

Efficacy of a Combination of Fixed Doses of Serratiopeptidases, Bromelain and Methylsulfonylmethane in Inflammatory Joint Diseases

Martin-Martin LS*, De Burgos-Mota M, Apa M, Pierangeli D, Ragno A and Silvestri A

Department of Internal Medicine, "Regina Apostolorum" Hospital – Albano Laziale (Rome), Italy

*Corresponding Author: Martin-Martin LS, Department of Internal Medicine, "Regina Apostolorum" Hospital – Albano Laziale (Rome), Italy.

Received: May 03, 2017; Published: June 13, 2017

Abstract

Rheumatic diseases are traditionally treated using symptomatic drugs (NSAIDs - Nonsteroidal Anti-Inflammatory Drugs) and specific drugs. Nevertheless, the inhibitory effect of traditional NSAIDs, caused by both types of COX enzymes, besides easing inflammation and pain, also has a number of damaging effects on gastric mucosa protection mechanisms. Therefore, NSAIDs administration is also contraindicated in patients who suffered or are suffering from chronic liver or kidney disease, or in patients on anticoagulants.

We therefore decided to study the effect of a combination of fixed doses of Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts in inflammatory joint diseases. From 1st December 2014 to 31st March 2015, we selected 74 patients with chronic inflammatory joint diseases of different types in an acute phase, as documented by high VAS (Visual Analogue Scale) rates and increased ESR and CRP values. Patients were randomly subdivided in two groups: in treatment group, during the first 3 months, patients also took a solution of Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts, before the main meal of the day; in control group patients did not take any therapy in addition to the background one.

Patients in the treatment group showed a statistically significant reduction in ESR and pain, measured with the VAS scale; moreover, intake of Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts led to no statistically significant change in liver (AST and ALT) and kidney (Creatinine) function in the treatment group as opposed to the control one.

In this preliminary study, the product containing Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts achieved optimum effectiveness and showed no side effects, although a long-term multi-centre study would be needed to confirm our results.

Keywords: Serratiopeptidases; Bromelain; Methylsulfonylmethane; Inflammatory Joint Diseases

Introduction

Rheumatic disorders are diseases of various kinds affecting bones, joints and connective tissues. Often linked to different contributing causes, they may also be of hereditary origin. Rheumatic diseases affecting bones, joints and connective tissues fall into 13 sub-groups: arthrosis (osteoarthritis), primary arthritis, microcrystalline and dysmetabolic arthropathies, non-traumatic painful affections of the spine, bone diseases, connective tissue diseases and vasculitides (systemic rheumatic diseases), arthritis caused by infectious agents, extra-articular rheumatic diseases, neurological, neurovascular and psychic disorders, congenital connective tissue diseases, cancer and related disorders as well as other diseases having rheumatologic manifestations.

Rheumatic diseases are traditionally treated using symptomatic drugs (that is drugs that act on the symptoms but are unable to change the course of the disease) and specific drugs (that is drugs acting on the causes of the disease that can slow down both its damage

progression and scale). Rheumatic diseases can be recognized as they share common symptoms, such as pain and swelling of hand and wrist joints or prolonged joint stiffness for more than an hour in the morning. Other symptoms are fingers turning white, dry eyes – like you have sand in them- and mouth, as well as joint or muscle pain.

Given the inflammatory nature of these diseases, the most commonly used drugs to treat them are NSAIDs. The acronym stands for Nonsteroidal Anti-Inflammatory Drugs, that is drugs that are able to reduce a number of inflammatory processes of the organism but do not fall in the steroids category. Although different in terms of chemical structure, NSAIDs constitute a rather homogeneous group of compounds with regard to their effect: besides having an anti-inflammatory action, they also have an analgesic and antipyretic one, that is they are efficient pain-killing and fever-reducing drugs.

