Nitroglycerin Ointment Strengthens Bone

BY MARY ANN MOON

FROM JAMA

Topical nitroglycerin ointment raises bone mineral density, cuts resorption, and alters bone structure so that bone strength is increased, according to results of a double-blind trial in 243 women.

The magnitude of improvement equals or exceeds that observed with other therapies, including teriparatide.

"Together, these findings suggest that nitroglycerin may significantly decrease the risk of fractures, including fractures in long bones such as the hip, legs, and upper arm, which are largely composed of cortical bone," wrote Dr. Sophie A. Jamal of the University of Toronto and her associates.

In a single-center double-blind clinical trial, they assessed the efficacy of daily application of 2% nitroglycerin ointment over the course of 2 years in increasing bone mineral density (BMD). The study was not large enough to directly determine the drug's effects on fracture risk.

The study subjects were randomly assigned to apply active 15 mg/d nitroglycerin or a matching placebo ointment to a piece of onion skin that was taped to the upper outer arm overnight, every night.

The study subjects were women aged 50 years or older (mean age, 62 years) who were at least 1 year past menopause. None had osteoporosis, but all had BMD T scores of 0 to –2.0 at the lumbar spine and higher than –2.0 at the total hip.

A total of 400 women were enrolled, but only 243 remained in the study long enough to be included in the analysis; 126 in the nitroglycerin group and 117 in the placebo group. A total of 106 subjects dropped out because of headache, nausea, or allergic reaction, and another 51 "lost interest" or became ineligible.

After randomization, another 30 subjects in the nitroglycerin group (24%) and 15 in the placebo group (13%) discontinued treatment or were lost to follow-up, including 26 who cited adverse reactions including headache.

The primary end point was change in lumbar spine areal BMD after 2 years of treatment. Compared with women in the placebo group, those who received active nitroglycerin showed a significant increase of approximately 7% in areal BMD at the lumbar spine.

They also showed comparable increases in areal BMD at the total hip (6%) and femoral neck (7%). Compared with placebo users, the nitroglycerin group also showed increases in volumetric trabecular BMD of 12% at the radius and 8.5% at the tibia; increases in cortical thickness of 14% at the radius and 25% at the tibia; and increases in periosteal circumference of 7% at the radius and 3% at the tibia. The latter finding has not been reported with any other agent, the investigators said (JAMA 2011;305:800-07).

Nitroglycerin therapy also was associated with increases in measures of bone strength, with rises of 11% and 10% in polar section modulus and of 7% and 14.5% in polar moment of inertia at the radius and tibia, respectively. These findings indicate significant improvement in bone bending and twisting strength, which in previous research has correlated with fewer fractures.

Compared with placebo, nitroglycerin treatment was associated with significant increases in bone-specific alkaline phosphatase, a marker of bone formation. This rose 14% at 3 months, 21% at 12 months, and 35% at 24 months.

At the same time, urinary N-telopeptide level, a marker of bone resorption, decreased by 20% at 3 months, 33% at 12 months, and 54% at 24 months.

This concomitant change indicates that nitroglycerin uncouples bone formation from bone resorption. Moreover, "the differential effects of nitroglycerin on formation and resorption appear to widen with time, suggesting that its efficacy continues or even increases during 24 months of use.

In contrast, the effects of other antiresorptives and teriparatide either plateau or wane with time," Dr. Jamal and her colleagues wrote.

The incidence of serious adverse effects did not differ between the two groups, at 4% in both. ■

VITALS

Major Finding: Compared with placebo, topical nitroglycerin ointment increased bone mineral density in the lumbar spine, total hip, and femoral neck by 7%; decreased bone resorption; and strengthened bone structure to the same or a greater degree than did other available therapies.

Data Source: A single-center, double-blind, placebo-controlled, randomized clinical trial involving 243 postmenopausal women followed for 2 years.

Disclosures: This study was supported by the Canadian Institutes of Health Research and Physicians' Services Inc. Dr. Jamal reported receiving support from Novartis, Amgen, Warner-Chilcott, Genzyme, and Shire, and her associates reported ties to numerous drug, device, and technology companies.

