Possible Role of Intravenous Hyaluronidase Treatment in Coronary Lesion and Hypertension

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Abstract

Background: Coronary artery disease is the major cause of death in many countries. It is treated by surgical measures in combination with anticoagulants to protect from thrombosis. In late stage and for patient rejecting the modern surgical procedures or drugs, no further treatment options exist. Case Report: A 60-year-old man suffered from painful peri-arthritis in the right shoulder. He also had arterial hypertension with occasional severe hypertensive crises. Successful treatment of the orthopedic problem by means of a series of ten intravenous high-dose hyaluronidase infusions removed not only the shoulder pain, but had additional beneficial effect on the coronary artery disease and hypertension. A stress-induced ischemia, which was detected by MRI prior to the treatments, disappeared, and the patient remained normotensive without further need for drugs for the next five years. Conclusion: A beneficial impact of intravenous hyaluronidase treatment on atherosclerotic lesions has been reported already 50 years ago and can be explained by the molecular action of the enzyme. However, research on this topic ceased, when stents and other more compelling treatment methods were detected. Appropriately designed clinical studies are required to confirm the value of hyaluronidase infusions as treatment alternative, in particular for late-stage atherosclerosis.

Keywords: Anticoagulants, Atherosclerosis, Coronary Artery Disease, Shoulder, Pain, Thrombosis.

Introduction

Macrovascular disease represents the major cause of mortality in industrialized countries. In Germany, myocardial infarction, stroke, and other consequences of atherosclerosis caused 40% of all reported deaths in 2012 [1]. Treatments for atherosclerosis may include lifestyle changes, medicines, and medical procedures or surgery. The goals of treatment include relieving symptoms, reducing risk factors in an effort to slow or stop the buildup of plaque, lowering the risk of blood clot forming, widening or bypassing plaque-clogged arteries, and preventing atherosclerosis-related diseases. In severe cases of the disease, when plaques have already been formed and start to impact vascular function and blood flow, surgical procedures are usually applied. Angioplasty with optional placing of a stent can improve blood flow to the heart and relieve chest pain. Coronary artery bypass grafting is used to bypass narrowed coronary arteries by using healthy blood vessels for replacement e.g., veins from the leg. Additionally, carotid endarterectomy may be applied to remove plaque buildup from the carotid arteries in the neck, and to restore blood flow to the brain for stroke prevention. These surgical measures in combination with anticoagulants to protect from thrombosis represent the current state of the art in late-stage atherosclerosis and no further approved treatment option exists at this stage. Therefore, there is need to develop further treatment alternatives in particular for patients.
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with late-stage atherosclerosis [2,3]. Next to other indications, intravenous treatment with the enzyme hyaluronidase is approved in Germany for treatment of inflammatory conditions of the connective tissue such as tendovaginitis, arthritis or myofascicular pain syndromes [4,5]. Because of the anti-inflammatory effects of hyaluronidase, it has been speculated that the enzyme may also have beneficial effects on other conditions driven by inflammation, such as atherosclerosis.

Here we report on a single case study, where treatment of an orthopedic problem by means of high-dose hyaluronidase infusion resulted in efficient removal of a previously unknown atherosclerotic lesion in the heart and in normalization of blood pressure and vascular elasticity.

Case Report

The patient was a 60-year-old man with arterial hypertension (treated with 5 mg bisoprolol/day) and a long-term history of painful peri-arthritis in the right shoulder. To remove the shoulder pain, the treating physician started a series of ten hyaluronidase treatment procedures over a period of three weeks. The employed hyaluronidase product is approved for arthritis treatment in Germany (Hylase-Dessau, Riemser Pharma). Infusions were made within 60 min with 15,000 U of hyaluronidase in physiological sodium chloride solution by means of an infusion pump. This dose is a three times higher dose than normally recommended to enhance anti-inflammatory efficacy. Therefore, the patient gave explicit written informed approval for this experimental treatment and each infusion was monitored with continuous pulse and blood pressure surveillance. All individual treatment procedures were very well tolerated, and no adverse event was reported. During the first infusion, blood pressure decreased within one hour from 140/90 mmHg to 115/80 mmHg. The patient decided to stop the anti-hypertensive medication on the next morning on his own because of low blood pressure values. He remained normotensive without medication for the further remaining treatment and observation period. Pulse wave velocity was 11.6 m/sec before the first and 9.5 m/sec directly after the last infusion.