NSAIDs exert their anti-inflammatory and analgesic effect mainly through the inhibition of cyclooxygenase (COX), an enzyme that allows the transformation of arachidonic acid into prostaglandin H₂, which is the precursor of all prostaglandins (PGs), chemical substances controlling several physiological and pathological body processes. Under normal conditions, PGs play a key role in guaranteeing the integrity of the gastric mucosa, standard renal circulation and efficient platelet functioning. COX enzymes can take two different forms, one is called COX-1, the other COX-2, where the former regulates the synthesis of PGs under physiological conditions and the latter is produced right where inflammation arises.

Nevertheless, the inhibitory effect of traditional NSAIDs, caused by both types of COX enzymes, besides easing inflammation and pain, also has a number of damaging effects on gastric mucosa protection mechanisms. This is due to the fact that PGs, as a rule, reduce acid secretion, stimulate the production of mucus and bicarbonates and improve blood circulation in the mucosa ultimately guaranteeing the integrity of stomach lining. In addition to this systemic action, NSAIDs have a detrimental local effect, which is independent from prostaglandin synthesis, mediated by their ability to facilitate the penetration of hydrochloric acid in the stomach lining with obvious corrosive effects on the mucosa.

The side effects of these drugs are largely due to the inhibition induced by prostaglandin synthesis. It goes without saying that the most common adverse reaction to NSAIDs intake is the appearance of digestive tract disorders with nausea, vomiting, heartburns and diarrhoea. If taken regularly or for a prolonged period of time, they may lead to the formation of real ulcers of the gastrointestinal mucosa with mild, but also, in some cases, severe bleeding requiring emergency hospitalization. Such side effects may be reduced if NSAIDs are taken right after meals, on a full stomach, or together with antacids or stomach-protective drugs. For the same reason, it is appropriate to avoid drinking alcohol while taking NSAIDs. Therefore, NSAIDs administration is contraindicated not only in cases of individual intolerance but also in patients who suffered or are suffering from gastro-duodenal ulcer, digestive haemorrhage, chronic liver or kidney disease, or in patients on anticoagulants. It has been widely proven that the risk of significant side effects increases with ageing and this phenomenon appears to be linked essentially to the fact that, with ageing, defences of the gastric and duodenal mucosa tend to lower.

Other risk factors are the intake of steroids, diabetes and some heart diseases, smoking as well as another factor: that is how long the patient has been taking NSAIDs. Besides, taking more than one NSAID at the same time, or associating NSAIDs and aspirin, as well as the type of NSAIDs is used are factors directly linked to the frequency and severity of damage to the digestive system. For example, some NSAIDs, such as piroxicam and ketoprofen, have a higher risk of complications, whereas ibuprofen and diclofenac prove to be less harmful. Finally, it should be noted that NSAID intake might also result in allergic skin rashes (itching, skin rashes, hives), dizziness and drowsiness.

To avoid all these side effects, scientists are currently looking for new molecules to reduce risks for patients. Three of these molecules are Serratiopeptidases, Bromelain and Methylsulfonylmethane.

Serratiopeptidases are proteolytic enzymes produced by an enterobacter belonging to the *Serratia* species. Serratiopeptidases have a proteolytic and fibrinolytic action and are used in every field of medicine as an anti-inflammatory and anti-oedema remedy. Serratiopepti-

dases improve microcirculation in the inflamed area by promoting the reabsorption of exudates: they accelerate the elimination of mucus, purulent exudate and fibrin exudates [1-3].

Bromelain is an enzyme having a proteolytic activity, extracted from pineapples' stems, and a strong anti-inflammatory action. It is able to reduce tissue oedema and relieve congestion in the mucosa when an inflammation occurs, by decreasing the production of pro-inflammatory prostaglandins [4-6].

Methylsulfonylmethane (MSM), also known as Dimethyl sulfone (DMSO₂), is an organic sulphur-containing compound that can be found in fruit, vegetables and animal species. MSM has an anti-radical and anti-inflammatory activity: an in vitro study on the cell lines of macrophages, where an inflammatory state was induced, showed that adding MSM significantly inhibited the release of nitric oxide and PGE₂. It also reduced the intracellular signals of inflammation such as IL-6 and TNF- α [7-10].

