

Subtrochanteric fractures in elderly people: functional and radiographic outcomes after intramedullary locked nail fixation with or without cerclage

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Abstract. – OBJECTIVE: Sub-trochanteric fractures are among the most challenging for trauma surgeons. The purpose of this study was to analyze our own experience about subtrochanteric fractures. We focused on functional and radiographic outcomes after intramedullary locked nail fixation with or without cerclage assist.

PATIENTS AND METHODS: A retrospective analysis on subtrochanteric fractures managed from January 2016 to April 2021 was conducted. Patients treated by closed reduction and intramedullary nail fixation were enrolled in Group A, while Group B included those patients who underwent wire-assisted intramedullary nail fixation. All patients performed clinical and radiological follow-up and complications were analyzed. The significance was established for a value of $p < 0.05$.

RESULTS: 80 patients were included in the present study. The mean age was 74.2 (± 19.2) years. The mean surgical time was 84.7 (± 24.6) and 254.7 (± 80.2) minutes in Group A and Group B, respectively. The mean blood loss was 87.3 (± 18.3) ml in Group A and 224.4 (± 37.8) ml in Group B. Quality of reduction was mainly superior in Group B. The mean time of union was 4.2 (± 1.4) months in Group A and 3.4 (± 2.1) months in Group B. Statistical differences were observed in Visual Analogue Scale (VAS) and in the Short Form 12 (SF-12) after 6 and 12 months of follow-up with better results in Group B. The complication rate was 18.2% in Group A and 12.2% in Group B.

CONCLUSIONS: We recommend the use of wires when acceptable closed reduction cannot be obtained because its use may be useful for medial wall stability. For elderly patients, closed reduction may be more appropriate as the quality of life and functional recovery between the two methods is almost overlapped.

Key Words:

Subtrochanteric fracture, Proximal femur fracture, Intramedullary osteosynthesis, Elderly, Cerclage.

Introduction

According to the AO Trauma definition, subtrochanteric fractures of the femur (classified OTA/AO 32A1.1, 32A1.2, 32A1.3) affect the region up to 3 cm distal to the lesser trochanter¹, although it is common to consider them up to 5 cm distal to it.

These fractures occur in young patients due to high-energy trauma (e.g., traffic accident) and in elderly people with poor bone quality. Proximal femur fracture is one of the most common types of fracture in the elderly, occurring in 18% of women and in 6% of men worldwide². The functional outcomes of these patients are determined by surgical timing, previous health status and associated comorbidities³⁻⁵. Non-union, malunion and delayed consolidation are very common. Indeed, the proximal femur is subject to great compressive and distraction forces due to body weight and abductor muscles; furthermore, the medial femur vascularization is precarious. The risk of non-union is higher in varus deformity.

Although intramedullary nail fixation with or without cerclage is considered the gold standard, literature reported a very high risk of non-union and high rate of complications that let us analyze our experience. The purpose of this study is to review subtrochanteric fractures managed at our

institution by using intramedullary nail alone or wire-assisted. In particular, we focused on quality of fracture reduction, time of union and on quality of life (QoL)⁶⁻⁸.

Patients and Methods

Study Design

The present study is a retrospective analysis of consecutive subtrochanteric fractures managed at our Emergency Department (ED), and consequently at our Orthopedics and Traumatology unit^{9,10}, from January 2016 to April 2021.

All patients signed a written consent concerning demographic and clinical data collection for scientific purposes according to institutional protocol. The study respects national ethical standards and the Helsinki Convention. A formal request for ethical approval was not considered necessary because the data collection does not differ from the institutional clinical and radiographic follow-up protocols.

As standard of care in our institution, all patients with sub-trochanteric fractures were clinically and radiographically evaluated at 1 month, 3 months, 6 months and at 1 year after trauma.

Institutional Database, Data Collection and Patients Setting

The data about patients affected by sub-trochanteric fractures were collected by using a standardized data collection system in our institution. Demographic data (age, sex, BMI), medical history, chronic therapies, smoke addiction, American Society of Anesthesiologists (ASA) score were recorded.

The patients enrolled in the study were divided into two groups. Group A was composed by patients surgically treated with Closed Reduction and Internal Fixation (CRIF) by a cephalomedullary nail without cerclage. Patients undergoing Open Reduction and Internal Fixation (ORIF) by using cerclage-assisted nails were enrolled in Group B.

