Injury, Int. J. Care Injured 46 (2015) 1425–1428

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

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

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ARTICLE INFO

Keywords:
Fragility fracture
Osteoporosis
Hip fracture
NOF
Antiosteoporotic therapy
Prospective randomized trial

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.

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 65years 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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http://dx.doi.org/10.1016/j.injury.2015.06.033
0020–1383/

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.

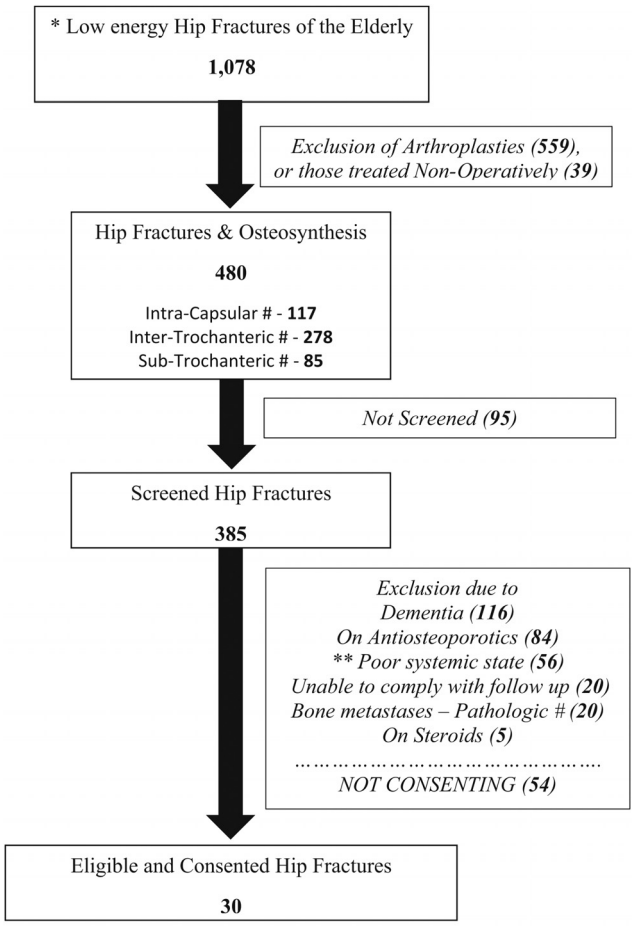
Following the appropriate institutional REC, R&D, and MHRA approvals the study with EUDRACT number 2009-015058-38, R&D OR09/9018, funded by the British Orthopaedic Association was launched in April of 2011. Initially was designed to recruit 120 patients from a single UK hospital, over a period of 12 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 6weeks, 3 and 6months 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



* ≥60years, 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

Table 1
Basic characteristics of the 30 patients that were recruited by the research team, randomized to one of the three antiosteoporotic drug therapies for 4weeks after their injury and followed up for 6months after their surgery.

	Overall	Control group – only VitD and Calcium	Bisphosphonates & VitD and Calcium	Parathormone & VitD and Calcium
No,	30	10	11	9
%	100%	33.3%	36.7%	30%
Female/Male ratio	24/6	7/3	9/2	8/1
Age	75 years	75 years	75 years	75 years
Mean, SD	8.89	8.85	9.18	8.98
Type of Fracture	22 I/Troch	22 I/Troch	22 I/Troch	22 I/Troch
	4 Sub/Troch	4 Sub/Troch	4 Sub/Troch	4 Sub/Troch
	4 I/Capsular #	4 Intra/Capsular #	4 Intra/Capsular #	4 Intra/Capsular #
Type of Fixation	20 DHS	7 DHS	6 DHS	7 DHS
	6 IMN	3 IMN	1 IMN	2 IMN
	4 CS	0 CS	4 CS	0 CS
Ambulatory status baseline	21 unaided	6 unaided	8 unaided	7 unaided
	5 walking stick	3 walking stick	2 walking stick	0 walking stick
	4 frame	1 frame	1 frame	2 frame
ASA score	2	2	2	2
Mean, SD	1.01	1.03	1.02	0.98
JHRQ baseline	69	68	69	69
Mean, SD	9.17	9.0	8.9	9.2
JHRQ at 6weeks	49	51	49	50
	22.4	23.8	23.1	24.1
JHRQ at 3months	56	57	56	56
	27.2	27.5	26.9	24.6
JHRQ at 6months	64	64	65	65
	32.7	33.1	33.0	31.9
Lost to follow up – Early drop outs	11	5	3	3
Complications	16 none	5 none	7 none	4 none
	10 systemic*	5 systemic*	3 systemic*	2 systemic*
	7 local**	3 local**	1 local**	3 local**
	4 deaths	3 deaths	1 deaths	0 deaths
Non-Unions at 6months	2	2	0	0