Combining these molecules with Vitamin C is capital for immune defences: in an inflammation, the concentration of Vitamin C in white blood cells decreases rapidly. Vitamin C affects the immune system by stimulating lymphocyte function and activity, by increasing interferon levels and obtaining therefore an antibody response. As a scavenger, it plays a crucial role in the body's defence mechanisms against free radicals, as it prevents lipid peroxidation and oxidative damage to DNA and proteins [11].

We therefore decided to study the effect of a combination of fixed doses of these substances (Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts) in inflammatory joint diseases.

Materials and Methods

From 1st December 2014 to 31st March 2015, we selected 74 patients (24 men and 50 women, average age 68 years) with chronic inflammatory joint diseases of different types: Polymyalgia rheumatica, rheumatoid arthritis, psoriatic arthritis, enteropathic arthritis, etc. These conditions were in an acute phase, as documented by high VAS (Visual Analogue Scale) rates indicating pain at baseline, and increased ESR and CRP values.

All patients were on a background therapy featuring DMARDs (Disease-modifying Antirheumatic Drugs) and NSAIDs (Nonsteroidal Anti-inflammatory Drugs), but they were not closely followed up or in the onset phase of their disease, so that a steroid therapy was the best option for better disease control. Average dose of prednisone administered to patients was 25.6 mg/day (or an equivalent dose of 6-methylprednisolone) once a day, in the morning, after breakfast.

All patients were informed of the purposes and methods of this study and, once obtained their informed consent, enrolled in the trial.

Patients were randomly subdivided in two groups,

- a) Treatment group (37 patients, 10 men and 27 women, average age 66 years; 38 ESR, CRP 2.5; VAS 6.3) during the first 3 months of steroid treatment patients also took, in addition to the background therapy for their illness, a solution of Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts, before the main meal of the day;
- b) Control group (37 patients, 14 men and 23 women, average age 70 years; 37 ESR, CRP 2.8; VAS 6.5): patients did not take any therapy in addition to the background one.

Throughout the duration of the study patients were asked not to change their therapy without asking their rheumatologist first (thus change in dosage/replacement/addition of other drugs was not allowed). Patients who needed to increase steroid or NSAIDs or DMARDs dosage or to change the drug used were considered dropouts and therefore excluded from the trial study.

Patients were assessed at baseline and 90 days thereafter. Throughout the study, the following parameters were taken into account:

1. Inflammatory markers: ESR, CRP, Protein electrophoresis (in particular Alfa 2 globulins and gamma globulins).

2. Indicators of tolerability of the product containing Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts: creatinine, AST, ALT and blood count.

3. Skinfold thickness between the 1st and the 2nd finger of the nondominant hand as we have assumed that, for the same BMI (Body Mass Index), any variation in the thickness of the skin fold can between fingers can be due only to skin atrophy, a well-known side effect of steroid intake. Finally, in order to assess the effect of our product, containing Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts and of the steroid therapy on reparative and regenerative processes, we evaluated the occurrence or absence of skin ulcers and/or the evolution of those present at baseline.

Results were statistically analysed to evaluate their statistical significance.

Results

Of 74 patients enrolled, 59 completed the study (three months of observation). In the treatment group 8 patients abandoned the trial due to non-compliance with the protocol; in the control group 7 patients withdrew from the study: 4 due to non-compliance with the protocol and 3 because they needed to change the therapy agreed upon at baseline.

None of the patients in the treatment group reported symptoms connected to drug intake or gastrointestinal disorders during the study period. In this group, no patient needed to add to the therapy H2 antagonists, proton-pump inhibitors or anti-reflux drugs.

The intake of Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts led to no statistically significant change in liver (AST and ALT) and kidney (Creatinine) function in the treatment group as opposed to the control one (Figure 1 and 2).

