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NEWS

Postoperative Management of Hip Fractures

Recent inaugural IBMS BoneKEy Online Forum focused on pharmacological and non-pharmacological approaches to managing patients post-hip fracture

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The management of patients who have experienced hip fractures poses a daunting challenge for clinicians who treat these injuries. Not only are hip fractures widely prevalent throughout the world – more than 1.6 million hip fractures are estimated to have occurred worldwide just in the year 2000 – but they are also costly in terms of the healthcare expenditures they require, with more than 12 billion dollars spent in the US, just in the year 2005, on the direct costs resulting from these fractures (1;2). Hip fractures are also associated with increased morbidity and mortality, with a one-year mortality of approximately 20%.

Strikingly, despite the extent of the problem, most hip fracture patients are neither screened nor treated for osteoporosis, and of those patients who do receive treatment, most receive only calcium and vitamin D, and rarely a bisphosphonate (3). This spotty handling of initial hip fractures represents a truly missed opportunity to prevent subsequent fractures since the former are a strong predictor of the latter. Indeed, pooled associations between prior and subsequent fractures, derived from a systematic review and statistical analysis of the literature, show that postmenopausal women with prior hip fractures have more than double the risk of experiencing future hip and vertebral fractures (4). Furthermore, one of the few studies specifically designed to assess future hip fracture risk among patients who had previously fractured found that almost 15% of 481 subjects who had experienced hip fractures went on to sustain a second hip fracture (5). While only 1% of subjects experienced a second hip fracture within six months of the first fracture, this number increased to 8% after 5 years, and 12% after 10 years.

During the inaugural IBMS BoneKEy Online Forum, Postoperative Management of Hip Fractures, Dr. Douglas Kiel and Dr. Sarah Berry of the Institute for Aging Research, Hebrew SeniorLife in Boston, Massachusetts offered the above facts as the backdrop to a presentation on the state of the scientific evidence supporting both pharmacological and non-pharmacological interventions for the secondary prevention of hip fractures (click here for PDF of the PowerPoint presentation). Following the presentation, a distinguished panel of experts (see acknowledgment) offered insight into key issues raised by the presentation, particularly regarding the use of bisphosphonates as a post-hip fracture treatment, as well as the use of hip protectors and the effectiveness of interventions to prevent falls.

Considering the prevalence of hip fractures, and their associated costs, morbidity and mortality, treatment to prevent future fractures appears justified. In addition, there is already some evidence to suggest which specific patients might benefit; in addition to a previous fracture, research has pinpointed some of the other risk factors that make a second hip fracture more likely to occur. “While most of the studies have been small and have produced some conflicting results, risk factors that have each been identified as a predictor of second hip fracture in at least two studies include older age, low bone mineral density and low weight,” Dr. Berry said during the presentation (5-8). “In addition, cognitive impairment, impaired

depth perception, a prior history of falls, high functional status at the time of the initial hip fracture, decreased physical activity, and poor self-reported health or dizziness have each been identified in at least one study," Dr. Berry noted (5;7-10).

This understanding of who might benefit from treatment seems to further justify interventions to prevent future hip fractures, but what kinds of interventions? On the pharmacological side, the Online Forum looked to the evidence particularly for the use of bisphosphonates as potential preventive agents.

Bisphosphonates

The evidence to support the use of bisphosphonates for the secondary prevention of hip fractures is limited, but the existing data do suggest these agents will be effective for this purpose. Meta-analyses have looked at clinical trials of the oral bisphosphonates alendronate and risedronate, most of which included primarily women under the age of 80 who had experienced prior vertebral fractures (14;15). Results revealed that these bisphosphonates were effective in reducing both vertebral and non-vertebral fracture risk in such individuals: relative risk reductions of 45% (95% CI 0.43-0.69) and 33% (95% CI 0.64-0.92) were found with alendronate for secondary vertebral and non-vertebral fractures, respectively. For risedronate, relative risk reductions of 39% (95% CI 0.50-0.76) and 20% (95% 0.72-0.90) were observed for secondary vertebral and non-vertebral fractures, respectively.

While the meta-analyses included studies that were not specifically designed to follow individuals who experienced recent hip fractures, there is one study, called the HORIZON trial, which was specifically designed for this purpose (16). This randomized, double-blind, placebo-controlled trial examined the effects of the powerful intravenous bisphosphonate zoledronic acid in over 2,000 subjects who had experienced a hip fracture within the past 90 days; three-quarters of subjects were female, with a median follow-up of almost 2 years. Results showed a statistically significant 35% decrease in the 3-year risk of clinical fractures in the zoledronic acid group (HR=0.65, 95% CI 0.50-0.84, P=.0012), compared to placebo, with an absolute risk reduction of 5.3%. The HORIZON trial also documented a reduction of 28% in all-cause mortality, though the explanation to account for this finding is unclear.