Inclusion and Exclusion Criteria

All patients with diagnosis of subtrochanteric fractures treated at our institution between January 2016 to April 2021 were potentially enrollable for the study.

Inclusion criteria were: (1) Type 31-A-3 32-A-1 32-A-2 32-B-1 32-B-2 32-C-1 fracture accord-

ing to AO/OTA classification; (2) complete radiological and clinical data set, (3) patients older than 65 years.

Exclusion criteria were: (1) pathologic fractures; (2) open fractures; (3) patients with a history of infectious diseases; (4) patients lost during follow-up.

Radiological Evaluation

All enrolled patients had performed an X-ray of the pelvis and femur as soon as they arrived at the ED, postoperatively and at each serial follow-up.

On reviewed images the following parameters were measured: (1) state of consolidation, (2) signs of pseudarthrosis, (3) signs of delayed union, (4) loosening or breakage of the nail. The assessment of the state of fracture union was performed by researching the formation of bone callus in serial radiographic controls (Figures 1-3). According to the literature¹¹, a non-union occurs when fracture healing is not achieved within 9 months following injury.

All images were stored on Picture archiving and communication system (PACS) powered by Carestream Clinic Imaging Solutions. All retrieved images were evaluated, using a dedicated workstation (Advantage Windows Workstation, GE Medical Systems, Milwaukee, WI, USA), by A.C., N.B., A.S. Any discordance was solved by consensus with the senior author (G.M.).

Clinical Evaluation

Pain intensity was assessed using a ten-point visual analogue scale (VAS) at hospital presentation, at 6 and 12 months of follow-up visits. Short Form 12 questionnaire (SF12), Activities of daily living (ADL), Instrumental ADL (IADL) were recorded at the first evaluation, at 3, at 6 and at 12 months of follow-up. The SF-12 was originally developed in the United States to provide a short alternative form to the SF-36 questionnaire. The SF-12 is made up of 12 items (taken from the 36 of the original SF-36 questionnaire), which produce two measures related to physical and mental health. Lower score corresponds to higher disability¹²⁻¹⁴.

ADL represents the activities focused on taking self and body care. The score ranges from 0 to 6. IADL refers to activities to support daily living in community life, and generally requires more complex interactions than ADL. Some examples

