Bisphosphonates Influence and Pain Assessment in Mobilization of Patients with Fragility Fracture of the Pelvis

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Fragility fractures of the pelvis have lately gained interest due to the increased incidence caused by aging populations. The aim of the study was to evaluate the results of the therapy in patients with pelvic fragility fracture admitted between January 2015 and September 2018 St. Spiridon Emergency Hospital in Iasi in order to improve the therapeutic approach. We assessed the correlation between pain and the early mobilization under the weight bearing condition in patients with and without osteoporotic therapy in history. The study emphasizes the role of pain in recovery process and underline the serious consequences of the late detection of bone fragility. Our study had revealed that previous osteoporotic treatment has benefits in the event of a fracture. As a result of this analysis, we consider that the age for the prophylactic measures in bone fragility should go below 60 years.

Keywords: bisphosphonates, pelvis fragility fracture, pain, mobility

Fragility fractures (FF) lately raised due to the increasing lifespan. Bone fragility is a severe medical condition due to immobilization, loss of individual independency and high mortality. Fragility fracture is defined as a fracture that occurs following a low intensity trauma and are mainly located in the spine, femur, proximal humerus, distal radius, and pelvis. Bone fragility is caused by bone structure damage (osteoporosis) or by prolonged glucocorticoid treatment, rheumatoid arthritis, bone tumors etc. The highest incidence of fragility fractures occurs over 60 years, mainly in women. In order to assess the risk of fragility fracture, a number of guidelines (FRAX, CAROC) [1, 2] associate individual risk factors (sex, age, alcohol intake, drugs, etc.) with clinical factors (bone mineral density). A particular case is the fragility fracture of the pelvis (FFP) in which both diagnosis and treatment raises serious difficulties. In order to facilitate the diagnosis and subsequently to improve the treatment guides for FFP classification were developed [3]. According to the initial classification the pelvic fractures are: type A stable, type B unstable rotating, type C unstable rotating and vertical. This classification did not reflect the severity of pelvic ring lesions in elderly patients. Based on radiographic assessment and fracture instability Rommens et al [4] proposed a new classification of FFP in four types presented in detail in the literature [5, 6]. Choosing the right treatment for FFP is difficult because of health and comorbidities in elderly patients; both conservative and surgical therapy involve equally large risks. As a general rule, literature recommends conservative treatment as long as it leads to pain relieve, allows mobilization and fracture does not show displacements [7]. Surgery is recommended when pain prevent patient to mobilize or when fractures are unstable [8, 9]. Alternatively to surgery, pharmacological therapy uses anti-osteoporotic (bisphosphonates, denosumab, raloxifene) or anabolic drugs (teriparatide) for bone repair. Depending on the pharmaceutical agent, it is estimated that pharmacotherapy can reduce the risk of fracture by 30% to 40%.

The chemistry of bisphosphonates (BP). In bone diseases characterized by bone resorption such as osteoporosis, bone metastases, Paget's disease, bisphosphonates have proven to be very effective. Bisphosphonates show an analogous structure to pyrophosphate (PP) which is a by-product of metabolism figure 1. The great efficacy of BP is conferred by two chemical properties: first they efficiently adsorb to hydroxyapatite and second they inhibit hydroxyapatite destruction thus suppressing bone resorption [10]. The roles of different chemical groups are shown in figure 2. Phosphate groups confer bisphosphonates a strong affinity for bone hydroxyapatite crystals similar to that seen in endogenous pyrophosphate. The hydroxyl group attached to the central carbon (the R_1 position for most of bisphosphonates) increases the ability of BP to bind calcium. The phosphates and hydroxyl groups generate a tertiary interaction that improves the BP specificity for the bone matrix. The structure of the radical in the R_2 position determines the extent of the bone resorption. Although the phosphate and hydroxyl groups are essential for the bisphosphonate affinity, the structure of the R_2 moiety determine the anti-resorbtion potency. Thus by introducing a nitrogen atom or an amino group at the R_2 position, the anti-resorption capacity of BP increases by 10 to 10,000 fold compared to the non nitrogen-containing bisphosphonates [11] (fig. 3).

