AGN1 local osteo-enhancement procedure for treatment of contralateral proximal femur bone loss in post-menopausal osteoporosis during acute hip fracture repair with two-year follow-up

Christian Fang, Evan Fang, Dennis King-Hang Yee, Tak-Wing Lau, Jake Cheung, Frankie Leung

Department of Orthopaedics and Traumatology, The University of Hong Kong

ABSTRACT

Purpose: AGN1 local osteo-enhancement procedure (LOEP) is an emerging surgical treatment intended to address the pathology of osteoporosis of the hip by increasing mechanical strength. This prospective single-centre study assessed the first cases in which AGN1 LOEP was performed on contralateral, unfractured hips during the same operative session as index hip fracture surgery.

Methods: The study was designed to enrol up to 20 post-menopausal women older than 65 who had recently suffered a hip fragility fracture requiring surgical repair. Immediately following fracture repair, the femoral enhancement site was prepared and filled with AGN1, a triphasic and osteoconductive implant material that is resorbed and replaced with bone in situ. Patients followed the standard care map for geriatric hip fracture both in hospital and post-discharge. Patient demographics and procedural data were collected, including peri-operative adverse events (AEs) and the additional operation time needed for AGN1 LOEP.

Results: A cohort of 13 patients were treated with AGN1 LOEP. The treatment, including patient repositioning, increased the operation time by an average of 24.9 minutes. The length of hospital stay and time to weight bearing were not affected by LOEP. None of the AEs reported showed a causal relationship with the AGN1 LOEP device or treatment. There was one death due to ischaemic heart disease and unrelated to the study material. Serial X-rays demonstrated complete implant material resorption and new bone formation in all patients by 12 months.

Conclusion: Our study suggests that AGN1 LOEP is feasible and well tolerated as a concomitant, surgical treatment of the contralateral hip in patients undergoing surgery to treat a first hip fracture. LOEP treatment altered neither the treatment nor the rehabilitation pathways for patients. Promising findings support the continued use and further clinical investigation of AGN1 LOEP as a treatment option for patients at risk of a secondary contralateral hip fracture.

KEYWORDS

Osteoporosis, femoral strength, local osteo-enhancement procedure (LOEP), bone mineral density.

Introduction

Globally, 1.6 million hip fractures occur each year [1], accounting for 14% of fragility fractures but 74% of the related cost [2]. Hip fractures are associated with high morbidity and mortality [3, 4]. Hip bone mineral density (BMD) is a significant predictor of hip fracture risk [5]. Even when treated with osteoporosis medications, patients with an initial hip fracture are at significantly increased risk of contralateral hip fracture, particularly within one year [6]. To address the risk of a secondary hip fracture, techniques such as prophylactic nailing and femoroplasty with polymethyl methacrylate (PMMA) have been evaluated [7,8]. These have shown limited success in clinical settings because of perceived invasiveness and the risk of thermal injury, respectively.

The AGN1 local osteo-enhancement procedure (LOEP) (AgNovos Healthcare LLC, Rockville, MD, USA) is an emerging surgical treatment for patients at high risk of hip fragility fracture. It entails injection of a triphasic, resorbable, calcium-based implant material (AGN1) to increase proximal femur strength [9]. Cadaveric femurs treated *in vitro* with AGN1 showed a 20.5% greater failure load [9]. One clinical study showed that AGN1 was resorbed and replaced by integrated bone as soon as 24 weeks after injection, increasing femoral BMD for at least six years [10]. Because AGN1 can be administered minimally invasively to fragile proximal femurs, it may have potential as a treatment option for secondary hip fracture prevention in hip fracture patients.

This was the second clinical study of AGN1 LOEP and also

Article history
Received 20 Aug 2024 – Accepted 3 Dec 2024

Contact
Christian Fang; fangcx@gmail.com
The University of Hong Kong, Pokfulam, Hong Kong (CH)

the pilot study of the treatment's feasibility, safety and tolerability when performed during the same operative session as index hip fracture surgery in post-menopausal women. A secondary aim was to evaluate AGN1 resorption and impact on BMD of the treated hip.

Methods

Study design and participants

A prospective, single-cohort study was conducted in a university teaching hospital between 2017 and 2019. The study received ethical approval (HKWC/UW 17-167). All subjects provided written consent. Up to 20 patients were to be recruited.