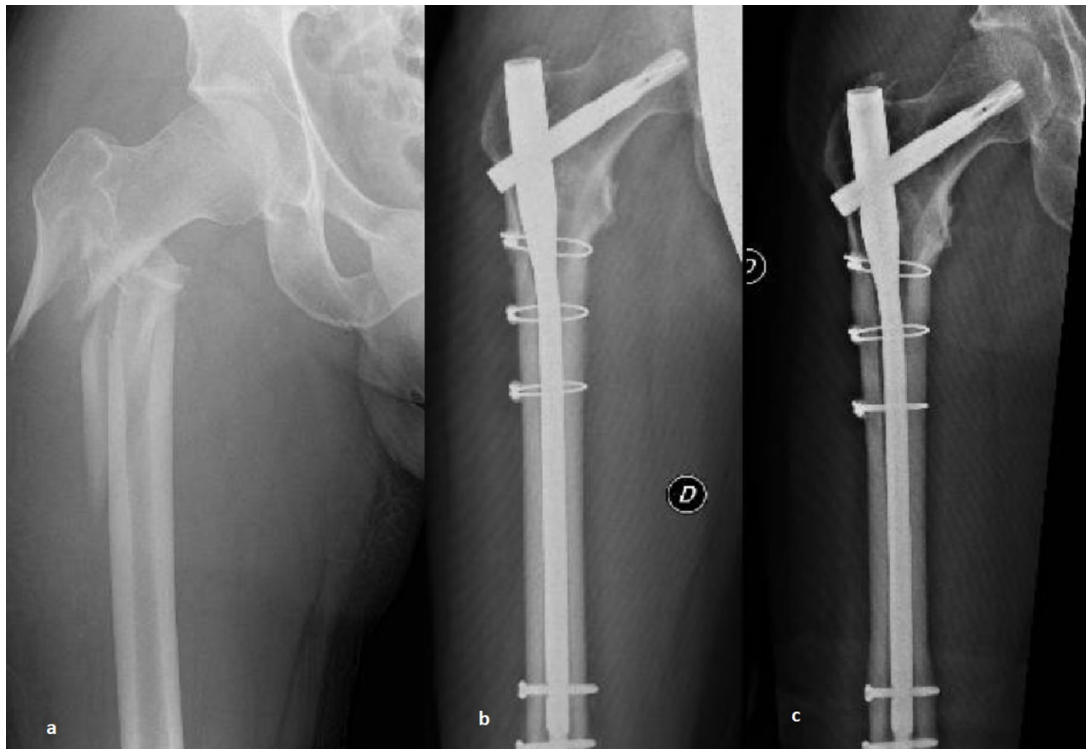


Figure 1. Exemplificative case of subtrochanteric fracture treated with ORIF and 3 cerclages: **a**, preoperative x-rays; **b**, postoperative x-rays; **c**, bone callus and healing of fracture at 3 months follow-up.

of these activities are: managing finances, house-keeping or taking medications. The greater the patient's autonomy, the higher the score¹⁵.

Outcomes

Radiological bony healing rate after 3 months was considered the primary outcome.

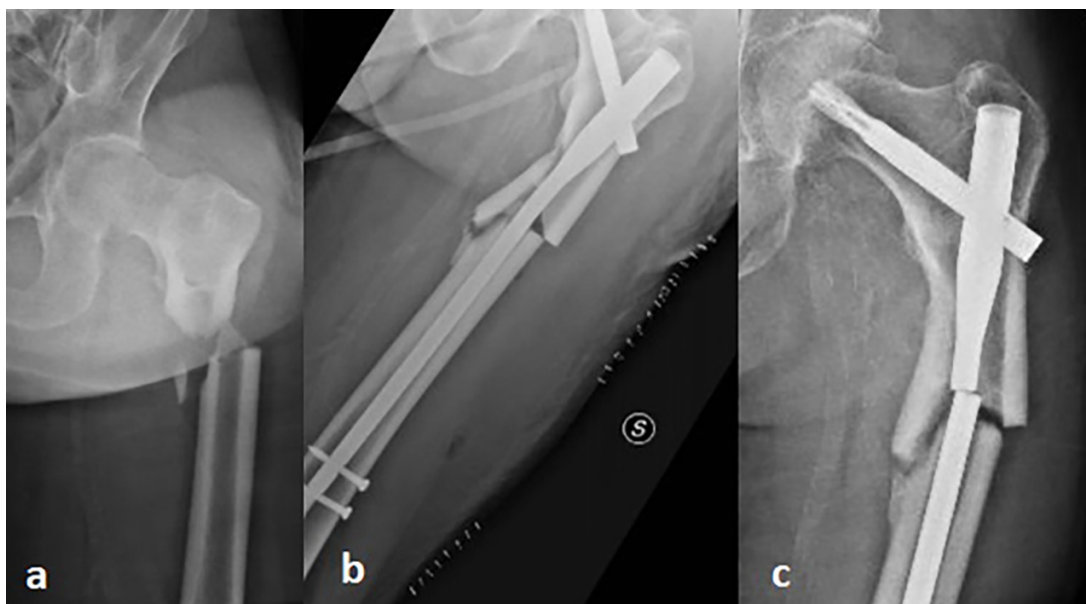


Figure 2. Exemplificative case of subtrochanteric fracture treated with CRIF without cerclage: **a**, preoperative x-rays; **b**, postoperative x-rays; **c**, nail break 9 months after surgery.



Figure 3. Simplified case of subtrochanteric fracture treated with CRIF without cerclage: **a**, preoperative x-rays; **b**, postoperative x-rays; **c**, bone callus and healing of fracture at 6 months follow-up.

The secondary outcomes were: the quality of reduction obtained, the perioperative complications, mortality at one year, SF-12 score, ADL and IADL score, VAS score. The quality of reduction was assessed using Baumgaertner's classification in good, acceptable and poor. Baumgaertner's classification is based on two main criteria: alignment and displacement. For each of the two criteria, there are two alternatives. On the basis of how many criteria are met, the degree of reduction is attributed¹⁶ (Table I).

Table I. Baumgaertner reduction quality criteria.