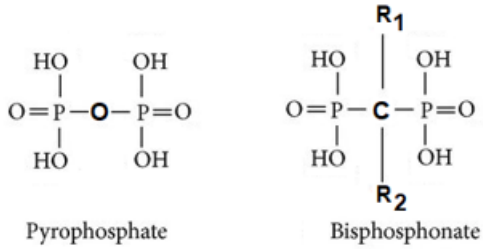

Fig. 1. Chemical structure of pyrophosphate and bisphosphonates

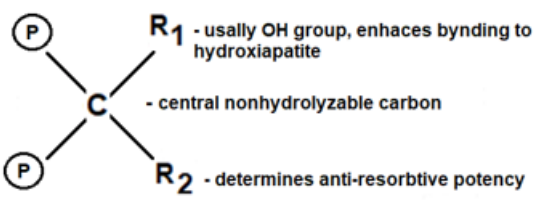

Fig. 2. The role of chemical components in bisphosphonate anti-resorption activity

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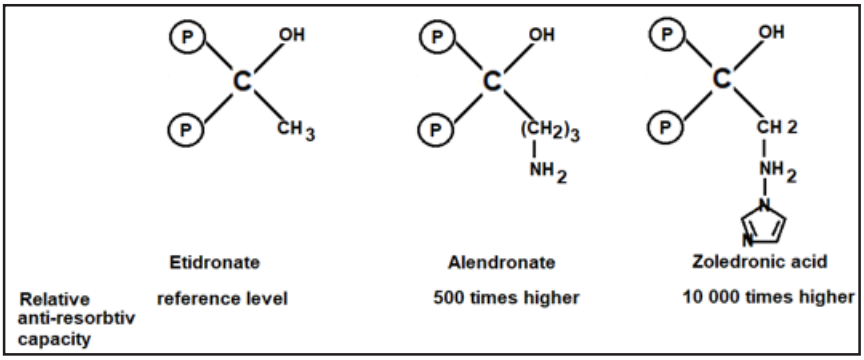

Fig. 3. Influence of the chemical structure of the R_2 group on the anti-resorbtion bisphosphonate activity

Regarding FFP in the literature there is little data compared to other FF and there is no data on the incidence, treatment, relapse, mortality in Romania. The aim of our study was to evaluate the results of the therapy in patients with pelvic fragility fracture admitted between January 2015 and September 2018 at the St. Spiridon Emergency Hospital, in Iasi, in order to improve the therapeutic approach.

Experimental part

Materials and methods

The inclusion criteria for the patients in the study were: patients aged 60 years and older who experienced pelvic fractures, admitted between January 2015 and September 2018 at our Trauma Center. Exclusions criteria were: patients with pelvis injuries from high energy trauma or oncological bone diseases. The fractures had to be confirmed by X-ray or computer tomography. Clinical parameters of interest as age, sex, comorbidities (diabetes, heart failure, renal failure etc), bone mineral density (BMD), osteoporosis therapy, history of fractures, alcohol/nicotine abuse and menopausal hormone therapy were recorded. Informed consent from all patients included in this study was obtained. The current research has been conducted in accordance to the ethical principles set out by the Helsinki Declaration.

Patients were divided in 2 groups: Group I- patients diagnosed with osteoporosis and receiving osteoporotic treatment (bisphosphonates) before fracture, Group II- patients not diagnosed with osteoporosis before fracture. Group I contains 41 patients aged between 65-87 years (34 women, 7 males). Group II contains 54 patients aged 60-85 years (46 women, 8 males). PacientPatients in both groups was conservatively treated and received pain medication. Mobility recovery was started for patients in both groups during hospitalization, in our clinic or in specialized recovery department.

All patients were monitored for both short and long term and the incidence of relapses and mortality were recorded. The short-term follow-up was performed during hospitalization and after hospital discharge at 14 days and 1 month. During hospitalization we monitored the time required to reduce pain at mobilization and early mobilization under weight bearing conditions. Patients who did not experience increased pain at mobilization continued recovery. Patients with increased pain at mobilization were re-evaluated with X-rays to identify fracture displacement or other causes and were excluded from the study. After discharge, at 14 days and one month after, patients were evaluated for residual pain and for bone injury assessment by X-ray. Long-term follow-up was done either by patient re-assessment or by interviewing patients by telephone. The residual pain, autonomy, relapses, osteoporosis therapy and mortality were recorded (fig. 4).

