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EDITORIAL

Topical Nitroglycerin for Osteoporosis: Old Drug New Application

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ABSTRACT

Osteoporosis is a progressive bone disease characterized by a decrease in the bone mass and density, which can lead to an increased risk of fracture. Multiple treatments have been formulated for it like calcium, vitamin D supplements, bisphosphonates, raloxifene, hormone replacement therapies, teriparatide and calcitonin. However, all of these have their own shortcomings. Topical nitroglycerin is a cost-effective, novel medication that not only increases bone formation but also decreases its resorption, and also has the potential to decrease vertebral fractures more than that provided by the existing treatments. Therefore, it could be the answer to the need of an efficacious, cost-effective, affordable, safe and a convenient form of therapy for the prevention of post-menopausal bone loss and osteoporosis as a whole. Therefore, we recommend that individuals with osteoporosis be treated with topical nitroglycerin ointment (15 mg/day).

Keywords: Bone mineral density, Fracture, Nitroglycerin, Osteoporosis, Topical.

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INTRODUCTION

Osteoporosis, derived from a Greek word that means 'porous bones', is a progressive bone disease characterized by a decrease in the bone mass and density, which can lead to an increased risk of fracture.[1] It is characterized by a decreased bone mineral density (BMD), distorted bone microarchitecture, and an altered amount and variety of proteins in the bone. Osteoporosis is defined by the World Health Organization (WHO) as a BMD of 2.5 standard deviations or more, below the mean peak bone mass as measured by dual-energy X-ray absorptiometry. Its incidence among women aged 20 to 44 years is approximately 13.1% in the lumbar spine and 17.9% in the femoral neck, with its incidence increasing progressively, with age to 50% and 31.1% respectively, in women aged 60 to 69 years. Thus, it is a major health problem associated with substantial morbidity and socioeconomic burden.

The current treatment options for the prevention and treatment of osteoporosis are limited. Calcium and vitamin D are an important nutritional combination in the management; however, its efficacy is questionable.[2] Bisphosphonates, although useful in individuals with osteoporosis and a history of fracture, are of minimal utility without a fracture history. They cannot be prescribed to individuals with impaired renal clearance[3] and there is no evidence that they lead to deposition of new bone.[4] Raloxifene, an SERM, is associated with an increased incidence in thromboembolic disease, hot flushes, leg cramps, leg swelling and influenza like syndrome.[3] Also, they have no effect on the risk of nonvertebral fractures.[5] Hormonal replacement therapies have potential adverse effects like breast malignancy, thrombotic episodes, etc. Calcitonin has the limitation of not stimulating osteoblastic activity and decreased compliance because of nasal/parenteral dosing. Teriparatide, the last in the list of the US-FDA approved drugs for osteoporosis, is an expensive parenteral therapy that not only increases bone formation but also bone resorption.

Hence, the need of the hour is a cost-effective, novel medication that not only increases bone formation but also decreases its resorption, and also has the potential to decrease vertebral fractures more than that provided by the existing treatments. Topical nitroglycerin is one such alternative. Nitroglycerin acts through the direct release of nitric oxide (NO), independent of intracellular nitric oxide synthase (NOS) activity. Nitric oxide appears to play an autocrine-paracrine regulatory role in bone cell metabolism. A number of studies have suggested that NO may have an anabolic effect on bone tissue.[6] Adding NO to bone cultures decreases osteoclast maturation and bone resorbing activity.[8] In addition, it enhances the differentiation of osteoblasts by inducing prostaglandin E

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production. It also induces the proliferation of osteoblasts and increases the production of collagen and osteocalcin.[7]

Sex hormones influence the constitutive production of NO by bone cells. The activity of NO synthase is directly related to the level of estradiol, because it acts as an upregulator of endothelial nitric oxide synthase (eNOS). During the reproductive years, estradiol leads to a positive NO balance, which in turn increases the osteoblastic and decreases the osteoclastic activity, resulting in a positive bone balance. Circulating estradiol is low in post-menopausal women and, therefore, an increased bone fragility is seen. In a nutshell, NO has an estrogen-like effect on the bone (predominantly inhibits osteoclastic bone resorption but also stimulates bone formation) but without the estrogenic side effects. Therefore, it can be an alternative to hormonal supplementation for osteoporosis.