Baumgaertner criteria	
I. Alignment	a. Anteroposterior view: normal or slight valgus neck-shaft angle b. Lateral view: less than 20° of angulation
II. Displacement	a. Anteroposterior view: less than 4 mm of displacement of any fragments b. Lateral view: less than 4 mm of displacement of any fragments
Reduction quality	
Good: both criteria met Acceptable: only one criterion met Poor: neither criterion met	

Surgical Technique

All patients enrolled in the study were treated by a single surgical team in supine position on traction operative table. The type of anesthesia was general or spinal according to the anesthesiologist indication.

Thirty minutes before incision, a single preoperative dose (2 g) of cefazolin was used as antimicrobial prophylaxis¹⁷. PFN-A long (DePuy Synthes, Raynham, MA, USA) and Gamma Nail long (Stryker, Kalamazoo, MI, USA) were implanted in both groups according to the surgeon's preference. Femoral canal reaming was not performed. In Group B a Synthes Cerclage 1.7 mm (DePuy Synthes, Raynham, MA, USA) or an ic-Cerclage (Implantcast GmbH, Germany) were used.

In group A, after anesthesia, a closed reduction of the fracture was obtained on the traction operative table. A small skin incision in line with the femoral shaft axis was made proximally at the tip of the greater trochanter up to the projection of the iliac crest. After fascia incision, the fibers of gluteus maximus split were made by blunt dissection in order to gain access to the tip of the greater trochanter. Then a guide wire was placed. After fascia incision, a guide wire was placed into the femoral canal by an entry point (great trochanter apex) established on C-arm

guidance. Subsequently, an appropriate-sized nail was placed into the femoral canal linked to the screws guide mask. The nail was then locked with an appropriate-sized cephalic screw and a distal screw placed through a guide mask under C-arm guidance.

In Group B, before nail implantation, a skin incision was made in correspondence with the fracture site. An open reduction of fracture was obtained and a temporally stabilization with 1, 2 or 3 cerclages was performed. After fracture reduction the nail was inserted as described previously. A drainage was positioned after surgery in all patients of Group B.

The total amount of blood loss was estimated for each patient using the following method: milliliters of fluid aspirated during surgery – total saline solution used for washing during surgery.

Post-Surgery Routine

All patients received antithrombotic prophylaxis with low-molecular-weight heparin once a day for five weeks postoperatively and a routine blood test was executed. Catheter was removed on the 1st day after surgery; drainage was removed on the 2nd day after surgery. Mobilization and physiotherapy began the day after surgery. Patients of Group B were allowed to partially weight-bearing with crutches; non-weight-bearing was allowed for the other group.

Statistical Analysis

Dedicated SPSS statistical calculation software (IBM Corp., Armonk, NY, USA) was employed. Data were described using means and standard deviations for quantitative variables and numbers and percentages for qualitative variables. The significance was established for a value of $p < 0.05$. Only one decimal digit was reported, rounded up. The Mann-Whitney U test for two independent ordinal variables. The Wilcoxon Signed-Rank Test was used for two dependent ordinal variables. The Chi-square test was used to analyze categorical variables.

Results

Patients

According to our inclusion and exclusion criteria from 347 patients treated in our institution during the study period, 80 patients (54 F and 26 M) were finally included in the present study. Among these patients 47 belonged to Group A, while 33 to Group B. The mean age was 73.9 (+/-19.2) and 74.4 (+/-18.6) years and the mean BMI was 26.8 (+/-3.5) and 27.1 (+/-4.2) in Group A and B, respectively. Demographic features of enrolled patients divided in 2 groups are summarized in Table II.

Table II. Demographic features of enrolled patients among the two groups.

	Group A	Group B	p-value
No. of patients	47 (58.7%)	33 (41.3%)	-
Age	73.9 (+/-19.2)	74.4 (+/-18.6)	> 0.05
Sex	F:29; M:18	F:25 M:8	-
BMI	26.8 (+/-3.5)	27.1 (+/-4.2)	> 0.05
ASA			
1-2	17 (36.1%)	13 (39.4%)	> 0.05
3-4	30 (63.9%)	20 (60.6%)	> 0.05
Side			
Right	27 (57.6%)	19 (57.5%)	> 0.05
Left	20 (42.4%)	14 (42.5%)	> 0.05
AO classification			
31A3	21 (44.6%)	3 (9.1%)	0.024
32A1	13 (27.6%)	11 (33.3%)	> 0.05
32A2	6 (12.7%)	6 (18.2%)	> 0.05
32B1	2 (4.3%)	6 (18.2%)	0.03
32B2	4 (8.6%)	3 (9.1%)	> 0.05
32C1	1 (2.2%)	4 (12.1%)	0.006
Hospital stay	12.4 (+/-8.3)	18.7 (+/-9.4)	0.0047
Follow-up	15.4 (+/-3.6)	16.1 (+/-4.2)	-

The values indicated in brackets and preceded by the +/- symbol indicate standard deviations. For numerical data in brackets the percentage is indicated. ASA: American Society of Anesthesiologists; BMI: Body Mass Index.

