

Low-dose diclofenac in patients with fragility fractures

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Summary

Most osteoporotic patients complain of back pain one year after a fragility vertebral fracture and the frequency of chronic back pain increases with increasing age. The use of the lowest effective dose of an analgesic which is able to control symptoms seems to be a possible solution in order to limit potential side effects in multi-treated elderly patients. Non-steroidal anti-inflammatory drugs (NSAIDs) have a proven efficacy in the treatment of back pain associated with fragility vertebral fractures and diclofenac is available at low-dose subcutaneous injective formulation. This is the rationale of ImPAVeDic study, acronym of Improvement of back Pain Associated with fragility Vertebral fractures with low-dose Diclofenac, an observational study that will be performed in a group of 50 elderly (≥ 65 years), male and female osteoporotic patients with symptomatic fragility vertebral fractures. The objective of the study is to evaluate the improvement of back pain in the study population treated with low-dose diclofenac and regularly monitored for 2-6 months. Visual Analogic Scale (VAS) and Numerical Rating Scale (NRS) will be used for pain monitoring. The reduction of the risk of occurrence of drug side effects can favour the optimization of elderly patients' care.

KEY WORDS: osteoporosis; elderly patients; fragility fractures; vertebral fractures; back pain; diclofenac; longitudinal study.

Introduction

ImPAVeDic study, acronym of Improvement of back Pain Associated with fragility Vertebral fractures with low-dose Diclofenac, is a longitudinal, prospective, observational No Profit study which has been recently approved by local Ethics Committee.

Clinical basis and implications and specific features of ImPAVeDic study are described in the present mini-review.

Clinical basis and rationale of ImPAVeDic study

Osteoporosis is a pathological condition characterized by increased bone fragility due to reduced bone mass and/or poor bone quality, thus leading to increased fracture risk (1, 2).

Epidemiological data indicate that osteoporosis is more frequent not only in females, but also in the elderly population. In fact, 22 millions of women and 5.5 millions of men are currently known to be affected by osteoporosis within the European Union (3). Moreover, primitive forms of osteoporosis (95% of cases) affect postmenopausal women (4) and both males and females after 70 years of age (5).

Fragility fractures are the most threatening complication of osteoporosis. They are typically non-traumatic fractures or they can be associated with low-energy ineffective trauma (6); they usually occur at specific skeletal sites, such as dorsal and lumbar vertebral bodies, proximal hip, distal radius, and proximal humerus (3). The incidence of osteoporotic fractures amounts to nearly 9 millions/year worldwide, and 1.4 millions of these fractures are clinically symptomatic vertebral fractures (2).

Patients with fragility vertebral fractures can develop complications which can seriously compromise their health and quality of life.

Indeed, the presence of vertebral fractures leads to a 5-fold increase in the risk of new vertebral fractures (Domino Effect) (7) and to a 2-3-fold increase in the risk of fragility fractures at skeletal sites other than vertebral bodies (1).

Moreover, back pain is typically associated with fragility vertebral fractures. At the moment of the fracture occurrence, back pain has an acute onset and is localized at the vertebral fracture site (8), so that the sudden occurrence of back pain in absence of documentable injury often reveals a fragility vertebral fracture in most osteoporotic patients. Back pain can last for 4-6 weeks (8), but it tends to become chronic in most patients: more than $\frac{3}{4}$ of whom complain of severe back pain one year after the fracture (9).

Contrary to pathogenetic mechanisms of fragility vertebral fracture-associated acute back pain, those of chronic back pain are significantly less understood. It has been hypothesized that bone marrow edema of the fractured vertebral body might play a role (8). Moreover, fragility vertebral fracture-associated height loss, dorsal kyphosis, and consequent permanent contraction of paraspinal muscles, required to

maintain the posture, can lead to spinal biomechanical changes, thus promoting back pain chronicity (3, 8). Finally, individual aspects of subjective pain perception have been supposed to have a role (3).

Current evidence shows that higher level of severity of vertebral deformity is associated with higher risk of moderate to severe back pain (10), and that more serious back pain-related disability and worse quality of life are correlated with more severe vertebral fracture (8). Dorsal vertebral fractures and crush vertebral deformities are known to be associated with worse prognosis in terms of complete *restitutio ad integrum* and restoration of good health (11).

Chronic back pain is more frequent in the elderly population and the increase of its frequency with increasing age (3) can have two main reasons.

The first one is that vertebral fracture risk is higher for elderly people than for young subjects, as age is a non-changeable fracture risk factor itself (2). The prevalence of osteoporosis increases with advancing age (3), as well as the risk of fall because of senescence-associated sedative drugs intake, visual defects, sarcopenia, and muscle weakness (1).

The second reason is specifically related to the sarcopenia and the muscle weakness which typically affect the elderly population. They could induce gradual bone loss which in turn could facilitate the development of dorsal kyphosis even in absence of vertebral fractures; this deformity and the consequent permanent muscle contraction could lead to chronic back pain (3).

A future increase in the prevalence of osteoporosis is expected because of the progressive ageing of the general population (5); consequently, a future increase of fragility fractures and their associated complications and costs is also expected (2), hence the problem of chronic back pain in the elderly population is going to increase. This is a problem of fundamental importance, because the presence of persistent chronic pain in every single person, but especially in older subjects, can seriously jeopardize their health and quality of life. Mood alterations, such as anxiety and depression, sleep and hunger defects can develop as a consequence of chronic pain. Gradual motor disability can also derive from chronic persistence of back pain and can increase the risk of immobilization which in turn can worsen osteoporosis, thus increasing the risk of vertebral fracture and, consequently, the risk of chronic back pain worsening. Therefore, pain treatment is mandatory in everyone, particularly in elderly people, and the right of every patient to be cured in order to mitigate and resolve pain is ratified by law.