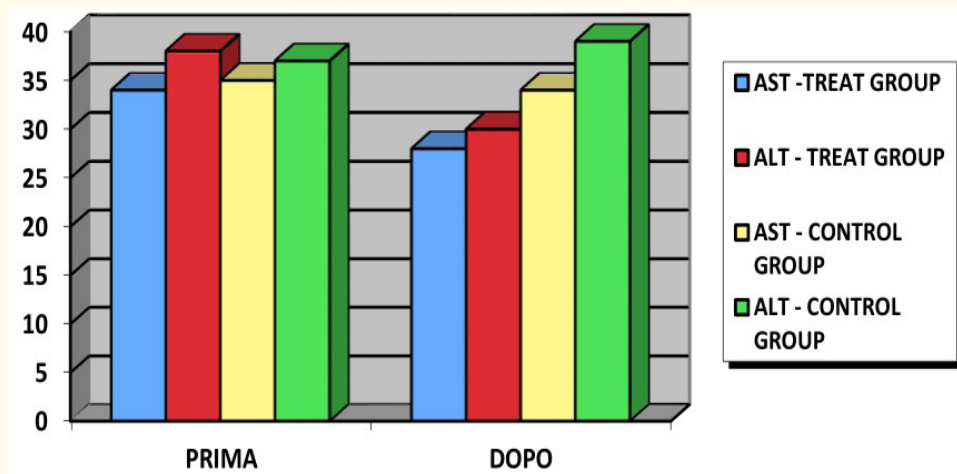


Figure 1: No variation in transaminase levels in the treatment group and in the control group both at baseline and at the end of trial.

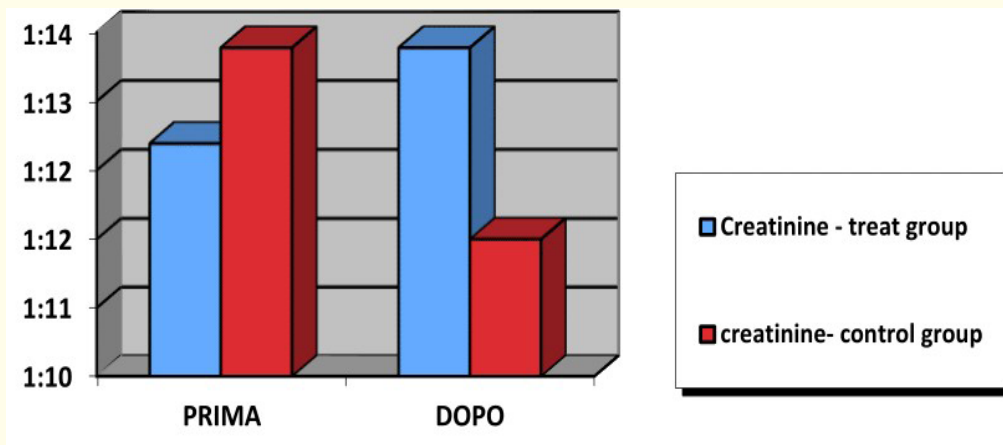


Figure 2: No variation in creatinine levels in the treatment group and in the control group both at baseline and at the end of trial.

Although drug intake was stable in dosage, patients in the treatment group showed a statistically significant reduction in ESR and pain, measured with the VAS scale (Figure 3 and 4). The difference in PCR values in the treatment group as opposed to the control group was not statistically significant, although a greater reduction of PCR values was observed in the treatment one.