* Systemic complications including anaemia, constipation, CVA, nausea, LRTI, transaminasemia, UTI.
** Local complications including DVT, implant failure, leg swelling, heel pressure sore, superficial SSI, CS; cannulated screw, CVA; cerebral vascular accident, DHS; dynamic hip screw, DVT; deep vein thrombosis, IMN; intramedullary nailing, I/Capsular; intracapsular fracture, I/Troch; intertrochanteric fracture, SD; standard deviation, SSI; surgical site infection, Sub/Troch; subtrochanteric fracture, JHRQ; Johanson hip rating questionnaire, UTI; urinary tract infection,

delays on its initiation. As previously recorded [33], compliance is problematic in patients of this age group, as well as in general when treating chronic conditions [34]. Recent data in the UK show that more than 68% of patients even if diagnosed and prescribed, are not taking their medication after one year [35].

Previous clinical research, has clearly indicated, in a cohort of 520 non-randomized cases, that antiosteoporotic treatment can be an important predictor of better outcome for fragility fractures treated operatively, affecting functional recovery, re-fracture rates, and overall patient's quality of life [19].

As evident from the attempted clinical trial, completing a prospective randomized study to identify and compare the effect of different antiosteoporotic drugs administered at the time of healing of fragility hip fractures, with adequate numbers and within strict restrictions on recruitment time and budget, is difficult. On the preparations of this pilot study, the performed sample size calculation led us to target a cohort of 120 patients (40 patients in each study arm), knowing that such a sample was not large enough to prove the tested hypothesis, but adequate to produce preliminary evidence to the feasibility of a pivotal large multicenter one. It was anticipated that the sample would be also able to detect any large differences between the treatment subgroups, mostly as far as their safety. Although we considered possible but unlikely to find large differences i.e. clinical healing rates of 80% versus 20% between 2 of the subgroups, with this sample we would have been able to demonstrate statistical significance of the proportions at the 5% level with 80% power. We were expecting an early drop-out due mostly to peri-operative mortality within 6months of 10% as found in numerous publications [19,36,37].

Clearly, testing with a two-level logistic regression with measurements grouped within patients as initially planned, was not feasible, as the final recruited sample reached just the 25% of the initial target. Furthermore, unpredictable deaths and dropouts made it impossible to deliver a meaningful power calculation for a future pivotal clinical trial.

We consider the study hypothesis still valid, and the importance of producing robust high level clinical evidence on the effect of the different antiosteoporotic agents to hip fracture healing, as great. We consider the difficulties on the eligibility and consenting process of such a study cohort, the obstacle that injectable therapies represent to a number of patients, the logistic problems of transferring and following up the recruited patients within the study specific time endpoints, as well as the significant cost that some of the antiosteoporotic drugs have, as the main parameters that should be taken into account in any future attempts of clinical investigators and research teams.

Conflict of interest

All patients declare no conflict of interest for the preparation and writing up of this article.

Acknowledgements

The authors wish to express their acknowledgement to the efforts of the research team for the period of recruitment of the study to Mr Suribabu Gudipati, Mr Daniel Morell, and Mr Oghofori Obakponovwe.

