

Enhancement of hip fracture healing in the elderly: Evidence deriving from a pilot randomized trial



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ABSTRACT

Enhancement of healing of osteoporotic fractures remains a significant objective of contemporary clinical care. Aiming to produce preliminary clinical evidence on the effect of antiosteoporotic drugs on the process of fragility fracture healing, a pilot prospective randomized assessor-blinded trial was performed. The tested hypothesis was that it is possible to accelerate the healing of hip fractures in the presence of osteoporosis with the administration of therapeutic agents.

However, significant difficulties of recruitment and completion of follow up did not allow the researchers to produce the preliminary evidence testing the study hypothesis, highlighting the challenges that contemporary clinical investigators face when conducting studies focusing on elderly patients, with high proportion of coinciding factors affecting patients' eligibility, compliance, and overall outcome.

Nevertheless, the significance of enhancing bone healing in this specific patient population, dictates further clinical efforts and future well designed and funded trials of adequate power and level of evidence are desirable to allow the effective and safer management of the consequences of the modern epidemic of osteoporosis.

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Osteoporosis is a very common disease in the elderly characterized by loss of trabecular bone mass and connectivity, as well as thinning of cortical bone. It increases the number of atraumatic/low energy fractures, contributes to the severity of traumatic fractures, and predisposes the local environment to a delayed bone healing response [1–3]. Fractures that result from this disorder affect 40% of women and 14% of men over the age of 50 years [4,5].

According to Eurostat's latest population projection scenario (Europop2010 [6]) for the 27 Member States of the European Union (EU) and the EFTA countries in 2010, 27 million women and men were estimated to have osteoporosis. At the same geographic areas, 3.5 million new fragility fractures are recorded per year, of which 620,000 were hip fractures, 520,000 vertebral fractures,

560,000 forearm fractures and 1,800,000 other fractures. The number of deaths causally related to fractures in 2010 was estimated at 43,000. Previous and incident fractures also accounted for 1,180,000 quality adjusted life years lost during 2010. The economic burden of incident and prior fragility fractures was estimated at €37 billion [6].

In the UK even from 2001, elderly over 60 years of age outnumbered the under 16 years, and by 2020 the population over 65 years is expected to reach for the first time the 25% overall [7]. Osteoporosis affects over 2 million people in the UK and every year more than 300,000 suffer a fragility fracture, including more than 70,000 hip fractures [8].

It is obvious that with the increasing number of elderly people in the developed societies, this disease and its consequences have become a real epidemic. Therefore, elderly patients will increasingly consume more hospital resources than patients from any other group, especially for the treatment of fragility fractures of both the upper and lower extremity [9,10].

The effective management of these fractures is challenging, not only due to the compromised mechanical and biological capacity of the elderly musculoskeletal system, but also due to the presence of

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serious comorbidities, the need for early mobilization and unprotected ambulation following fracture surgery, as well as due to the high rates of complications. These can be fracture specific ones (non-union, mal-alignment, metal work failures, surgical site infection, re-operations), but also systematic ones as incapacity and/or even death.

This high rate of complications has stimulated extensive research in the development of special techniques and implants; such as the new generation of angle stable fixation devices (locking plates and nails) [11–14], the augmentation of fracture fixation with local bone graft substitutes [15–18], as well as the administration of systemic drug therapies affecting the bone metabolism [19–21].

Aiming to produce preliminary clinical evidence on the effect of antiosteoporotic drugs on the process of fragility fracture healing, a pilot prospective randomized assessor-blinded trial was attempted. The tested hypothesis was that it is possible to accelerate the healing of hip fractures in the presence of osteoporosis with the administration of therapeutic agents, and thus reduce pain and functional impairment at 3 and 6 months postoperatively. Vitamin D and calcium (control), plus bisphosphonate (Alendronate – 70 mg orally), or plus Parathyroid hormone (Forsteo – 20 mcg subcutaneously) were randomly administered to patients with acute low energy hip fractures requiring surgery. Patients, following their informed consent, received the allocated treatment for a period of 4 weeks at doses recommended for osteoporosis treatment.