Surgical Results

The mean surgical time was respectively 84.7 (+/-24.6) minutes and 254.7 (+/-80.2) minutes in the Group A and Group B and the difference was statistically significant ($p = 0.0032$). The mean blood loss was respectively 87.3 (+/-18.3) ml and 224.4 (+/-37.8) ml in Group A and in Group B, and the difference was statistically significant ($p = 0.0023$). According to Baumgartner's Classification, in Group A good reduction was obtained in 13 (27.6%) patients, while an acceptable reduction was performed in 27 (57.2%) patients. A poor reduction was obtained in 7 (15.2%) patients. In Group B a good reduction was obtained in 23 (69.8%) patients, while in 8 (24.2%) patients an acceptable reduction was performed. A poor reduction was obtained in 2 (6%) patients. Other surgical data are resumed in Table III.

Radiological and Clinical Outcomes

The mean union time was 4.2 (+/-1.4) months and 3.4 (+/-2.1) months in Group A and Group B, respectively; this difference was not statistically significant. In Group A we observed 7 (14.8%) cases of non-union while in Group B 2 (6.3%, $p = 0.012$) (Table IV).

The VAS scale showed significantly better results at 6 and 12 months of follow-up in Group B. The same trend was observed concerning SF-12 (P). No statistical differences were observed between the two Groups regarding SF-12(M), ADL and IADL. However, a substantial improvement of these outcomes between the 1-month follow-up visits and the 12 months follow-up visit was recorded in both groups (Table III).

Complications and Mortality

The complications rate was 18.2% in Group A and 12.2% in Group B. Seven patients in Group A developed implant breakage at a mean of 7 months (3-10 months) from surgery. Nail breakage represented the prevalent complication in Group A (7 patients, 77.8% of total complications), while in Group B the infections were more frequent with respect to Group A (12% vs. 2.1%).

The 1-year mortality rate was respectively 4.2% and 9.1% in Group A and Group B, and these different results were statistically significant ($p = 0.0042$). The patients belonging to Group B presented a mortality relative risk (RR) of 2.14 compared to patients belonging to Group A.

Discussion

Subtrochanteric fractures still pose a challenge to orthopedic surgeons. The instability due to the deforming muscle forces and the tenuous blood supply to the medial cortex affect the healing of the fracture, contributing to treatment failure. In the subtrochanteric fractures the most frequent pattern is varus deformity due to the fragmentary disruption of medial cortical support. The proximal fragment may be shortened and deformed in flexion, abduction and external rotation due to the forces acted by gluteus medius and minimus, psoas and external rotators¹⁸⁻²⁰.

The nearly anatomical reduction is very important for good outcomes and reducing the risk of complications, but for this type of fracture obtaining an acceptable reduction could be technically difficult. Some studies²¹⁻²³ support the

Table III. Surgical data, complication and mortality among the two groups.

	Group A	Group B	p-value
Operative time (minutes)	84.7 (+/-24.6)	254.7 (+/-80.2)	0.0032
Anesthesia type			
General	38 (81%)	27 (81.8%)	> 0.05
Spinal	9 (19%)	6 (18.2%)	> 0.05
Type of Nail			
Synthes PFN-A Long	41 (86.9%)	28 (74.7%)	> 0.05
Stryker Gamma Nail Long	6 (13.1%)	5 (25.3%)	> 0.05
Reduction achieved (Baumgaertner)			
Good	13 (27.6%)	23 (69.8%)	0.006
Acceptable	27 (57.2%)	8 (24.2%)	0.002
Poor	7 (15.2%)	2 (6%)	0.004
Blood loss (ml)	87.3 (+/-18.3)	224.4 (+/-37.8)	0.0023

The values indicated in brackets and preceded by the +/- symbol indicate standard deviations. For numerical data in brackets the percentage is indicated.