Although the pain treatment has a very important value, it also represents a quite complex challenge for clinicians within their daily clinical practice. Elderly patients are often affected by multiple comorbidities, hence they are treated with multiple drugs. Therefore, the addition of an analgesic as a new drug among those already taken can facilitate the occurrence of one or more adverse effects which can worsen pre-existing diseases or even lead to the development of new pathologies. Overall, this can seriously compromise both already precarious health condition and already unstable psychophysical balance of elderly patients.

Besides surgical treatment (vertebroplasty, kyphoplasty), which are limited to selected cases, both opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are pharmacological therapies widely used for the treatment of back pain

associated with fragility vertebral fractures (3).

NSAIDs are drugs of proven efficacy for the treatment of this kind of pain, both as acute and chronic back pain (3, 12). Nevertheless, NSAIDs are burdened by a series of potential adverse effects, such as gastrointestinal bleeding and renal impairment (13). Therefore, the use of low-dose analgesic drug could be a possible solution for the challenge of pain treatment in the elderly, that is the use of the lowest effective dose of the drug which is able to control symptoms, in order to limit potential side effects. This solution, which appears simple, can actually result quite complex to be realized in clinical practice.

Among NSAIDs, diclofenac seems to represent a valid therapeutic tool for this purpose. Indeed, diclofenac has a very wide literature which can confirm both its efficacy as anti-inflammatory, analgesic, and also antipyretic drug (12, 14, 15) and its tolerability. Many studies showed a lower risk of complications and fewer side effects, particularly gastrointestinal ones, with the use of diclofenac rather than with the use of the other NSAIDs (14, 16).

Diclofenac is a derivative of aminophenylacetic acid; it acts through the inhibition of cyclooxygenase (COX) enzyme, and it has a significantly higher affinity for the constitutive form of the enzyme (COX-1) rather than for the induced form (COX-2) (17).

Diclofenac is available at low and very low-dose; its injective formulation can ensure a faster plasmatic absorption and its subcutaneous formulation has the further advantage of self-injection by the patient himself (18).

Study population

ImPAVeDic study will be performed in a group of 50 elderly (≥ 65 years), male and female osteoporotic patients referring to the Mineral and Bone Metabolism Diseases Unit who present with clinically-symptomatic (back pain) fragility vertebral fractures. Patients will be enrolled independently of the period of vertebral fracture occurrence, so that both incident and prevalent vertebral fractures will be considered. Previous or current anti-fracture pharmacological therapy will not be an exclusion criterion for patients' recruitment, whereas oncologic patients will be excluded.

Patients who will meet these inclusion criteria and will also receive the prescription of low-dose subcutaneous diclofenac as analgesic drug, in accordance with the routine clinical practice, will be considered for the enrolment in the present study. Selected patients will be enrolled after written informed consent.

Study procedures

Presence and intensity of back pain should always be evaluated in osteoporotic patients with fragility vertebral fractures during medical examination and this will also be performed with enrolled patients.

Back pain will be evaluated using two specific pain evaluation scales, the Visual Analogic Scale (VAS) and the Numerical Rating Scale (NRS).

Enrolled patients will receive the prescription of diclofenac at a weight-dependent dose, particularly 25 milligrams (mg)/millilitre (ml) 1 subcutaneous (sc) vial/day in case of body weight < 50 kilograms (Kg) and 50 mg/ml 1 sc

vial/day if body weight \geq 50 Kg. Diclofenac will be taken for 6 days long.

On the 7th day, patients will receive a phone call, during which they will be asked to fill out again the pain evaluation scales VAS and NRS, in order to detect changes in back pain. In case of persistence of pain, analgesic therapy with diclofenac may be temporarily continued according to the medical opinion.

Enrolled patients will undergo routine medical visits for pain monitoring every month, for a period of time ranging from a minimum of 2 months and a maximum of 6 months, which will be individualized on the basis of the presence and the extent of back pain complained by each single patient. At each visit, VAS and NRS will be used again for pain monitoring. In case of back pain persistence, diclofenac will be prescribed again, and it will be taken with the same modalities of the first prescription. On the 7th day since the beginning of every new 6-day regimen, back pain will be re-evaluated through a phone call asking patients to fill out again VAS and NRS.

Quality of life will be also evaluated using the specific questionnaire SF-36.

Objective, endpoint, and aim of the study

The objective of ImpPAVeDic study is to evaluate the improvement of both back pain and quality of life in our study population of patients treated with low-dose diclofenac and longitudinally followed-up for a minimum period of time of 2 months and a maximum of 6 months, through the endpoint of the evaluation of changes in VAS, NRS, and SF-36 questionnaire scores, respectively.

The aim of the present study is to demonstrate the improvement of back pain in elderly patients affected by fragility vertebral fractures with low-dose diclofenac.

Conclusions

In conclusion, the possibility of giving patients the lowest dose of a drug which is able to control symptoms can allow to minimize the risk of the occurrence of adverse events, thus leading to the optimization of patients' care, especially when the patient is elderly.

Financial disclosure

All Authors declare that they have no conflicts of interest.

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