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Inpatient zoledronic acid in older hip fracture patients is well tolerated and safe

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Abstract

Summary Administering zoledronic acid (ZA) to older hip fracture patients during the hospital stay has faced safety concerns. However, in this study of 161 patients, no ZA-related side effects or readmissions were observed, demonstrating that ZA administration during hospitalization is safe and effective for secondary fracture prevention.

Purpose According to the 2022 Dutch ‘Osteoporosis and fracture prevention’ guideline, zoledronic acid (ZA) is the preferred osteoporosis treatment for hip fracture patients. Less than 25% of hip fracture patients visit the outpatient fracture liaison service, therefore inpatient administration of ZA during the hip fracture hospitalization is now recommended in patients > 75 years. In the OLVG Hospital, inpatient administration of ZA during hospitalization for hip fracture in older patients has been standard of care since 2020.

Methods This single center retrospective observational follow-up study included hip fracture patients > 75 years admitted to the orthogeriatric ward of the OLVG Hospital, and treated with 5 mg of ZA intravenously on the day of hospital discharge between June 2020 and December 2022. Life expectancy estimated < 12 months, creatinine clearance < 35 ml/min, hypocalcemia, and high risk of osteonecrosis of the jaw were contra-indications. During three months of follow-up (FU) adverse events, emergency room visits, hospital readmissions, and death were recorded.

Results In 161 consecutive hospitalized hip fracture patients (mean age 86 ± 6 years, 65% female, 18% nursing home) ZA was administered and no adverse events were recorded. During 3 months of FU, 8 patients (5%) visited the emergency room, 19 patients (12%) were re-admitted to the hospital, 3 with a new fracture (2 contralateral hip, 1 radius), and 17 patients (11%) died of reasons unrelated to ZA.

Conclusion This study shows that inpatient administration of zoledronic acid during hip fracture hospitalization is safe and feasible to prevent future fragility fractures in older hip fracture patients.

Keywords Hip fracture · Zoledronic acid · Osteoporosis · Safety

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Introduction

Hip fracture is a deleterious medical condition, particularly in older adults. In the Netherlands, 18,000 patients sustain a hip fracture annually. These fractures are associated with a high morbidity and mortality; 40% of patients are unable to walk independently after rehabilitation, 10–20% require long-term nursing care and 25% die within one year [1]. The main cause of fragility fractures, including hip fractures, is osteoporosis. Osteoporosis is a chronic condition characterized by a low bone mass and a deterioration in bone structure leading to an increased fracture risk. Hip fractures most often occur in frail older patients with multimorbidity and a high risk of falling, resulting in a high re-fracture risk in these patients. This increased risk of falling also contributes to the high subsequent fracture risk in this frail population [2, 3].

Over the last decades, multiple effective osteoporosis drugs have become available, of which bisphosphonates remain the most widely used. In older hip fracture patients, annual zoledronic acid administration within 90 days of hip fracture effectively reduced fracture risk with 35% for new clinical fractures and reduces mortality with 28% after three years of treatment [4]. However, only 25% of hip fracture patients visited the outpatient fracture liaison service (FLS) after their hospital stay and the vast majority of hip fracture patients did not initiate pharmacotherapy [5]. Thus, osteoporosis remains underdiagnosed and undertreated. Treatment adherence rates are notoriously low, leading to high secondary fracture rates. Both patient and professional osteoporosis societies have recognized this ‘osteoporosis treatment gap’ and called for action. For example, the International Osteoporosis Foundation has initiated a program ‘Capture the Fracture’ designed to optimize secondary fracture prevention and professional societies have issued clinical guidelines advising on optimal screening and treatment strategies in fracture patients. To improve secondary fracture prevention by increasing treatment rates and adherence, a recent update of the Dutch Osteoporosis and Fracture Prevention guideline recommends treating older hip fracture patients with zoledronic acid *during* the hip fracture hospitalization.