Females who presented to the emergency department with a hip fracture in which operative treatment was indicated were screened for participation. Eligible patients met all the inclusion criteria: (i) post-menopausal female, (ii) aged ≥ 65 years, (iii) with an acute, low-energy fragility hip fracture requiring surgical repair. Patients were ineligible if they met one or more exclusion criteria: (i) prior diagnosis of secondary osteoporosis, (ii) any previous history of surgery or fracture of the non-fractured hip, (iii) undiagnosed hip pain over the previous six months suggestive of underlying bone or joint pathology (e.g., osteoarthritis, fracture), (iv) calcium levels outside the normal laboratory range, (v) moderate to severe renal insufficiency, (vi) diagnosis of insulin-dependent diabetes mellitus, (vii) body mass index (BMI) > 30, (viii) excessive tobacco or alcohol use, (ix) evidence of gross or bony joint pathology of the non-fractured hip, (x) treatment with corticosteroids or systemic glucocorticoids for 10 or more days in the previous six months (xi), use of immunosuppressive drugs in the previous 12 months, (xii) history of metabolic bone disease other than osteoporosis, (xiii), history of autoimmune arthritic disease, (xiv) other severe comorbidity or general poor health precluding participation, (xv) history of radiation therapy to the hip or pelvic region, (xvi) history of malignancy or chemotherapy within the previous five years, and (xvii) known allergy to the implanted device. Eligible patients who consented underwent standard-of-care surgical treatment of the fractured hip. After fracture repair, the subject was repositioned and AGN1 LOEP was performed on the contralateral hip by the same surgeon.

AGN1 LOEP treatment

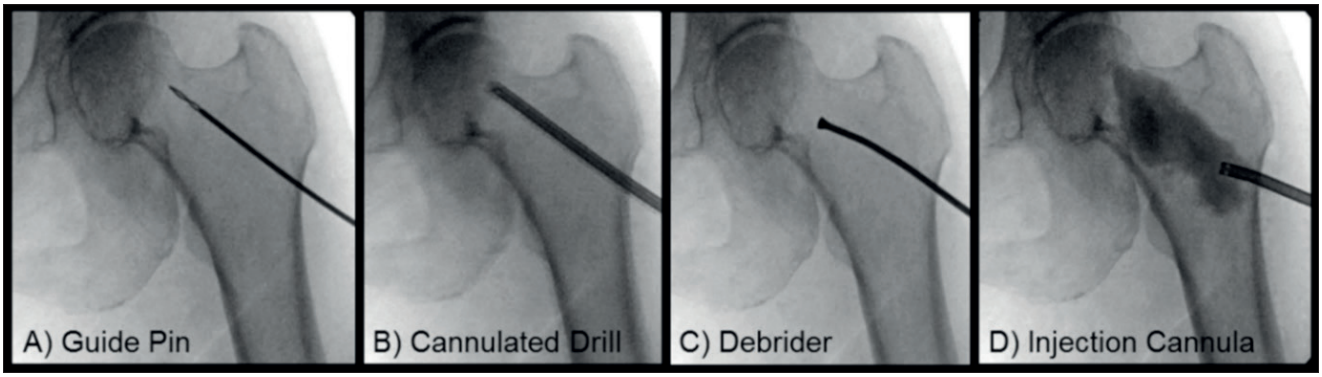
Following standard hip fracture treatment (5 hemiarthroplasties and 8 internal fixations), subjects were re-draped and repositioned supine for contralateral AGN1 LOEP treatment. LOEP was performed under fluoroscopic guidance as depicted in figure 1.

A 1 cm incision was made colinear with the anticipated path of the guide pin lateral cortical entry site. A 2.5 mm guide pin was carefully positioned proximal to the upper level of the lesser trochanter. Positioning the cortical entry distal to the most proximal level of the lesser trochanter was avoided to minimise the risk of weakening the proximal femur. The 2.5 mm guide pin was advanced to the base of the femoral head and overdrilled with a 5.3 mm cannulated drill. A curved probe was used to loosen non-structural material (e.g., fat, fluid, loosely connected trabecular bone) and define the boundaries of the enhancement site. Suction and irrigation with normal saline was performed to prepare the empty site for a low-pressure injection. The AGN1 implant material was mixed and the cannula was inserted and advanced to the sub-capital apex of the enhancement site. The low-pressure injection was commenced from proximal to distal with intermittent pauses while the cannula was rotated, repositioned and withdrawn to achieve complete filling of the enhancement site. Throughout the injection, vital signs were monitored for evidence of physiological response. Complete filling was determined via fluoroscopy and/or evidence of extravasation of AGN1 through the cortical portal. Confirmatory bilateral anterior-posterior (AP) and lateral hip radiographs were obtained, and the incision was closed without a surgical drain.