In a parallel approach to also investigate the potential reason for the occasional hypertensive crises, a stress MRT was performed at an independent site as part of an annual cardiology check prior to initiation of the hyaluronidase treatment. The stress MRI immediately prior to the first hyaluronidase procedure gave evidence of a sub-endocardial ischemic lesion not known before occurring during the stress phase of the MRI after adenosine application [Fig.1a], which was classified as requiring a stent intervention by the radiologist and the cardiologist. However, when receiving this information, the patient had already passed half of the planned hyaluronidase infusions and felt comfortable. Against medical advice, he decided on his own to finish the treatment and re-run the MRI analysis after several weeks. In the meantime, he did not require any anti-hypertensive medication and did not experience any hypertensive crisis.

In repeated MRI examination six weeks after the last hyaluronidase treatment, there was no further evidence of any ischemia anymore [Fig.1b] and the results were classified as “normal heart

Subendothelial ischaemia posterolateral (after adenosin application) No stress-induced ischaemia (after adenosin application)

Fig.1: MRI assessments before and after the hyaluronidase infusions (both screen shots made during the stress phase after adenosin application). An endocardial ischemic lesion became visible prior to the hyaluronidase intervention, which had disappeared 10 weeks after the treatment.
for age in contrast to the previous analysis” by the same investigator. The pain in the shoulder had disappeared and in the course of the following five years, the patient remained normotensive without requiring anti-hypertensive medication. In addition, he reported about a subjective increase in physical fitness, e.g., when doing his usual weekend biking tours, which was also confirmed by his wife.

**Discussion**

Proteoglycans and hyaluronan play a key role in the genesis, formation, progression and composition of atherosclerotic plaques. Together with lipids, lipoproteins and calcium, they form complexes that built the morphological skeletal backbone of the atherosclerotic plaque. Hyaluronan (also known as macromolecule of hyaluronic acid, HA) is a large, non-sulfated glycosaminoglycan that is ubiquitously present in the extra-cellular matrix of all vertebrates, with high-molecular weight forms being the physiologically normal isoform. It has been shown that during inflammation and tissue injury, low-molecular-weight fragments are predominantly built, which exert angiogenic and pro-inflammatory effects [4-6]. In consequence, remodeling of the HA content of the glycocalix in favor of high-molecular weight isoforms may be a therapeutic target for treatment of atherosclerosis [7]. Hyaluronan is a dynamic molecule with a high rate of metabolism. In humans, the turnover rate for hyaluronan is 5 g/day of the total 15g in the body [8]. The majority of the hyaluronan in the vasculature is incorporated into the endothelial glycocalyx and the extracellular matrix of the underlying tissue [9-12]. Hyaluronan content and composition of the glycocalix plays a major role in the permeability of the layer. Treatment with hyaluronidase has been shown to increase permeability in post-capillary venules in the rat [10].

It is therefore postulated that treatment of the vasculature with hyaluronidase may result in the rapid formation of a new and less damaged glycocalix in patients with chronic system inflammation. In addition, the enhanced permeability after intravenous administration may allow the enzyme to also penetrate into the smooth muscle cell layer. The hyaluronidase molecules may reach the plaques, where hyaluronan is also present as one of the major skeletal components of the plaque itself [13-16]. After cleaving the solid proteoglycans, the plaque may become more flexible and may better be targeted and dissolved by further self-repair mechanisms within the arterial wall. In animal experiments, exposure of atherosclerotic tissues with plaque lesions to bacterial hyaluronidase resulted in fast and effective degradation of the plaques [18]. In anecdotal clinical cases, it has been demonstrated that atherosclerotic plaques can be reduced or even removed by intravenous administration of high doses of hyaluronidase in patients with coronary heart disease and/or arterial obstructive disease resulting in improved vascular function in late-stage atherosclerosis [18,19]. A beneficial impact of intravenous hyaluronidase treatment on atherosclerotic lesions has been reported already 40-50 years ago [20-22] and can be explained by the molecular action of the enzyme. However, research on this topic ceased, when stents and other seemingly more compelling treatment methods were detected. Based on our experience, we recommend restarting this research and investigate hyaluronidase infusions as treatment alternative, in particular for improvement of late-stage atherosclerosis.

**Conclusion**

Intravenous treatment of a joint inflammation with hyaluronidase resulted in additional sustained normalization pressure and elimination of a previously unknown stress induced ischemia in the coronary arteries. Controlled clinical studies are now warranted to verify and confirm the anti-atherosclerotic activity of hyaluronidase, when given by intravenous infusion.
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