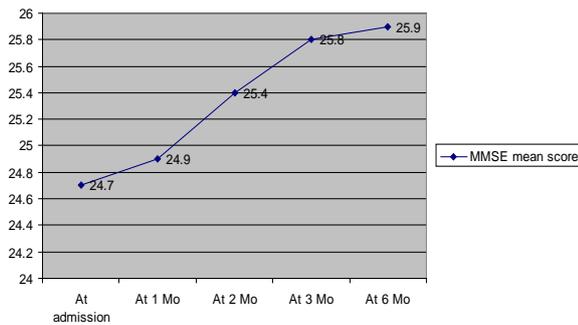
MMSE mean score in Aspirin arm



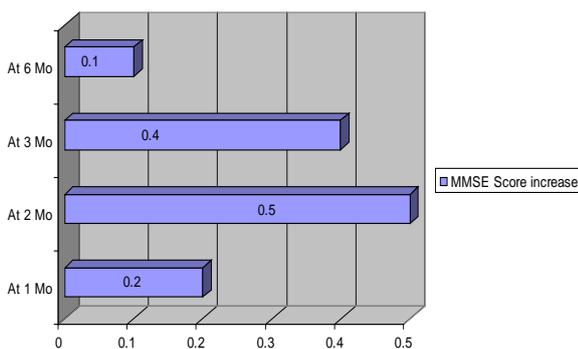
CRP levels in the two arms and the influence of medication



MMSE mean score in Thienopyrimidines arm



MMSE score increase in Thienopyrimidines arm



DISCUSSIONS

The best improvement on the MMSE was during the third month for the aspirin arm, while both arms showed no significant improvement in the last three months of surveillance. The CRP levels in the two groups modified in respect to Aspirin use. The Aspirin group showed an average CRP decrease at 6 months of 0.1 mg/L.

CONCLUSION

Subjects with high CRP and PAD with mild cognitive impairment have a better cognitive outcome when administered aspirin therapy for primary cardiovascular prevention, unless other medication/therapy is needed, associated to pramiracetamum.

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