Post-operative care

The post-operative standard-of-care protocols for the hip fracture repair and systemic osteoporosis treatment were not altered for the LOEP treatment. Patients were allowed full

Figure 1 3D illustration of LOEP steps. (**A**) 1 cm stab incision was made at the subtrochanteric level of the non-fractured femur. A 2.5 mm guide pin was placed through the lateral femoral cortex towards the centre of the femoral neck. (**B**) A 5.3 mm cannulated drill was then passed over the guide pin, stopping short of the femoral head. (**C**) A curved, debridement probe was used to loosen non-structural cancellous bone, fat, and debris to define the boundaries of the enhancement site. These materials were then removed by suction and irrigation using normal saline. (**D**) The AGN1 implant material was mixed according to the manufacturer's instructions and immediately injected into the treatment site. The implant material was injected while rotating the injection cannula within the enhancement site to distribute the material to the entire enhancement site. The volume of AGN1 injected varied (10-20 mL) according to patient anatomy and degree of osteoporotic bone loss. Injection was stopped when the site was filled based on fluoroscopy or extravasation of the implant material outside of the enhancement site.



weight bearing on both hips immediately post-operation and active mobilisation was encouraged. As is standard of care for hip fracture patients, all patients followed a protocol-driven, therapist-supervised rehabilitation program in a convalescent hospital [11].

Outcomes and data collection

The primary outcome was serious adverse events (SAEs) occurring between the date of operation and 24 months post-operatively. SAEs were defined, as per Good Clinical Practice guidelines, as any untoward medical occurrence (unfavourable sign, symptom, laboratory finding, disease), whether related to the product or not, that (i) results in death, (ii) is life-threatening, (iii) requires inpatient hospitalisation or prolongation of existing hospitalisation, (iv) results in persistent or significant disability/incapacity. Non-severe adverse events (AEs) were defined as any untoward medical occurrence, whether related to the product or not, that did not meet any of the five criteria for SAEs but were reported by patients at follow-up or noted in patient electronic health records. Secondary outcomes included (i) incidence of fragility fractures unrelated to the AGN1 LOEP device, procedure, or implant material (ii), AEs definitely related to the AGN1 LOEP device, procedure, or implant material, (iii) femoral BMD and AGN1 resorption and replacement with bone.

Subject demographics and baseline characteristics were collected preoperatively. Total operation time was recorded, including time for patient repositioning and skin-to-skin time for LOEP. Patients were monitored for AEs prior to hospital discharge.

AGN1 resorption was assessed using standard AP radiographs. Pre-LOEP radiographs were reviewed to confirm trabecular bone scarcity in the proximal femur at baseline. AGN1 volume visible on post-operative LOEP radiographs was considered to correspond to 100% of the implanted AGN1. The percentage of AGN1 remaining at follow-ups was judged by comparison with the volume of AGN1 implant material visible on the post-operative radiographs. The marginated boundaries of the peripheral trabecular marrow space represented the limit of the enhancement area. An intermediate density zone of newly mineralised tissue was visible where AGN1 was resorbed, and the higher-density, inner zone of unresorbed AGN1 was estimated.

Dual-energy X-ray absorptiometry (DXA) was performed at discharge, 12 months, and 24 months post-operatively to determine the BMD of the LOEP-treated femur and distal radius. All DXA scans were performed with a Horizon A (Hologic, Marlborough, MA, USA) DXA machine.

Results

Study population

Thirteen post-menopausal women with a median age of 83 years (range: 72–94) underwent LOEP (Table I). Eleven patients completed their 12- and 24-month follow-ups (Figure 2). One patient was lost to follow-up due to emigration (Patient 12). A second patient died of an acute cardiac event at the conclusion of the concurrent hip repair and LOEP procedure. All patients were included in the analysis.

The mean BMI was 23.6 (range: 18.2–29.1). All patients were of Asian ancestry. Only one patient reported prior treatment for osteoporosis (Patient 1). This subject received bisphosphonates for 21 months prior to enrolment and continued to be prescribed bisphosphonates during the trial. Eight subjects were started on systemic osteoporosis therapy from index fracture through final follow-up. Patient compliance with medication was not documented.

Adverse events

A total of 49 AEs, including 17 classified as SAEs, in 12 subjects were reported from the date of the procedure through two-year follow-up 2 (Table II). The length of hospital stay and time to weight bearing were not affected by LOEP. None of the AEs showed a causal relationship with the study device or treatment.