References

[1] Nikolaou VS, Efstathopoulos N, Kontakis G, Kanakaris NK, Giannoudis PV. The influence of osteoporosis in femoral fracture healing time. Injury 2009;40: 663–8.
[2] Guido G, Scaglione M, Fabbri L, Ceglia MJ. The "osteoporosis disease". Clin Cases Miner Bone Metab 2009;6:114–6.
[3] Thormann U, El Khawassna T, Ray S, Duerselen L, Kampschulte M, Lips K, et al. Differences of bone healing in metaphyseal defect fractures between osteoporotic and physiological bone in rats. Injury 2014;45:487–93.
[4] Eastell R, Lambert H. Strategies for skeletal health in the elderly. Proc Nutr Soc 2002;61:173–80.
[5] Winzenberg T, van der Mei I, Mason RS, Nowson C, Jones G. Vitamin D and the musculoskeletal health of older adults. Aust Fam Physician 2012;41:92–9.
[6] Lanzieri G. The greying of the baby boomers. A century-long view of ageing in European populations. EUROSTAT, European Commision; 2011. 23.
[7] Department of Economic and Social Affairs UN. World Population Ageing 1950–2050. New York 2001.
[8] Dr Foster Health. Osteoporosis facts & figures. 2009.
[9] Wu TY, Jen MH, Bottle A, Liaw CK, Aylin P, Majeed A. Admission rates and in-hospital mortality for hip fractures in England 1998 to 2009: time trends study. J Public Health (Oxf) 2011;33:284–91.
[10] Borgstrom F, Lekander I, Ivergard M, Strom O, Svedbom A, Alekna V, et al. The International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) – quality of life during the first 4 months after fracture. Osteoporos Int 2013;24:811–23.
[11] Kanakaris NK, Giannoudis PV. Locking plate systems and their inherent hitches. Injury 2010;41:1213–9.
[12] Eschler A, Brandt S, Gierer P, Mittlmeier T, Gradl G. Angular stable multiple screw fixation (Targon FN) versus standard SHS for the fixation of femoral neck fractures. Injury 2014;45(Suppl. 1):S76–80.
[13] Leonidou A, Moazen M, Lepetsos P, Graham SM, Macheras GA, Tsiridis E. The biomechanical effect of bone quality and fracture topography on locking plate fixation in periprosthetic femoral fractures. Injury 2015;46:213–7.
[14] Lenz M, Perren SM, Gueorguiev B, Richards RG, Hofmann GO, Fernandez dell'Oca A, et al. A biomechanical study on proximal plate fixation techniques in periprosthetic femur fractures. Injury 2014;45(Suppl. 1):S71–5.
[15] Kanakaris NK, Petsatodis G, Tagil M, Giannoudis PV. Is there a role for bone morphogenetic proteins in osteoporotic fractures? Injury 2009;40(Suppl. 3):S21–6.
[16] Lindner T, Kanakaris NK, Marx B, Cockbain A, Kontakis G, Giannoudis PV. Fractures of the hip and osteoporosis: the role of bone substitutes. J Bone Joint Surg Br 2009;91:294–303.
[17] Jones CB. Augmentation of implant fixation in osteoporotic bone. Curr Osteoporos Rep 2012;10:328–36.
[18] Moroni A, Hoang-Kim A, Lio V, Giannini S. Current augmentation fixation techniques for the osteoporotic patient. Scand J Surg 2006;95:103–9.
[19] Makridis KG, Karachalios T, Kontogeorgakos VA, Badras LS, Malizos KN. The effect of osteoporotic treatment on the functional outcome, re-fracture rate, quality of life and mortality in patients with hip fractures: a prospective functional and clinical outcome study on 520 patients. Injury 2015;46: 378–83.
[20] Chavassieux P, Asser Karsdal M, Segovia-Silvestre T, Neutzsky-Wulff AV, Chapurlat R, Boivin G, et al. Mechanisms of the anabolic effects of teriparatide on bone: insight from the treatment of a patient with pycnodysostosis. J Bone Miner Res 2008;23:1076–83.
[21] Aw D, Sahota O. Orthogeriatrics moving forward. Age Ageing 2014;43: 301–5.
[22] Johanson NA, Charlson ME, Szatrowski TP, Ranawat CS. A self-administered hip-rating questionnaire for the assessment of outcome after total hip replacement. J Bone Joint Surg Am 1992;74:587–97.
[23] Royal College of Physicians. NHFD Annual Reports – The National Hip Fracture Database. London 2011–2012–2013.
[24] Compston J, Bowring C, Cooper A, Cooper C, Davies C, Francis R, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas 2013;75:392–6.
[25] Jorgensen NR, Schwarz P. Effects of anti-osteoporosis medications on fracture healing. Curr Osteoporos Rep 2011;9:149–55.
[26] Bukata SV. Systemic administration of pharmacological agents and bone repair: what can we expect. Injury 2011;42:605–8.
[27] Namkung-Matthai H, Appleyard R, Jansen J, Hao Lin J, Maastricht S, Swain M, et al. Osteoporosis influences the early period of fracture healing in a rat osteoporotic model. Bone 2001;28:80–6.
[28] Walsh WR, Sherman P, Howlett CR, Sonnabend DH, Ehrlich MG. Fracture healing in a rat osteopenia model. Clin Orthop Relat Res 1997;218–27.
[29] Mitchell PJ. Osteoporos Rev 2009;17:14–6.
[30] Edwards BJ, Bunta AD, Simonelli C, Bolander M, Fitzpatrick LA. Prior fractures are common in patients with subsequent hip fractures. Clin Orthop Relat Res 2007;461:226–30.
[31] Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008;19:385–97.
[32] Johansen A. QFracture is better than FRAX tool in assessing risk of hip fracture. BMJ 2012;345:e4988.
[33] Rossini M, Bianchi G, Di Munno O, Giannini S, Minisola S, Sinigaglia L, et al. Determinants of adherence to osteoporosis treatment in clinical practice. Osteoporos Int 2006;17:914–21.
[34] Seeman E, Compston J, Adachi J, Brandi ML, Cooper C, Dawson-Hughes B, et al. Non-compliance: the Achilles' heel of anti-fracture efficacy. Osteoporos Int 2007;18:711–9.
[35] Li L. OP54 Non-persistence to anti-osteoporosis medications in the UK using the general practice research database (GPRD). Rheumatology 2010;49. i23–i5.
[36] Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359:1761–7.
[37] Leung F, Lau TW, Kwan K, Chow SP, Kung AW. Does timing of surgery matter in fragility hip fractures? Osteoporos Int 2010;21:S529–34.