Table IV. Surgical, radiological and clinical outcomes.

	Group A	Group B	p-value
Time of union (months)	4.2 (+/-1.4)	3.4 (+/-2.1)	0.03
Union	40 (85.2%)	31 (93.7%)	0.008
Nonunion	7 (14.8%)	2 (6.3%)	0.012
VAS (1 month)	5.9 (+/-1.4)	6.3 (+/-1.8)	> 0.05
VAS (3 months)	4.8 (+/-0.9)	5.1 (+/-1.3)	> 0.05
VAS (6 months)	3.4 (+/-1.2)	4.3 (+/-1.7)	> 0.05
VAS (12 months)	1.9 (+/-2.1)	3.9 (+/-1.5)	0.032
SF-12 (P, 1 month)	31.4 (+/-8.2)	29.8 (+/-10.2)	> 0.05
SF-12 (P, 3 month)	34.8 (+/-7.9)	33.4 (+/-9.5)	> 0.05
SF-12 (P, 6 months)	41.7 (+/-14.2)	39.9 (+/-16.2)	> 0.05
SF-12 (P, 12 months)	55.9 (+/-17.6)	52.2 (+/-18.3)	> 0.05
SF-12 (M, 1 month)	37.2 (+/-12.3)	36.9 (+/-14.4)	> 0.05
SF-12 (M, 3 month)	42.9 (+/- 10.8)	41.5 (+/- 7.3)	> 0.05
SF-12 (M, 6 months)	49.8 (+/-16.3)	47.1 (+/-18.7)	> 0.05
SF-12 (M, 12 months)	59.8 (+/- 18.2)	60.7 (+/-21.5)	> 0.05
ADL (1 month)	3.5 (+/-1.2)	3.7 (+/-1.1)	> 0.05
ADL (3 month)	3.9 (+/-0.8)	4.0 (+/-0.9)	> 0.05
ADL (6 months)	4.1 (+/-0.9)	4.2 (+/-1.4)	> 0.05
ADL (12 months)	4.3 (+/-1.6)	4.4 (+/-1.5)	> 0.05
IADL (1 month)	2.8 (+/-1.1)	3.1 (+/-0.8)	> 0.05
IADL (2 month)	3.2 (+/-0.8)	3.4 (+/-1.1)	> 0.05
IADL (6 months)	4.2 (+/-1.3)	4.4 (+/-1)	> 0.05
IADL (12 months)	5.9 (+/-2.1)	6.0 (+/-1.7)	> 0.05
Mortality (12 months)	2 (4.2%)	3 (9.1%)	0.0042
Complication	9 (18.2%)	8 (24.3%)	> 0.05
Nail breakage	7 (77.8%)	0	< 0.0002
Need of blood transfusion	0	4 (50%)	< 0.0003
Wound infection	1 (11.1%)	2 (25%)	> 0.05
Deep tissue infection	0	2 (25%)	< 0.0006
Other	1 (11.1%)	0	> 0.05

The values indicated in brackets and preceded by the +/- symbol indicate standard deviations. For numerical data in brackets the percentage is indicated. ADL: Activities of daily living; IADL: Instrumental Activities of daily living; SF-12 M: Mental Short Form 12; SF-12 P: Physical Short Form 12; VAS: Visual Analogue Scale.

theory that the disruption of the periosteal blood flow by open reduction contributes to fracture healing failure.

Extramedullary with plates and screws has many disadvantages such as severe blood loss, large surgical dissection and soft tissue damage. Furthermore, intramedullary fixation ensures superior mechanical performances due to load sharing with a smaller bending moment of intramedullary devices allowing early weight bearing and preventing excessive collapse compared to plating devices²⁴.

We reviewed all subtrochanteric fractures treated with intramedullary nail fixation which is currently considered the gold standard since

it has demonstrated biomechanical superiority through controlled fracture compression and a weight-bearing axis near the femoral shaft axis^{19,25-27}, although the varus malreduction, non-union, malunion and delayed consolidation are very common complications^{18-20,28,29}. In particular, we focused attention on the differences between assisted treatment with and without cerclage wire.

Controversial opinions^{21,30-35} concern the use of the cerclage cables or wires to achieve better reduction at the expense of hypothetical vascular damage to the bone. Some surgeons prefer to renounce anatomical reduction to avoid bone devascularization and the risk of non-unions

and infections attributed to the use of cerclage^{21,30} while several studies³¹⁻³⁵ encourage its use since they have shown that vascularity is preserved.