The reported death was determined to be possibly related to the surgical procedure, including hip fracture repair treatment. This subject underwent sliding hip screw fixation of an intertrochanteric fracture and LOEP. Cardiac arrest occurred following wound closure after the LOEP. Cardiopulmonary resuscitation was unsuccessful, and the patient died 50 minutes after surgery. There was no abnormal ventricular reaction or blood pressure drop upon injection of the AGN1 material.

The investigating team initially suspected the arrest to be thromboembolic in origin and ordered an autopsy which subsequently found no thrombo-emboli or foreign bodies in the pulmonary arteries or veins, femoral veins, iliac veins, inferior vena cava or lungs. Coronary atherosclerosis was noted during autopsy, and the pathology findings suggested the cause of death to be ischemic heart disease.

Six new fall-related injuries occurred during follow-up, but no secondary fractures in hips treated with LOEP. No patients complained of pain at the LOEP injection site. No intra-operative procedural AEs, wound complications or cases of avascular necrosis of the LOEP-treated hip were observed through the two years of follow-up.

AGN1 implant material resorption and BMD changes

Progressive AGN1 resorption was evident based on decreased radiodensity of the AGN1 core versus radiodensity immediately post-LOEP (Figure 3). The estimated mean volume of remaining AGN1 was less than 30% at six months based on radiographic evaluation. By 12 months, the AGN1 core was completely replaced by new bone that was integrated with the surrounding bone in all patients.

DXA scans showed a mean total hip BMD T-score of +0.05(SD:0.96) at 3 months post-LOEP, which decreased to –1.32 (SD:1.01) at 12 months, and –1.48 (SD:1.22) at 24 months. The mean densitometry T-score for the lumbar spine was –1.61 (SD:0.75) post-LOEP, –1.83 (SD:0.86) at 12 months, and –1.53 (SD:1.13) at 24 months. The mean densitometry T-score for the distal forearm was –3.4 (SD:0.86) post-LOEP, –3.35 (SD:0.79) at 12 months, and –3.57 (SD:1.02) at 24 months. After treatment with AGN1 LOEP, all subjects had a higher T-score at the total hip than at the distal radius at all timepoints.

Procedural outcomes

The mean total operation time was 80.4 minutes (range: 51–131), including hip fracture repair. Contralateral LOEP treatment added 25 minutes to the operative session on average (range: 12–34). Mean skin-to-skin time for the LOEP was 16 minutes (range: 10–30).

Mean time for patient repositioning was 9 minutes (range: 2–16).

Table I Characteristics of recruited patients.

PATIENT ID	MEDICAL CONDITIONS	AGE AT LOEP	BMI	ESTIMATED AGE AT MENOPAUSE	PREVIOUS OSTEO-POROSIS DIAGNOSIS	HIP FRACTURE TYPE	HIP FRACTURE SURGERY	TOTAL INJECTED AGN1 (ML)	WALKING FUNCTION BEFORE INJURY	WALKING FUNCTION AT 2 YEARS
1	Osteoporosis, coronary artery disease, renal impairment, hypertension, chronic duodenal ulcer, hyperlipidaemia, collapsed L1, anaemia	80	28.2	55	Yes	Neck of femur	Cannulated screw	15	Outdoors with stick	Outdoors with stick
2	Diabetes, old stroke, hypertension, Parkinson's disease, hyperlipidaemia, chronic otitis, constipation	79	22.0	50	No	Neck of femur	Hemiarthroplasty	13	Outdoors with stick	Indoors with frame
3	Old stroke, hypertension	86	22.0	50	No	Intertrochanteric	Cephalomedullary nail	18	Indoors with frame	Wheelchair bound
4	Diabetes, stroke, hypertension, benign meningioma, hyperlipidaemia, central pain syndrome	77	19.5	48	No	Intertrochanteric	Cephalomedullary nail	12	Indoors with quadripod	Wheelchair bound
5	Diabetes, stroke, hypertension	94	26.3	45	No	Intertrochanteric	Cephalomedullary nail	17	Indoors with quadripod	Wheelchair bound
6	Osteoporosis, stroke, hypertension, Parkinson's disease, dementia, hyperlipidaemia	77	28.3	55	Yes	Intertrochanteric	Cephalomedullary nail	14	Indoors with frame	Wheelchair bound
7	Reflux disease, hypertension, constipation, hyperlipidaemia, impaired fasting glucose, cataract, old distal radius fracture	81	21.9	56	No	Intertrochanteric	Sliding hip screw	14	Outdoors unaided	Outdoors with stick
8	Osteoporosis, hypertension, vestibular neuronitis, depression	90	18.2	55	Yes	Neck of femur	Hemiarthroplasty	14	Indoors with stick	Indoors with frame
9	Hypertension, asthma, hyperlipidaemia, fibromyalgia	72	24.6	35 (surgical)	No	Neck of femur	Hemiarthroplasty	10	Outdoors unaided	Outdoors with stick
10	Hypertension	85	23.9	50	Yes	Intertrochanteric	Cephalomedullary nail	17	Outdoors with stick	Outdoors with stick
11	Hypertension	89	19.5	35	No	Neck of femur	Hemiarthroplasty	14	Outdoors unaided	Indoors with quadripod
12	Hypertension	85	29.1	45	No	Neck of femur	Hemiarthroplasty	13	Outdoors unaided	Lost to follow-up
13	Hypertension, depression	83	X	55	No	Intertrochanteric	Sliding hip screw	20	Indoors with stick	Died