When Should Bisphosphonates Be Given?

While the meta-analyses and results from the HORIZON trial bulwark the case for bisphosphonates for the secondary prevention of hip fractures, many questions remain regarding the use of these drugs. Chief among them is precisely when bisphosphonates should be administered following a hip fracture; Online Forum panelists expressed several worries in this regard.

The first concern relates to the hip fracture patient's vitamin D status. "The optimal time to start postoperative bisphosphonates is after you are assured that the patient is vitamin D replete," emphasized panelist Michael McClung, director of the Oregon Osteoporosis Center in Portland. "It's probably bad for patients, especially with potent bisphosphonates, to administer therapy in the setting of vitamin D deficiency, because of the risk of symptomatic hypocalcemia," Dr. McClung said.

In the HORIZON study, aware of a report (17) in the *New England Journal of Medicine* documenting a case of severe hypocalcemia in a vitamin D-deficient patient given intravenous pamidronate, the researchers, taking a cautious approach to ensure vitamin D repletion, waited two weeks after surgery before administering zoledronic acid. "What we didn't want to do was run this risk [of significant hypocalcemia], since we already knew, as the trial was going on, how many patients there were with vitamin D deficiency," stressed panelist Kenneth Lyles, lead author of the HORIZON trial and a professor of medicine at Duke University School of Medicine in Durham, North

Carolina. “We didn't have any clinically significant hypocalcemia, in the people that received zoledronic acid; that's the best data we have.”

Exactly how to ensure that patients have adequate vitamin D levels so that powerful bisphosphonates like zoledronic acid can be safely administered presents a challenge for clinicians. “This is still a bit of an art – I wish we had a little bit more pharmacologic data to guide us on exactly what the best regimen is for patients at various levels of vitamin D deficiency” according to panelist Cathleen Colón-Emeric, a co-author of the HORIZON study. “Based on our experience in HORIZON, I'm generally comfortable giving patients bisphosphonates once their level of 25-hydroxyvitamin D is above 20 nanograms per milliliter or if they have received at least 100,000 units over a 2-week period,” noted Dr. Colón-Emeric, also an associate professor of medicine at Duke University Medical Center. Because it may be difficult, logistically, to measure vitamin D levels in all patients, and because vitamin D deficiency is such a common problem, panelists agreed that empiric supplementation can be a desirable approach to ensuring that patients achieve adequate vitamin D levels.

While vitamin D repletion is necessary before giving bisphosphonates post-fracture, does vitamin D supplementation itself help to prevent subsequent fractures from occurring? While there are only limited data to support a role for vitamin D in the postoperative management of hip fracture patients, the evidence that does exist suggests that this treatment may be effective in reducing falls and fractures. One small, prospective, randomized, controlled trial investigated the effects of calcium and vitamin D supplementation in 150 post-menopausal women who had previously experienced a hip fracture; the study was not blinded and placebos were not used. (11). Study participants received either a single injection of 300,000 International Units (IUs) of intramuscular vitamin D_2; 300,000 IUs of intramuscular vitamin D_2 plus 1 gram of calcium per day; or 800 IUs of oral vitamin D_3 per day plus 1 gram of calcium per day, and were compared to subjects receiving no treatment. In all three groups, results showed a statistically significant decrease in the percentage of subjects who experienced a fall, with 7-8% of treatment groups experiencing a fall, versus 22% of the no treatment group (P=0.02). When specifically considering falls that resulted in a fracture, the two groups receiving both vitamin D and calcium were at lower risk for this outcome (8% experienced fracture-producing falls) than those receiving no treatment (14%), but this finding was not statistically significant (P=0.30).

Meta-analyses also suggest benefit from the use of vitamin D as a secondary prevention strategy (12;13). These analyses found that vitamin D reduced the risk of falls by 22% (OR=0.78, 95% CI 0.64-0.92), and the risk of non-vertebral fractures by 23% (OR=0.77, 95% CI 0.68-0.87), compared to calcium or placebo. Dr. Berry stressed that while the studies included in the meta-analyses did not specifically examine people with a history of fracture, many of them did not exclude such individuals, and because participants in these studies were elderly, at least some participants are likely to have experienced previous fractures.