After publication of the Dutch guideline, the implementation of this recommendation in clinical practice in the Netherlands was delayed due to concerns regarding potential increases in length of hospital stay and readmission rates due to potential side effects such as the acute phase response and hypocalcemia following zoledronic acid administration. In contrast to these national concerns, the administration of zoledronic acid to older hip fracture patients admitted to our orthogeriatric ward was already integrated in 2020. The aim of this study was to address

these concerns and describe the rate of adverse events and readmissions after inpatient zoledronic acid administration in older hip fracture patients.

Methods

Study design

This observational study included patients aged 75 years and older with a hip fracture admitted to the Onze Lieve Vrouwe Gasthuis (OLVG) hospital in Amsterdam, the Netherlands, a large teaching hospital between 1st of June 2020 and 1st of January 2023.

Hip fracture care pathway

The hospital has a specific care pathway for all patients with a hip fracture. As part of this pathway, all patients aged 70 years and older presenting with a hip fracture are admitted to the orthogeriatric trauma ward. Patients included in this pathway receive standard laboratory testing, a comprehensive geriatric assessment (CGA) and a bone health consultation by a specialized nurse supervised by a geriatrician in addition to regular surgical fracture care upon admission. A CGA is an assessment to identify somatic, psychological, social and functional deficits in older patients [6, 7]. The outcome of this CGA was used to optimize the treatment during admission. The blood tests included, amongst others, creatinin, calcium, albumin, phosphorus, 25-OH vitamin D, alkaline phosphatase, thyroid stimulating hormone and a basic metabolic panel. Vitamin D and calcium were supplemented in case of deficiency. All patients received a personal bone health management plan depending on the outcome of the CGA, the laboratory results, the life expectancy and the patient’s preferences. Patients aged 75 years and older, with a creatinine clearance > 35 ml/min, normocalcemia and vitamin D levels > 50 nmol/L (or pre-treatment supplemented), and a life expectancy estimated > 12 months were treated with zoledronic acid intravenously. This administration was performed on day 3 or 4 after surgery. Surgical treatment was usually performed within 24 h upon admission. The average length of stay for hip fracture patients in the Netherlands is 5 to 7 days. The patients aged 74 years or younger or the patients with a contraindication for zoledronic acid were referred to the outpatient FLS.

Patient selection

All patients aged 75 years and older with a hip fracture and treated with zoledronic acid during hospital admission between June 2020 and January 2023 were included in this

study. Ethical approval was obtained from the institutional review board (WO23.001).

Follow-up

We chose a three-month observation period to assess side-effects that could lead to a longer hospital stay and/or hospital re-admission; most side effects of zoledronic acid appear in the days and weeks following the administration. In addition, with a longer follow-up period the causative relation between the symptoms or side effect and the administration of zoledronic acid would become less likely and more difficult to establish, especially in this patient category with many other diseases and medications.

Follow-up was conducted three months after hospital discharge by a consultant from either the geriatric or the trauma department. This follow-up included information about the mobility, living situation, dependency in daily living, hospital encounters and complications. To measure the mobility the Fracture Mobility Score [8] was used. Four different types of living situations were categorized: living independent, living independent with (home) care, living in a rehabilitation center, and living in a nursing home. A hospital encounter was defined as either an emergency room visit, or a hospital admission and the number of encounters were extracted from the electronic patient file. Hospital encounters within one week and within three months were recorded separately.

Data collection and statistics

A database with all the patients aged 75 years and older with a hip fracture were obtained from the local Hip Fracture Database by a data-analyst. Patients who received zoledronic acid were selected. Additional clinical data not available from the database was extracted using the CTcue software package (version 1.2.10, CTcue BV, Amsterdam, The Netherlands). CTcue functions as a search engine for medical information registered in Electronic Health Records (CTcue—an IQVIA business, Amsterdam, The Netherlands). CTcue is a search engine that facilitates searching in electronic medical files, giving a structured overview of the data. All the data were stored into the CASTOR Electronic Data Capture (EDC) database, an electronic data management system.