Figure 2 STROBE flowchart.

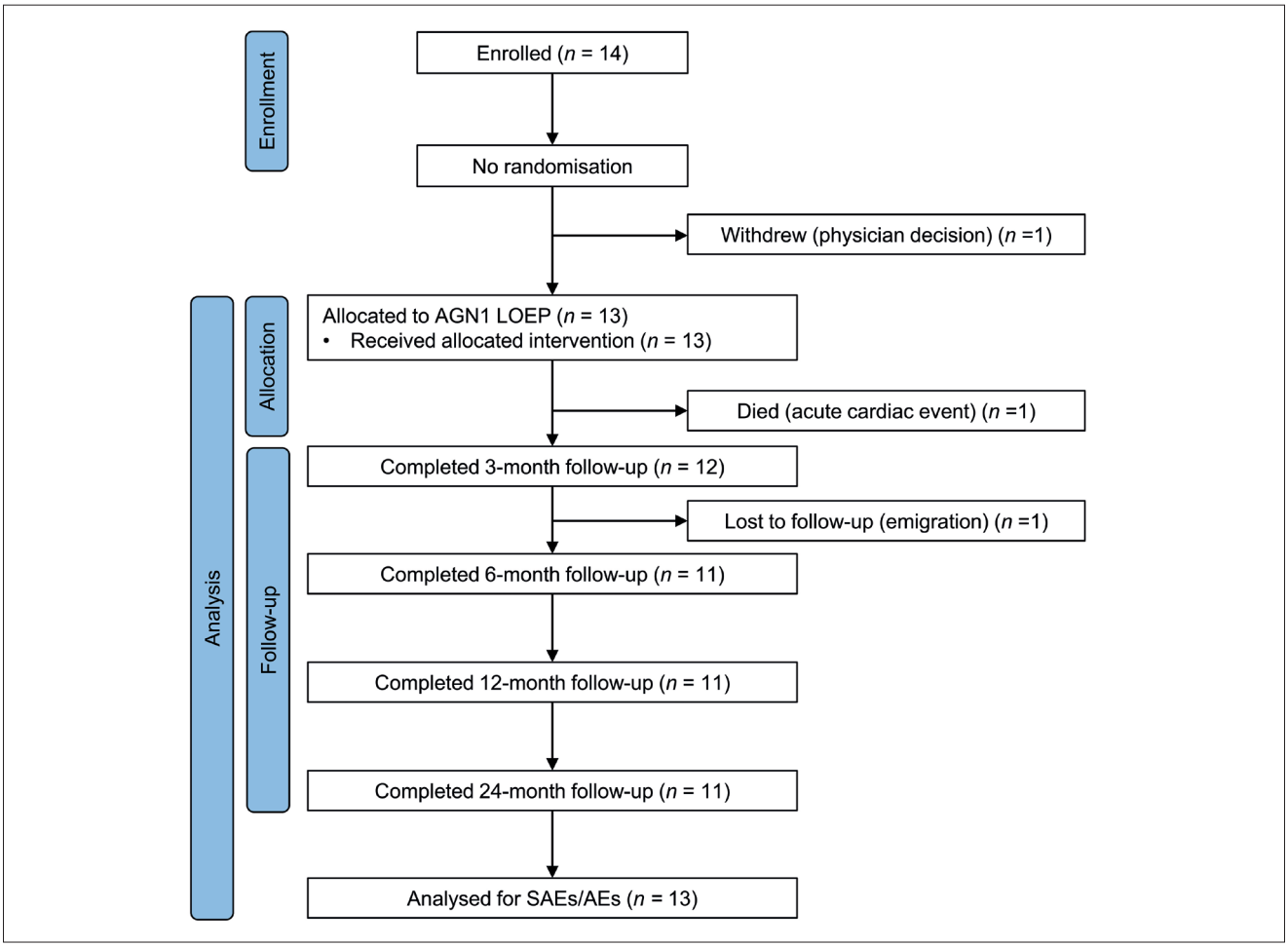