The pain assessment was realized by using the visual analog scale or VAS. VAS pain is a continuous line

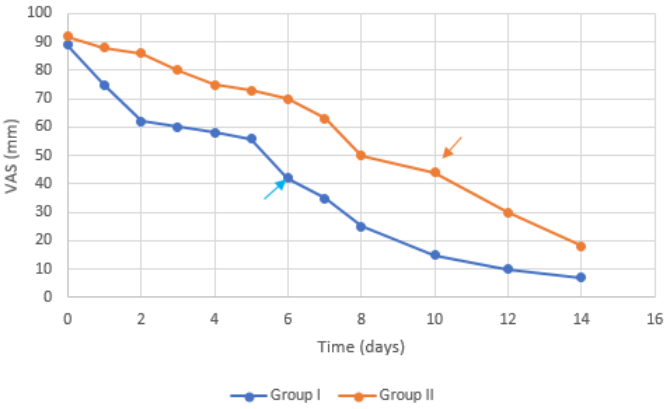

Fig. 4. Pain assessment during hospitalization

(horizontal-HVAS or vertical-VVAS), usually 10 cm (100 mm), framed by 2 verbal descriptors, one for each extreme of symptom [12]. The intensity of pain goes from *no pain (*score of 0) to *worst imaginable pain* (score of 100 coresponding to100 mm). The VAS score interpretation after Jensen [13,12*] is: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm) and severe pain (75-100 mm).

The early mobilization was assessed in dinamic way in weight bearing conditions. Dynamic mobilization was achieved by walking for a distance (counted as a number of steps) where the pain does not prevent movement. Relieving pain is a favorable sign in the healing process. Thus mobilization began when the patient experienced the pain at mobilization acceptable or lower than the initial pain (according to the VAS score).

Results and discussions

Pain assessment was done by measuring the time required to relieve pain at mobilization. For group I, the time to decreased pain was noticed within 14 days in 86.3% (34 patients) and after 14 days in 13.7% (7 patients). The pain relief time for group II was noticed within 14 days in 83.3% (45 patients) and after 14 days in 16.7% (9 patients). Patients with pain relief time higher than 14 days were excluded from the study. Pain assesment for pacients with pain reduction within 14 days, in both groups, during hospitalization, is shown in figure 4. Pain assesment during hospotalization. In group I with patients that previously received osteoporotic treatment, the pain at mobilization decreases and reach the mild range around the 6th day after admission. In group II with patients not detected for osteoporosis before the fracture, the pain reach the mild range around the 10 days of hospitalization. From day 10, pain gradually decreases but remains in the mild range at a higher level for group II when compared to group I. These data suggest a significant change in bone structure, for group II, caused by osteoporosis not being diagnosed on time. In the absence of the treatment, the osteoporosis

becomes advanced thus increasing the recovery period. These data indicate that previous osteoporotic treatment provides the bone with a better morphology that helps the healing process even if a fracture occurs. An indirect effect of osteoporotic previous treatment was the smaller time for the pain relieve found in Group I versus group II.

Mobilization assesment was realised in a dynamic way throuh a method used in our hospital since currently there is no standardized method in literature [14]. Recently Valiani try to adapt the Braden mobility subscale [15] but the model shows limitations and was not generalized. In our clinic the mobilization was initiated as early as possible depending on the degree of pain experienced by the patient. Patients were encouraged to perform light movements then to mobilize in the seated position on the bedside. If the pain caused by mobilization was felt as acceptable, patients began the dynamic mobilization under weight bearing conditions. Dynamic mobilization was achieved by walking on a distance that gradually increases. The progression of dynamic mobility and pain relieve is presented for both groups in figure 5, VAS and dynamic mobility evolution for Group I respectively in figure 6, VAS and dynamic mobility evolution for Group II. Data from group I show that pain intensity decreases to moderate level within 3 days, allowing mobilization to start. In the days following the mobilization (between 3rd and 5th day), the pain remains to the same level probably due to the mobilization effort. After that, the pain progressively diminishes to the low *mild* range. Data from group II show a similar pattern but the pain persists longer and mobilization starts later, in the 6th day. Between 6th and 8th day the pain remains to the same level, in a similar way to group I. After that even pain decreases it has a higer level as compared to group I. The time span for early mobilization with weight bearing found in our study is similar to literature for group I but slightly higher than in literature for group II [16]. Analyzed data indicate the benefits of the osteoprosis early detection and therapy.