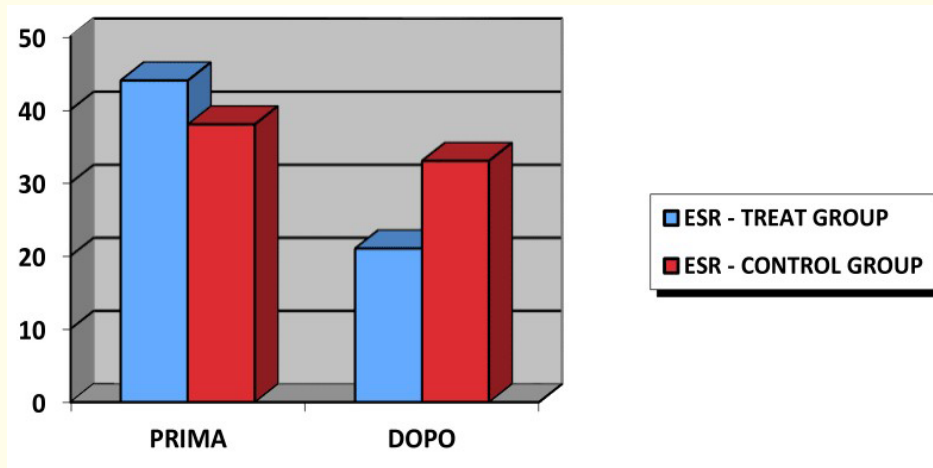


Figure 3: Significant reduction of ESR in the treatment group before and after therapy ($p < 0.5$) compared to the control group.

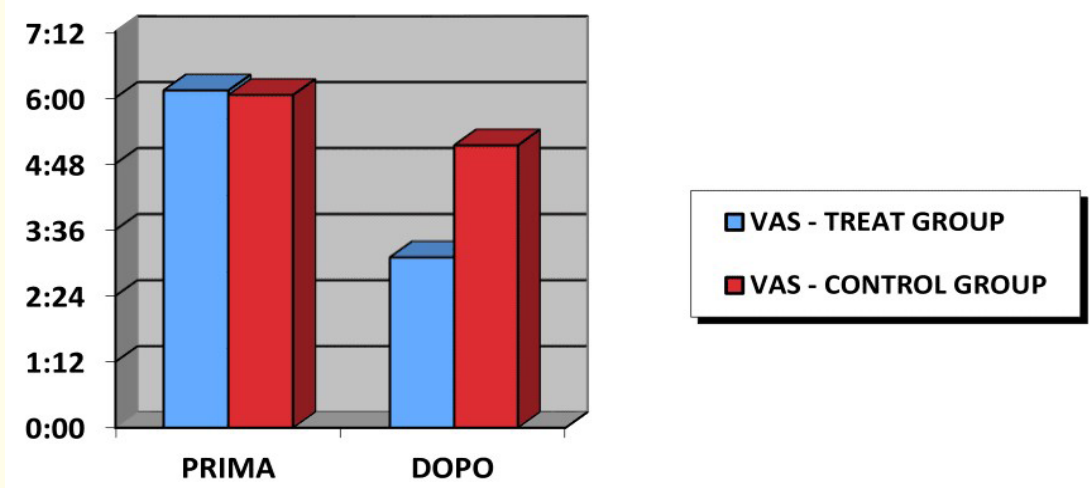


Figure 4: Pain reduction - quantified by the VAS scale - in the treatment group before and after therapy was significant ($p < 0$) if compared to the control group.

No patient in the treatment group developed skin ulcers as opposed to 3 patients in the control group (two of them experienced ulcers at the tibia and one on the forepart of the foot).

Discussion

Joint diseases are painful and debilitating diseases that are among the most common and widespread ones in the world. They are on the rise in industrialized countries for several reasons: on the one hand the increase in life expectancy helping the diffusion of diseases associated with ageing (including precisely rheumatic diseases and bone and joint diseases). On the other hand, other factors related to life-style such as obesity, widespread diabetes and physical inactivity favour the onset of inflammation and joint damage even at a young age.

Arthrosis - which affects mainly the small joints of the hands, the neck (neck vertebrae and nape) and the knee - is nothing but the progressive, chronic and irreversible “wearing and tearing” of cartilage lining the bones and preventing bone-to-bone contact. When the cartilage tissue gets thinner, bones end up “rubbing” against each other and nerves get inflamed causing pain and a significant amount of stiffness.