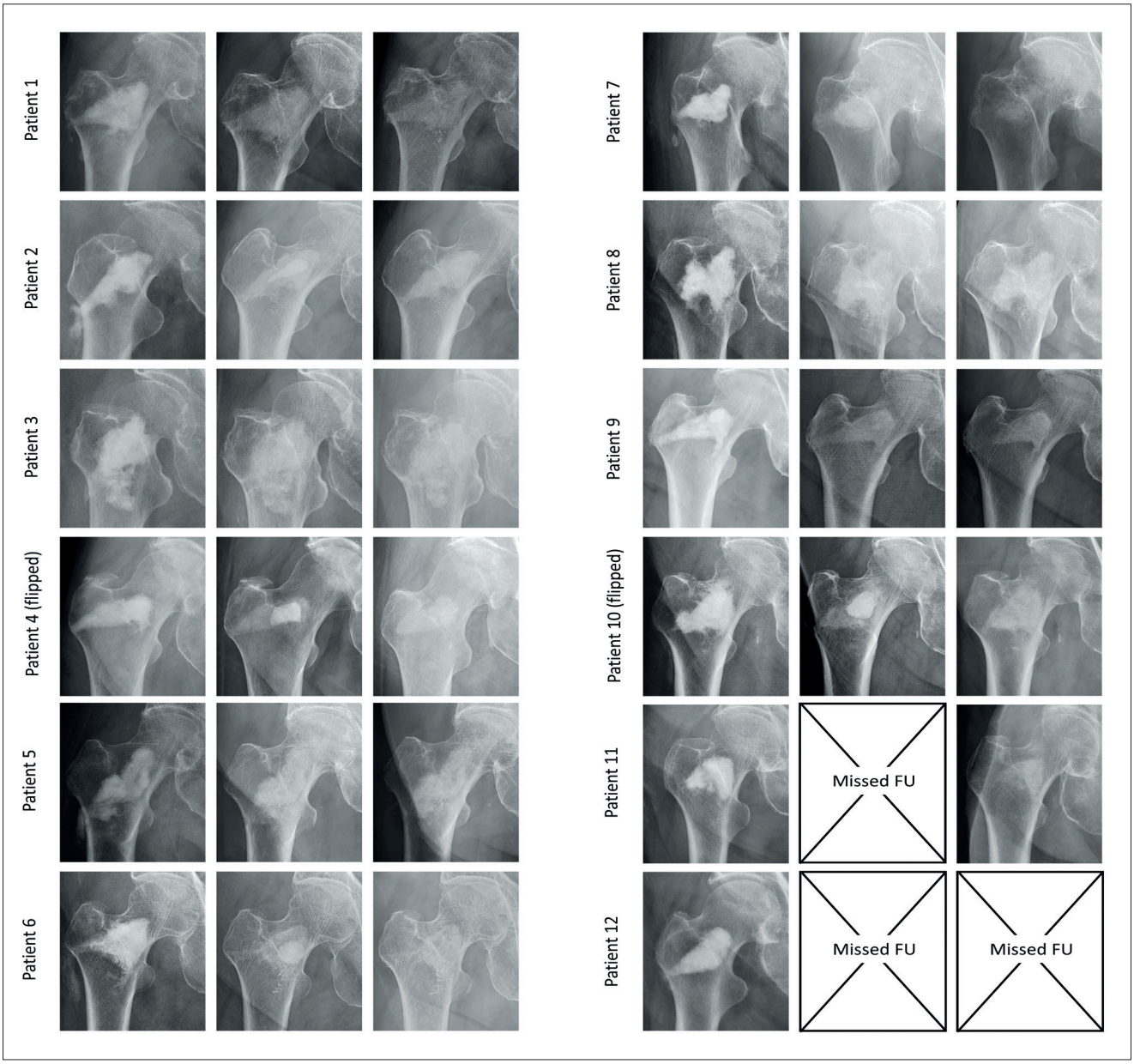


Table II Summary of all serious adverse events.