Additional Concerns About the Timing of Bisphosphonate Administration

In addition to questions about hip fracture patients' vitamin D status, a second concern is whether giving patients bisphosphonates at an inopportune time may interfere with fracture healing. While animal studies have shown that treatment with bisphosphonates results in a larger, less remodeled fracture callus, the best time to begin postoperative bisphosphonates in humans, to minimize potential detrimental effects on fracture healing, remains unclear. “There would be value in a clinical trial that simply compared early onset bisphosphonate treatment with delayed onset bisphosphonate treatment” in terms of effects on fracture healing, according to panelist David Marsh, also a professor of clinical orthopedics at University College London. In this regard, the HORIZON study once again offers the best clinical trial evidence to date. “We found that there really wasn't any difference in fracture

healing with treatment from 14 to 90 days after surgery," Dr. Lyles said.

A third, related concern is that using bisphosphonates at the time of fracture healing may make them less effective for treating skeletal osteoporosis. "Since bisphosphonates are sequestered where bone is being formed, is there a risk that by giving bisphosphonates at the time of fracture healing, much of the bisphosphonate may be sequestered in the fracture and therefore not give systemic protection?" wondered Dr. Marsh. Patients suffering from Paget's disease suggest this prospect. "In patients with an active Pagetic lesion, we are quite certain that virtually all of the bisphosphonate is deposited there and not in the rest of the skeleton, so one has to keep in mind this theoretical possibility," according to Dr. McClung. Dr. Lyles also noted that some evidence exists from animal studies showing that intravenous bisphosphonate is sequestered in a fracture for the first week after that fracture is created.

Given all of these concerns, waiting two weeks post-surgery is the safest approach. "Giving IV bisphosphonates before two weeks is probably not the way to act – that's the data we have now," according to Dr. Lyles, who noted that licensing agencies in both the US and Europe recommend that bisphosphonates not be administered in the first two weeks following surgery.

Femoral Shaft Fractures

Another potential concern about using bisphosphonates in hip fracture patients is whether they will increase the risk of femoral shaft fractures. Case series have reported these unusual fractures in patients who have received long-term bisphosphonates (for instance, see (18;19)). Might the risk for these types of fractures among hip fracture patients differ from that observed in other patients treated with bisphosphonates?

"Unfortunately we can't definitively answer that question, based on our current state of knowledge about this type of fracture and severe suppression of bone turnover," said panelist Joseph Zerwekh, a co-author of the first case series (18) to describe these atypical fractures. Dr. Zerwekh, a professor of internal medicine at the University of Texas Southwestern Medical Center at Dallas, said that the evidence is inconclusive because not enough is known about the history of patients included in the case series. "In all of these reports, we do not know whether patients were put on bisphosphonates because of a vertebral or a nonvertebral fracture, or whether they were put on the bisphosphonate because of osteopenia, or low bone density. So, in some cases, there was no pre-existing fracture," Dr. Zerwekh said.

Not only is it unclear whether hip fracture patients are at increased risk of femoral shaft fractures, but it is also uncertain which specific subsets of hip fracture patients might be identified in advance as being more likely to suffer from these types of fractures. However, doctors should pay attention to the duration of bisphosphonate therapy as well as other drugs taken concomitantly with bisphosphonates, according to panelist Fergus McKiernan, co-author of a recent paper (19) describing three cases of femoral metadiaphyseal fractures in patients on long-term alendronate. "From the case series that have been presented, I think we should be alert to those patients who have been on bisphosphonates for a lengthy period of time, particularly in combination with steroids or other anti-resorptive agents," Dr. McKiernan emphasized.

In contrast, both Dr. Lyles and Dr. Colón-Emeric noted that in the HORIZON study, they saw a small number of these atypical fractures, but they were evenly divided between the two arms of the study.

Other Agents

In addition to bisphosphonates, there are a few small studies that have investigated other pharmacological agents. For instance, a small, prospective, randomized trial of calcitonin in 50 women who had experienced a hip fracture found that their relative risk of a second hip fracture was 0.3,

compared to placebo, but the finding was not statistically significant (20). Another study, a retrospective cohort study of 632 women from the Study of Osteoporotic Fractures (SOF), found that estrogen decreased the relative risk of a second hip fracture, but this study was an observational one, and not a randomized trial (7).

Non-Pharmacological Approaches

Preventing Falls

In addition to medications, the geriatrics field has also focused on preventing falls as a secondary prevention tactic, and meta-analyses have identified several effective interventions for individuals living in the community (21), to improve the risk factor profile for falling. The most effective interventions appear to be exercise, particularly tai chi, that is targeted towards improving strength and balance; a home hazards assessment; and the withdrawal of psychotropic medications. In contrast, research has been unable to identify interventions that are effective for people living in nursing homes (22); findings suggest that targeting nursing home residents' major risk factors for falls does reduces falls, but these findings are only trends that have not reached statistical significance.