VIEW ON THE NEWS

Next Step: Assess Effect on Fractures

When added to previous research, the findings reported by Dr. Jamal and her associates suggest that nitroglycerin both inhibits bone resorption and stimulates bone formation, which no single drug can do. These results "should set the stage for an adequately powered, larger study using nitroglycerin ointment, with fracture as an outcome," said Dr. Sundeep Khosla.

"If such a study demonstrates efficacy for reducing fractures, clinicians would have a novel and inexpensive therapy for osteoporosis."

The results of the current study also should spur development of other agents that act as nitric oxide donors, preferably drugs with better adverse effect profiles that don't cause so many headaches.

Future research also should report data on any blood pressure changes associated with nitroglycerin therapy, which Dr. Jamal and her associates did not report on, he added.

DR. KHOSLA is in the endocrine research unit at the Mayo Clinic, Rochester, Minn. He reported serving on a scientific advisory board for Amgen. These remarks were taken from his editorial accompanying Dr. Jamal's report (JAMA 2011:305:826-7).

Bisphosphonates: Absolute Risk of Atypical Fractures Is Low

BY NASEEM S. MILLER

FROM JAMA

Prolonged use of oral bisphosphonates is associated with an increased risk of subtrochanteric or femoral shaft fractures in older women. However, the absolute risk for these fractures is low, according to a large population-based study.

"This study adds another piece to the puzzle," lead author Laura Y. Park-Wyllie, Pharm.D., said in an interview. "There wasn't good research about what the absolute risk of the fractures was. This study adds that piece."

During the 7-year study period, women aged 68 years or older who used bisphosphonates for 5 years or longer were 2.74 times more likely to have subtrochanteric or femoral shaft fractures after minimal trauma, compared with women who took the medications transiently (JAMA 2011;305:783-9). The study also showed that the absolute risk of such atypical fractures was at 1 in 1,000 women.

"If you combine all the information that we have about osteoporosis and the information we have about the risk versus benefits [of bisphosphonates] they would favor the continuation of treatment," Dr. Park-Wyllie said.

Bisphosphonate therapy reduces the risk of osteoporotic fractures, judging from findings from a number of studies. But bisphosphonate-related suppression of bone remodeling could have an adverse effect on bone strength, resulting in atypical fractures, the authors noted.

The growing number of reports on the issue and conflicting studies prompted the group to launch the study, said Dr. Park-Wyllie, a research fellow at Li Ka Shing Knowledge Institute of St. Michael's Hospital in Toronto.

The American Society for Bone and Mineral Research recently released a task force report about the issue. The Food and Drug Administration has announced that it intends to monitor instances of such cases. There have also been several studies on the topic, but the authors of this report say that the studies were too small to establish or negate an association. The population-based, nested case-control study examined 205,466 women 68 years or older who were treated with bisphosphonates between April 1, 2002, and March 31, 2008. The women were followed until the first fracture, death, or end of the study. Women with a history of conditions that could affect bone integrity were excluded.

In the group, 716 women (0.35%) had subtrochanteric (411) or femoral shaft fractures (305). Each case was matched with up to five controls – 3,580 total – from the cohort not hospitalized for either type of fracture, according to the study.

When compared with women who had used bisphosphonates transiently during the study period (less than 100 days in total), women who used the medication for 5 years or longer had an increased risk of subtrochanteric or femoral shaft fracture, the authors concluded.

To validate their findings, the investigators also conducted a secondary analysis, examining the risk of typical osteoporotic fractures among women who used bisphosphonates for 5 years or more, compared with women who used the medication transiently. Of the cohort, 9,723 women sustained femoral neck or intertrochanteric region fractures. "As expected, we found that extended bisphosphonate use was associated with a reduced risk of fracture compared with transient use," the authors wrote.

The absolute risk was estimated from 52,595 women in the cohort with at least 5 years of bisphosphonate therapy. Seventy-one, or 0.13%, sustained subtrochanteric or femoral shaft fractures during the following year and 117 (0.22%) within 2 years.

One of the coauthors – Muhammad M. Mamdani, Pharm.D. – reported financial relationships with Boehringer Ingelheim, Janssen-Ortho, Novartis, and Pfizer. The study was funded by the Ontario Ministry of Health and Long-Term Care. ■