SUBJECT ID	DAYS POST-TREATMENT	EVENT	SEVERITY	RELATIONSHIP TO LOEP DEVICE	RELATIONSHIP TO LOEP PROCEDURE
	15	Fever, convulsions	Moderate	No	No
2	243	Injury - left clavicle and orbit fracture	Moderate	No	No
	332	Fever	Moderate	No	No
	229	Acute urinary retention	Moderate	No	No
4	544	Haematuria	Moderate	No	No
	606	Haematuria	Moderate	No	No
	648	Haematuria	Moderate	No	No
5	52	Injury - subdural haematoma	Moderate	No	Unlikely
6	280	Lower limb weakness (index hip fracture side)	Mild	No	No
	344	Unilateral numbness (index hip fracture side)	Mild	No	No
	8	Post-operative pneumonia	Moderate	No	Unlikely
9	289	Unilateral weakness and numbness (index hip fracture side)	Moderate	No	No
	514	Influenza A pneumonitis	Moderate	No	No
10	725	Injury - right humeral shaft fracture	Moderate	No	No
11	537	Urinary tract infection and acute urinary retention	Mild	No	No
12	5	Pulmonary embolism	Severe	No	No
13	0	Cardiac arrest	Severe	No	Possible

Figure 3 Matrix of X-rays showing AGN1 implant material resorption over time in all patients. The implanted material is progressively and completely replaced with radiopaque osseous structures corresponding to the originally filled basal neck and intertrochanteric regions after two years.



Anabolic and anti-resorptive osteoporosis medications are intended to treat the bone loss that contributes to fragility fractures. However, these medications are often started late, if at all, have a delayed effect, and show low patient adherence.

Several studies have assessed the biomechanical impact of AGN1 LOEP and its support of bone formation. AGN1-treated cadaveric femurs showed immediate biomechanical improvement: a 20.5% increase in failure load overall, and 26% increase within the osteoporosis subset, 24 hours after treatment [9]. The first human study of AGN1 LOEP demonstrated that AGN1 material resorption was coupled with bone formation by 12 weeks and through at least 5–7 years based on radiographic evaluation [10]. Furthermore, femoral strength increased by 41%, 37% and 22% at 12 weeks, 24 weeks and 5–7 years post-treatment, as estimated by finite element analysis.

Our findings showed a consistent response to AGN1 LOEP treatment in all subjects. The high-radiopacity AGN1 implant material yielded an immediate increase in radiodensity followed by a gradual decrease in BMD (by DXA) as the implant was resorbed and replaced with bone. The rate of decrease stabilised by 12 months, likely once the implant material had been fully resorbed. In all subjects, 24-month X-rays and DXA values appeared virtually identical to those of 12-month scans. New bone formation was confirmed by previously published histological analysis of dogs which showed bone formation in critical-sized humeral defects treated with AGN1.

AGN1 LOEP is a minimally invasive procedure in which the material can be administered to the femur through an incision as small as 1 cm. In our study, the mean skin-to-skin time for LOEP was 16.4 minutes, a period significantly shorter than that required for nail implantation. AGN1 LOEP appears to be technically repeatable and patient repositioning during the op-

erative session did not was not found to be a particular challenge. Patients, both in hospital and post-discharge, followed the standard care map for geriatric hip fracture without modification. AGN1 sets through an exothermic hydration reaction that does not exceed 35°C and is complete within 60 minutes of mixing [9], eliminating the risk of high-temperature bone necrosis, a known risk with PMMA.

The advantages of immediate biomechanical treatment of underlying bone loss may lead to wider acceptance of AGN1 LOEP. It has already been used to treat over 400 hips in patients with or without a contralateral hip fracture. In an analysis of secondary fractures in patients with index hip, wrist or shoulder fractures, Bynum *et al*. found that hip fractures were the most common secondary fracture among hip, wrist and shoulder fractures [6]. An ongoing multi-centre randomised controlled study of AGN1 LOEP is evaluating its safety and ability to prevent secondary hip fractures up to five years post-procedure [16].

This study had several limitations. First, our sample was not large enough to meaningfully compare rates of secondary hip fracture versus the general population. Our results support further investigation of AGN1 LOEP in larger samples. Concurrently, this procedure is being investigated worldwide in multiple centres (ClinicalTrials.gov registration identifiers: NCT04511364, NCT05202678, NCT04796350 and NCT02916953). Second, as DXA scans were not taken preoperatively, we were unable to compare post-operative BMD changes with preoperative values. Third, the case of the last patient, who suffered a cardiac arrest and died following hip fracture repair and LOEP, raises a potential safety concern. Although detailed autopsy findings showed no embolic event leading to the patient's death, the chronological relationship of events led us to halt and review further recruitment, especially of individuals perceived to have very high medical co-morbidity risks.