A cross-sectional clinical study, which was carried out in 1989 on 450 cardiac patients who were on various doses of nitrates demonstrated a dose-dependent effect of nitrates on the BMD when compared to age and sex matched controls.[9]

Rejnmark et al found that the use of nitrates was associated with an 11% reduced risk of any fracture and a 15% reduced risk of hip fracture with the use of nitrates over a period of 5 years. The risk of fracture was decreased for both men and women.[10] Therefore, we can conclude that the risk of fracture is decreased significantly with the use of nitroglycerine.

Jamal et al conducted a double blind placebo controlled randomized trial on postmenopausal women with lumbar spine T scores between 0 and –2.0, with changes in lumbar BMD as the primary end point. They found that treatment with 15 mg/day of nitroglycerin for 24 months increased bone formation and decreased bone resorption, resulting in an increased areal BMD at the spine and proximal femur and an increased volumetric trabecular BMD in the distal radius and tibia. Not only did it increase the cortical thickness and area in the radius and tibia along with statistically significant increase in the periosteal diameter but also was associated with statistically significant increase in bone specific alkaline phosphatase which is a marker of bone formation. These findings suggest that nitroglycerin can significantly decrease the risk of fractures, including that of long bones which are mostly cortical in nature. The only significant side effect was headache, which too was found to decrease with use. Only seven of the 243 cases discontinued the treatment in the 1st year due to the same, with no one discontinuing after 12 months of use.[11]

Jamal et al also did a study to determine whether isosorbide mononitrate at 20 mg/day or nitroglycerin ointment at 15 mg/day lead to more headaches. The study concluded that it was the former, which gives the topical form a clear advantage in this regard.[4] Nitroglycerin patch is not useful because it has a long duration of action, which can lead to tachyphylaxis.

A study carried out in young oophorectomized women aged between 36 and 45 years compared the efficacy of nitroglycerin [topical nitroglycerin therapy (15 mg/day) with estrogen replacement therapy (0.625 mg premarin/day taken orally), the therapy started 3 to 4 weeks after surgery, for the prevention of oophorectomy-induced early post-menstrual bone loss showed that nitroglycerin was as effective as estrogen, if not better, in preventing bone loss in these surgically induced menopausal women. No significant changes were found in the BMD of the hip and spine after 6 and 12 months of treatment between both the two groups, thereby proving that both these drugs were equally effective in preventing bone loss in these doses. However, nitroglycerin was also found to increase serum osteocalcin and bone specific alkaline phosphatase levels, whereas estrogen decreased both of these. Since both of these are markers of bone formation, nitroglycerin may actually be better than the time tested estrogen replacement therapy for the prophylaxis/treatment of osteoporosis. Therefore, it may emerge as an effective, cheap, safe and convenient form of therapy for the prevention of postmenopausal osteoporosis, especially as an effective alternative to hormone replacement therapy.[10]

Nitroglycerin in this dose is safe and it was not found to be associated with any significant adverse effect, or change in blood pressure in the subjects during and after the treatment.[10] It is recommended in the dosage of 15 mg/day (roughly an inch of 2% nitroglycerin ointment which is to be applied at the upper outer arm at bedtime). Headache was the most common adverse effect documented. These are actually a marker of drug activity, and patients should not alter their treatment or dosing schedule to avoid them as a loss of headache in such individuals is most likely associated with loss of efficacy. It is to be used with caution in individuals on phosphodiesterase inhibitors like sildenafil. The only contraindication is in individuals who develop an allergy to it. Should preferably be avoided with calcium channel blockers (may cause marked symptomatic orthostatic hypotension) and patients should abstain from alcohol (vasodilatory action of NTG gets increased). It should be used in a pregnant woman only if clearly needed (pregnancy category C) and caution should be exercised if given to a nursing mother, as it is not known whether it is excreted in the human milk.

To conclude, nitroglycerin could be the answer to the need of an efficacious, cost-effective, affordable, safe and a convenient form of therapy for the prevention

of postmenopausal bone loss and osteoporosis as a whole.[12] Therefore, we recommend that individuals with osteoporosis be treated with topical nitroglycerin ointment (15 mg/day).

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