Descriptive statistics were used to summarize the patient's characteristics. Baseline characteristics were presented as frequencies and percentages. Analyses were performed using IBM SPSS statistics for Windows version 27.

Results

Patient characteristics

A total of 161 consecutive hospitalized hip fracture patients were included in the study. The mean age of the patients was 86 ± 6 years and 65% were female. Before hospitalization, 56% of the patients were living independently at home, 26% at home with care and 18% were living in a nursing home. Most patients had either a femoral neck fracture (56%) or an intertrochanteric fracture (42%) and only 2% had a subtrochanteric fracture.

Zoledronic acid was administered with a mean of 5 days after surgery. No adverse events were recorded during the remaining hospital stay (Table 1). The majority of patients (88%) were transferred to a rehabilitation or geriatric care facility after hospital discharge.

Readmissions, fractures and mortality

During 3 months of follow-up, 8 patients (5%) visited the emergency room, and 19 patients (12%) were readmitted to the hospital (Table 2).

Most hospital encounters were related to complications of the hip fracture surgery, falls or infections (Table 3 and Supplementary table), none were related to side-effects of zoledronic acid. Three patients suffered a new fracture (2 contralateral hip, 1 radius), and 17 patients (11%) died of reasons unrelated to zoledronic acid.

Discussion

This study investigated the safety of administration of zoledronic acid during hospital admission in older hip fracture patients. Our data showed that there were no adverse events in this cohort consisting of 161 patients. Moreover, there were no adverse events or deaths related to zoledronic acid during 3 months of follow-up and we can therefore conclude that it is safe to administer zoledronic acid in older patients during hospitalization for a hip fracture.

Only a few studies investigated the effect of *early* administration of zoledronic acid in hip fracture patients during hospital admission and these studies focused mostly on fracture healing and effect on BMD. In a post hoc study of the Horizon trial (an international, multicenter, randomized, double-blind, placebo-controlled trial), it was suggested that the efficacy in early administration within two weeks after fracture was less [9], although only a minority (5.3%) of the patients was treated within two weeks and these patients were considerably older and with more comorbidities. No

Table 1 Baseline characteristics

Variable	N = 161
Sex – no. (%)	
Male	56 (35)
Female	105 (65)
Age	
Mean – yr*	85.9 ± 6.0
Range – no. (%)	
75–84 yr	70 (43.5)
≥ 85 yr	91 (56.5)
Body-mass index – kg/h2*	23.9 ± 4.2
Living Situation – no. (%)	
Independent	90 (55.9)
Independent with home care	41 (25.5)
Nursing home	30 (18.6)
Mobility – no. (%)	
Mobile without aid	62 (38.5)
Mobile outside with one aid	27 (16.8)
Mobile outside with two aids or a walker	58 (36.0)
Mobile indoors, but not outside without help of a person	10 (6.2)
No functional mobility or mobile with a wheelchair	4 (2.5)
Previous osteoporosis treatment – no. (%)	
No	155 (96.3)
Yes	6 (3.7)
Impact of trauma – no. (%)	
Low energy trauma	161 (100.0)
Injury type – no. (%)	
Femoral neck fracture	90 (55.9)
Intertrochanteric fracture	68 (42.2)
Subtrochanteric fracture	3 (1.9)
Surgery type – no. (%)	
Hip (Hemi-)arthroplasty	83 (51.6)
Trochanteric Fixation Nail Advanced	56 (34.8)
Dynamic Hip Screw	17 (10.6)
Cannulated Screws	4 (2.5)
No Surgery	1 (0.6)
Days between surgery and zoledronic acid**	5 (4.7)

* Plus-minus value is mean ± SD

** Variable is median (first quartile, third quartile)

studies until recently studied safety and length of hospital stay after early administration. Although adverse event rates in the Horizon trial were reassuring (0.6% of patients were reported to develop influenza-like symptoms and 6.8% pyrexia), only 5.3% of patients were treated within 2 weeks of hip fracture surgery. In a recent smaller study on early administration of zoledronic acid between one to two weeks after surgery it was shown to be safe in a group of 84 hip fracture patients [10]. Another recent study conducted in the United States reported no influence of zoledronic acid