Conclusion

In conclusion, this first in-human study suggests that contralateral AGN1 LOEP is feasible and well tolerated as a concomitant surgical treatment in patients undergoing surgery for a first hip fracture. The study's promising findings, in terms of safety, implant material resorption and bone formation, support the continued use and clinical investigation of AGN1 LOEP as an emerging treatment option for patients at risk of secondary, contralateral hip fracture.

References

1. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17(12):1726-33.
2. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22(3):465-75.
3. Magaziner J, Simonsick EM, Kashner TM, Hebel JR, Kenzora JE. Predictors of functional recovery one year following hospital discharge for hip fracture: a prospective study. J Gerontol. 1990;45(3):M101-7.
4. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20(10):1633-50.
5. Stone KL, Seeley DG, Lui LY, et al.; Osteoporotic Fractures Research Group. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res. 2003;18(11):1947-54.
6. Bynum JPW, Bell JE, Cantu RV, et al. Second fractures among older adults in the year following hip, shoulder, or wrist fracture. Osteoporos Int. 2016;27(7):2207-15.
7. Varga P, Hofmann-Fliri L, Blauth M, Windolf M. Prophylactic augmentation of the osteoporotic proximal femur-mission impossible? Bonekey Rep. 2016;5:854.
8. Varga P, Inzana JA, Schwiedrzik J, et al. New approaches for cement-based prophylactic augmentation of the osteoporotic proximal femur provide enhanced reinforcement as predicted by non-linear finite element simulations. Clin Biomech (Bristol). 2017;44:7-13.
9. Stroncek JD, Shaul JL, Favell D, et al. In vitro injection of osteoporotic cadaveric femurs with a triphasic calcium-based implant confers immediate biomechanical integrity. J Orthop Res. 2019;37(4):908-15.
10. Howe JG, Hill RS, Stroncek JD, et al. Treatment of bone loss in proximal femurs of postmenopausal osteoporotic women with AGN1 local osteo-enhancement procedure (LOEP) increases hip bone mineral density and hip strength: a long-term prospective cohort study. Osteoporos Int. 2020;31(5):921-9.
11. Lau TW, Fang C, Leung F. The effectiveness of a multidisciplinary hip fracture care model in improving the clinical outcome and the average cost of manpower. Osteoporos Int. 2017;28(3):791-8.
12. Vochteloo AJ, Borger van der Burg BL, Röling MA, et al. Contralateral hip fractures and other osteoporosis-related fractures in hip fracture patients: incidence and risk factors. An observational cohort study of 1,229 patients. Arch Orthop Trauma Surg. 2012;132(8):1191-7.
13. Sawalha S, Parker MJ. Characteristics and outcome in patients sustaining a second contralateral fracture of the hip. J Bone Joint Surg Br. 2012;94(1):102-6.
14. Faucett SC, Genuario JW, Tosteson AN, Koval KJ. Is prophylactic fixation a cost-effective method to prevent a future contralateral fragility hip fracture? J Orthop Trauma. 2010;24(2):65-74.
15. Beckmann J, Springorum R, Vettorazzi E, et al. Fracture prevention by femoroplasty--cement augmentation of the proximal femur. J Orthop Res. 2011;29(11):1753-8.
16. ClinicalTrials.gov. (13 August 2020). Identifier: NCT04511364, Long-term Follow-up of AGN1 Treated Patients. Retrieved 27 April 2021 from https://clinicaltrials.gov/ct2/show/NCT04511364.

Statements and Declarations

Acknowledgements: *The authors wish to acknowledge Kathine Ching, Grace Ho and Janice Oentaryo for their assistance with data collection and maintenance and Annemarie Tilton for manuscript preparation.*

Conflict of Interest: *Christian Fang is a shareholder of Lifespans Ltd and is also a speaker for Depuy Synthes. He has received research support from AO Foundation, Koln 3D Medical Ltd, and Agnovos LLC. Frankie Leung is a shareholder of Lifespans Ltd and is also a speaker for Depuy Synthes. He has received research support from AO Trauma. Evan Fang, Dennis King-Hang Yee, Tak-Wing Lau and Jake Cheung declare no conflicts of interest.*

Funding: *This study was sponsored by AgNovos Healthcare LLC.*

Ethical Approval: *All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was given ethical approval (HKWC/UW 17-167).*

Informed Consent: *All subjects provided written consent to participate.*