Such is the verdict from research findings, but what actually happens in clinical practice now to help prevent falls? “Fortunately, most patients get aggressive physical therapy, are evaluated for an assisted device, and are prescribed lower extremity balance and strengthening exercises after their hip fracture already in the normal course of rehabilitation,” Dr. Colón-Emeric said in describing her clinical experience with the hip fracture patients she sees at Duke. She also noted that she would like her patients to have home safety evaluations, but has found that Medicare and Medicaid are reluctant to reimburse for this. Dr. Colón-Emeric also emphasizes to house staff and primary care physicians at Duke the importance of reviewing patients' psychotropic medications, particularly since such medications may have been prescribed for postoperative delirium; measuring orthostatic hypotension, since patients may have lost blood or have changed their heart medications; and treating vitamin D deficiency, all as ways to prevent falls post-hip fracture.

Hip Protectors

The use of hip protectors has also been investigated as a non-pharmacological approach to the secondary prevention of hip fractures, but with decidedly mixed results. Two recent meta-analyses found that hip protectors did not reduce the risk of fractures for individuals living in the community, while they did appear to be effective for people living in residential centers, though such findings have not always reached statistical significance in the latter case (23;24). However, many of the studies that have been included in these meta-analyses have been flawed because of problems with compliance with wearing hip protectors and also because of issues of study design. For instance, many of the studies included in the meta-analyses are of the cluster randomized variety. In such trials, an entire group of people (for instance, all the residents of a nursing home) wear hip protectors, and are compared to another group (residents of another nursing home) not receiving this intervention. “The cluster randomization approach has some intrinsic limitations for bias, in that it's not blinded, and institutional co-interventions occurring in the groups who received the hip protectors might also bias the results,” according to Online Forum co-presenter Douglas Kiel.

To try to overcome some of these limitations, Dr. Kiel and colleagues conducted a randomized clinical trial of 1,042 nursing home residents who were randomized to wear a hip protector on the right or left hip (25). Published in *JAMA* in 2007, the study found that, when comparing hip fracture rates between protected and unprotected hips, there was no statistically significant difference, and the hip protectors were found ineffective even in those subjects who exhibited good compliance by wearing the protectors more than 80% of the time.

Dr. Kiel, however, remains optimistic in hip protectors as an approach to preventing fractures, as do many other hip protector experts, stressing that flaws in the design and testing of hip protectors may account for recent null results. Indeed, currently there is no standard protocol to test hip protectors in the laboratory before moving them into clinical trials; it is not surprising that devices that have never been tested in a systematic and rigorous fashion fail to provide protection for human subjects. In this regard, the hip protector field is still young and evolving. “It is interesting that the field of bicycle helmets, and other protective gear, has followed the same learning curve, where it was soon realized how important it was to make sure that the products being manufactured and sold on the market are efficacious,” Dr. Kiel explained. “This requires that the materials and the products be tested in a state-of-the-art device, when thus far there has been no uniformity of testing and very little testing of the products that are used in clinical trials.” Dr. Kiel is now part of an international group of experts that is working to devise standard laboratory testing protocols for hip protectors. The group is also aiming to identify what the most appropriate clinical trial for a hip protector should look like – in terms of study population, whether to use a placebo group, and related issues – since there is still no agreement on these matters.

Dr. Kiel and others hope these challenges can be overcome, because there is much to like about the hip protector approach. “It's not a pharmacologic approach, and if we can design a better hip protector that would be worn, the protection provided is immediate – as soon as an effective product is worn – and the fracture risk is reduced,” Dr. Kiel stressed, in contrast to slower-acting pharmacological approaches.

Conclusion

Treating hip fracture patients with the goal of preventing future fractures will not be easy. “In the US, we are struggling against the fragmented delivery of health care following hip fracture, the lack of recognition of osteoporosis by physicians, and some reluctance to treat individuals with medications, because of cost, side effects or even concerns about delayed healing of the primary fracture,” according to Dr. Kiel, who also noted that many patients who have experienced hip fractures do not know that they suffer from osteoporosis and do not adhere to interventions to prevent future fractures. Nevertheless, as the first IBMS BoneKEy Online Forum demonstrated, the scope and seriousness of the hip fracture problem merits intervention, since the limited evidence that exists supports the use of both pharmacological and non-pharmacological approaches. It is simply time for physicians to incorporate the research into clinical reality.

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Presenters

Douglas P. Kiel and Sarah D. Berry (The Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA)

Invited Panelists

Michael R. McClung (Oregon Osteoporosis Center, Portland, OR, USA); Kenneth W. Lyles (Duke University Medical Center, Durham, NC, USA); Cathleen Colón-Emeric (Duke University Medical Center, Durham, NC, USA); David Marsh (University College London, London, UK); Fergus E. McKiernan (Marshfield Clinic, Marshfield, WI, USA); Joseph E. Zerwekh (University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA)

Moderator

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