After discharge, all patients were advised to investigate BMD and FRAX score to assess the risk of a new fracture.

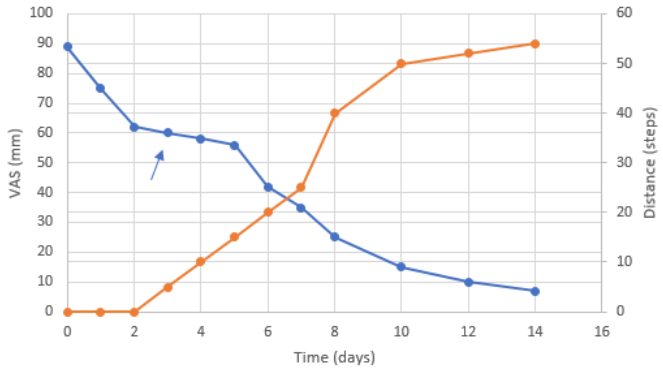

Fig. 5. VAS and dynamic mobility evolution for Group I

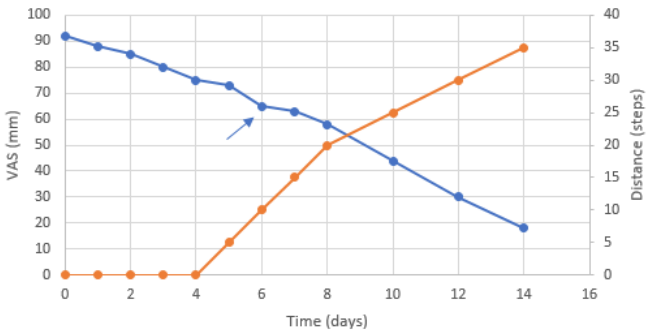

Fig. 6. VAS and dynamic mobility evolution for Group II

Fourteen days after discharge, patients who came back for assessment showed different degrees of bone injury evolution in the X-Ray with better healing results for Group I as compared to group II. Patients report tolerable pain and some need for painkillers. One month after discharge 85% of patients reports a mild pain and some need for pain medication. No relapses were reported during this time span, but 5 deaths were recorded for all period of study.

The long-term follow-up shows that one year after FFP 10% (9 patients) died thus confirming the high mortality risk of FFP. From the 65 patients responding to the long–term follow-up only 63% (41patients) sustained the osteoporosis treatment. One year from discharge not recurrent FFP was reported but three case of other fragility fracture occured, two with femoral neck fracture and one with right forearm ankle fracture.

The osteoporotic pacients included in our study received bisphosphonates, the main osteoprosis medication used in Romania. This study emphasises the benefit of BP administration that promotes the bone repairing process and leads to the better recovery observed for this group. BP delays remodeling of the callus but increase its volume by blocking the bone turnover [17] thus allowing subsequently the bone mass restoring. Currently literature indicates two new effiecient drugs with targeted action on osteoporotic bone, teriparatide and strontium ranelate that exert anabolic activity favoring the formation and maturation of callus [17,18]. Latest research regarding bone fraglility try to identify the mechanism that lead to osteoporosis. Some studies indicate the mechanism of reactive oxygen species as a possible cause of bone fragility [19-22], other consider homocysteine as a possible cause for the disease [23-26]. Many literature data show that homocysteine levels are directly linked to oxidative mechanims and both may be involved in bone remodeling [27,28,29,30].

Conclusions

Our study highlights the importance of treatment for osteoporosis to prevent pelvic insufficiency fractures and underline the serious consequences of the late detection of bone fragility. The study emphasizes the role of pain in recovery process. Our study had revealed that previous osteoporosis treatment has big benefits in the event of a new fracture. As a result of this analysis, we consider that the age of prophylactic measures should fall well below 60 years. The awareness of the early process, namely osteopenia, is mandatory to prevent the subsequent development of osteoporosis.

The limitation of the study consists in the fact that one years later most of the patient refuses to come to control or to make the bone density test.

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