Both Rheumatoid and psoriatic arthritis, which are the two of the most common forms - are autoimmune in origin, and affect mainly young adults (of which 2/3 are women), aged between 40 and 60 years of age. The symptoms are severe joint pain and a “migrant” inflammation (that is moving from one joint to another) with obvious swelling and redness, difficulty in performing simple movements and walking and accentuated morning stiffness that fades with each passing hour.

These chronic inflammatory joint diseases can be successfully controlled by administering immunosuppressive drugs (DMARDs) or state-of-the-art biological drugs, as well as anti- NSAIDs and cortisone-based drugs to ease the pain and reduce inflammation. Unfortunately, the side effects, sometimes severe, of these drugs are well known and therefore it is not always possible to administer them in the exact dosage the patient needs.

The aim of this preliminary study was to assess whether the combination of Serratiopeptidases, bromelain and Methylsulfonylmethane extracts, together with vitamin C, could prove to be an effective therapy in rheumatic diseases, for the anti-inflammatory and anti-oedema effects each of these substances has. Our assumption proved right, as the product containing Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts achieved optimum effectiveness: a sharp reduction of inflammatory parameters and pain, confirming the results of studies carried out on each single component separately [2,5,9].

Drugs used in combination were successfully tolerated: none of the patients had to discontinue therapy due to intolerance and/or side effects. Liver and kidney function parameters were normal and did not change over the course of the therapy. The moderate reduction of AST and ALT values observed at the end of therapy could be explained by the known effect of MSM in reducing hepatic cytolysis [8].

Conclusion

In our preliminary study, the product containing Serratiopeptidases, Bromelain and Methylsulfonylmethane extracts achieved optimum effectiveness and showed no side effects, although, given the small number of patients included in the trial and the short observation time, a long-term multi-centre study would be needed to confirm our results.

Bibliography

1. Esch PM., *et al.* "Reduction of postoperative swelling. Objective measurement of swelling of the upper ankle joint in treatment with serrapeptase: a prospective study". *Fortschritte der Medizin* 107.4 (1989): 67-68,71-72.
2. Kee WH., *et al.* "The treatment of breast engorgement with Serrapeptase: a randomised double-blind controlled trial". *Singapore Medical Journal* 30.1 (1989): 48-54.
3. Nakamura S., *et al.* "Effect of the proteolytic enzyme serrapeptase in patients with chronic airway disease". *Respirology* 8.3 (2003): 316-320.
4. Fitzhugh DJ., *et al.* "Bromelain treatment decreases neutrophil migration to sites of inflammation". *Clinical Immunology* 128.1 (2008): 66-74.
5. Braun JM., *et al.* "Therapeutic use, efficiency and safety of the proteolytic pineapple enzyme Bromelain-POS in children with acute sinusitis in Germany". *In Vivo* 19.2 (2005): 417-421.
6. Inchingolo F., *et al.* "Clinical trial with bromelain in third molar exodontia". *European Review for Medical and Pharmacological Sciences* 14.9 (2010): 771-774.
7. "Methylsulfonylmethane (MSM). Monograph". *Alternative Medicine Review* 8.4 (2003): 438-441.
8. Amirshahrokhi K and Bohlooli S. "Effect of methylsulfonylmethane on paraquat-induced acute lung and liver injury in mice". *Inflammation* 36.5 (2013): 1111-1121.
9. Kim YH., *et al.* "The anti-inflammatory effects of methylsulfonylmethane on lipopolysaccharide-induced inflammatory responses in murine macrophages". *Biological and Pharmaceutical Bulletin* 32.4 (2009): 651-656.
10. Mohammadi S., *et al.* "Protective effects of methylsulfonylmethane on hemodynamics and oxidative stress in monocrotaline-induced pulmonary hypertensive rats". *Advances in Pharmacological Sciences* (2012): 507278.
11. Frei B., *et al.* "Ascorbate is an outstanding antioxidant in human blood plasma". *Proceedings of the National Academy of Sciences* 86.16 (1989): 6377-6381.

Volume 6 Issue 6 June 2017

© All rights reserved by Martin-Martin LS., *et al.*