Table 2 Rates of patients' hospital encounters

Variable	N = 161
Patients with hospital encounters – no. (%)	
No	134 (83.2)
Yes*	27 (16.8)
In first week after discharge	
Emergency Room	3 (1.9)
Readmission	4 (2.5)
From 1 week to 3 months after discharge	
Emergency Room	10 (6.2)
Readmission	19 (11.8)

* Of the 27 patients who returned to the hospital, 7 patients were present in more than one group, resulting in a higher amount in de categories

administration on the average length of hospital stay or on the rate of readmission within 30 days of discharge [11]. The data in our study adds to this data on safety up to three months. In addition, a recently published consensus paper on this topic recommended inpatient treatment after hip fracture as a call to action to prevent frail patients from subsequent fractures after observing a huge practice variation in use of bisphosphonates after hip fracture in The National Hip Fracture Database of England, Wales, and Northern Ireland, varying from 0 to 75% of the patients receiving zoledronic acid timely [12].

Strengths of our study are that it consisted of “real world data” from the Netherlands of both men and women 75 years or older admitted to the hospital with a recent hip fracture. All patients received an extensive analysis including a comprehensive geriatric assessment and osteoporosis treatment according to the recent Dutch guidelines. Furthermore, patients with a life expectancy estimated to be less than one year during the comprehensive geriatric assessment, were not treated with zoledronic acid because of a lack of time to benefit. Therefore, we minimized the exposure of vulnerable, frail patients to a drug with potential side effects but without the potential benefit in terms of fracture reduction. However, the assessment of life expectancy is difficult in the absence of validated tools. It remains possible that the life expectancy was underestimated for some patients and therefore they did not receive a potential beneficial treatment. Therefore, the development and validation of better tools to predict life expectancy in this patient group is an important future research question.

Our study also has limitations. The sample size is relatively small, and we lack an untreated control group. In addition, despite active follow-up using telephone calls, a considerable number of patients were lost to follow-up, although we did ascertain if patients were still alive in the national civil administration. Due to the retrospective design

Table 3 Specification of patients' hospital encounters in the first week after discharge

Number*	Sex	Age – yr	Reason of admission	Duration of admission– days **	Conclusion at discharge	Days between discharge and admission
1a	Male	80	Dislocation of hemiarthroplasty	-	Luxation hip hemiarthroplasty	4
2a	Female	86	Skin rash	-	Skin rash due to Vancomycin	4
3a	Male	78	Fever	11	Fever due to pneumonia	4
4a	Female	96	Wound leakage	11	Infected hip hemiarthroplasty	6
5	Female	83	Hypokalemia	2	Hypokalemia due to vomiting	5
6	Female	88	Femoral neck fracture	10	Femoral neck fracture contralateral Urinary tract infection	3
7	Female	88	Dizziness	-	Clinic with no neurological origin	1

* Each patient who was presented to the hospital got their own number. Patients who were presented more than once in the hospital have their specific number corresponding to a letter presenting the presentation. The numbers and letters are corresponding with Supplementary Table 1

** – Means a patient was treated at the Emergency Room

of the study, we could not estimate whether some patients might have had a prolonged hospital stay as a consequence of the infusion of zoledronic acid, however the mean hospital stay was similar to previously reported lengths of hospital stay and prolonged stays were not mentioned in the patient charts.

Conclusion

Our study, reporting real-world data, showed that it was feasible and safe to administer zoledronic acid during hospital admission in a group of frail older patients with hip fracture. This study therefore shows that the strategy to treat older hip fracture patients with zoledronic acid during the hospital stay is feasible in order to prevent subsequent fractures and to improve survival, since these patients might otherwise be lost to follow-up and not be treated with osteoporosis medication.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11657-024-01453-9>.

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Declarations

Conflicts of interest None.

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