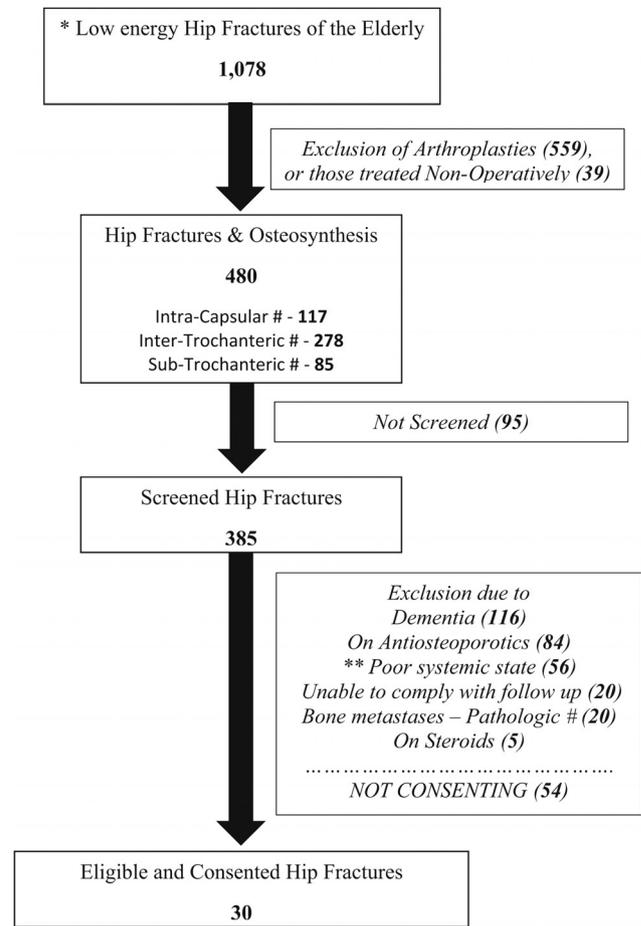
Following the appropriate institutional REC, R&D, and MHRA approvals the study with EUDRACT number 2009-015058-38, R&D OR09/9018, funded by the British Orthopaedic Association was launched in April of 2011. Initially was designed to recruit 120 patients from a single UK hospital, over a period of 12 months, and follow them up clinically and radiologically for 6 months post-surgery.

Patients younger than 60 years of age, with contraindications to any of the study drugs, or currently on any of them or on steroids, patients with dementia or unable to complete the study protocol, with bone metastases, open or pathologic fractures, known metabolic bone disease, rheumatoid arthritis or chronic renal failure were all excluded. Outcome measures including the Johanson Hip Rating Questionnaire [22], radiological union/nonunion, as well as local and systemic complication rates were recorded at 6 weeks, 3 and 6 months post-surgery.

As identified from the hospital's local hip fracture database, whose data are further submitted to the National Hip Fracture database [23], for the 19 months that the study was open to recruitment (between the years 2011–2012–2013), in total 1078 patients were treated following a low energy hip fracture. Of these 480 (44.5%) were treated with some form of osteosynthesis. 385 (80.2%) were screened from the study associates, and 84 (17.5%) were found to be eligible for recruitment according to the selection criteria (Fig. 1). Of those eligible, 30 (38%) consented to take part to the study. From the total population who sustained a hip fracture and underwent surgical fixation, only 6.3% were both eligible and consented to the study.

Eleven patients (36.7%) did not complete the study; 3 due to death within the study period, and 8 declined to attend at some point of the study follow up – early drop outs. The basic characteristics of all recruited patients are presented to Table 1. No meaningful statistical comparative analysis was possible due to the small sample that was possible to enrol and follow up, as this pilot randomized clinical trial was closed due to limited recruitment rates and funding resources.

Augmentation of healing of osteoporotic fractures remains a significant objective of contemporary clinical care. The pressure added by the climbing figures of this epidemic [2,24], together with



* ≥ 60 years, over a 19 month period of active recruitment, within the years 2011–2012–2013.

** Poor systemic state including Chronic Renal Failure, Metabolic Bone disease other than osteoporosis, Rheumatoid Arthritis, Acute Confusion.
fractures.

Fig. 1. Flowchart of application of the study specific selection criteria to the cohort of patients admitted at the Leeds General Infirmary over the period of recruitment with low energy hip fractures.

the evidence emerging from basic science and animal studies [25–28], creates a challenging environment for clinical researchers.

There are several encouraging reports on the effect of common and less common pharmaceutical agents to the healing process [15,20,26]. The antiosteoporotic drugs represent a quite attractive category of such agents [19], as they are quite often already prescribed to this cohort of patients mainly to prevent fragility fractures. They are administered either as a result of previous bone density investigations, or following a previously sustained fragility fracture [29,30]. In the UK, the initiation of antiosteoporotic therapy is guided by the use of the FRAX[®] and the QFracture[®] tools [31,32], and the guidelines of the National Osteoporosis Guideline Group – NOGG [24], and managed usually from primary care physicians.

In this small cohort of 30 elderly patients, none was on any antiosteoporotic drugs, and during screening only 21.8% (84/385) were excluded due to being already on any of these agents. Hence, these observations accord with the most significant limitation of antiosteoporotic treatment, which is poor compliance and/or

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