Obviously, care should be taken while passing cerclage or wire in order to avoid intraoperative complications due to major vessel injury^{36,37}.

In our series, 33 cases of nailing fixation with cerclage and 47 cases without cerclage were reviewed. As expected, patients with cerclage wires had a longer operating surgery time and higher blood loss than in the non-cerclage group: 84.7 (+/-24.6) minutes vs. 254.7 (+/-80.2) minutes; even the length of hospital stay was longer in those patients undergoing wire-assisted nail fixation. Those results are in line with literature^{20,25}.

A better reduction was obtained in Group B with respect to Group A. Similar results were reported by Codesido et al²⁰, Karayiannis and James³⁸, and Hoskins et al³⁹ revealing the significant superiority of wire-assisted fixation in achieving the optimal reduction.

The reconstruction of medial wall support while using an intramedullary nail has demonstrated to be the key element in ensuring correct load transfer and stable osteosynthesis⁴⁰. Hence, according to Kilinc et al¹⁹ experience, wire application can help in the determination of the nail entry point, which is difficult to obtain before the reduction due to the forces on the fractured fragments.

As regards the time of union, it was shown to be shorter in the group with cerclage, although this difference was not statistically significant as in the Codesido et al study²⁰. Only 2 cases of non-union have been documented in the cerclage group (6.3%) vs. 14.8% in Group A.

Even the absolute complication rate was higher in the group without cerclage (18.2%) where 7 implant breakages occurred. Four complications (12.2%) have been reported in Group B: they consisted of 2 wound infections and 2 deep infections. None of this required revision and were solved with antibiotic therapy. Similar results have been reported by Codesido et al²⁰. Few studies^{25,38} have shown higher complication rates in those patients undergoing nail fixation with cerclage. 8.3% of cerclage-related complications in Karayiannis and James³⁸ review were attributed by authors themselves to confounding factors such as complexity and comminution of the fracture patterns, increasing the likelihood of cable being used and potential grade of the operating surgeons.

According to literature⁴¹, most of the complications related to subtrochanteric fractures consist of implant failure, withdrawal of the screws implant cut out, and implant ruptures. Furthermore, the use of cerclage seems to high the mortality relative risk at 1-year from surgery.

Concerning functional scores, no differences emerged between both groups about ADL and IADL index. Both Physical and Mental SF scores increased in both groups over time, from 1-month follow up visit to the 12 months follow up visit. Even pain evaluation by VAS score, showed similar results. The major VAS and the lower Physical SF scores up to 3-months follow-up in group B could result from a more invasive surgical approach leading to major trauma to the soft tissues that can take time for total healing. Despite this, at 6 and 12 months the trend reverses and the best results were found in group B.

There is still no consensus on which is the best surgical technique. Surely, an accurate evaluation of the fracture pattern according to OTA classification and a clinical preoperative evaluation of the patient is useful for the treatment and surgical decision.

Limitations

The main limitation of this study is that it is a retrospective analysis so there is no preoperative evaluation that can give us information about comorbidities or clinical conditions that may have influenced the post-operative period and the parameter analyzed.

Another limitation is the relative low number of patients. Then, this study includes subtrochanteric and intertrochanteric fracture patterns which are very different from each other and not homogeneous due to the complexity of the fracture patterns. We consider that it may be useful to make an assessment for each of these patterns. At last, the different distribution of fracture types between the two groups represents another limit.

Conclusions

Anatomical reduction of subtrochanteric fractures should remain the main goal in order to ensure earlier fracture healing and reduce the risk of secondary displacement of the fracture.

We recommend using cerclage wire in those irreducible fractures or if an acceptable closed reduction cannot be achieved since its use may help consistently in medial wall reconstruction and stability.

Since operating surgery times and the amount of perioperative blood loss are greater in the open reduction, in the elderly patient it is preferable to have a lower reduction since the quality of life and functional recovery between the two methods is almost overlapped.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Not applicable.

Informed Consent

All patients signed a written consent concerning demographic and clinical data collection for scientific purposes.

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Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

All the authors approved the submitted version (and version substantially edited by journal staff that involves the author's contribution to the study) and agree to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature. Conceptualization and Methodology: A. S., N. B., A. C.; Validation: G. M., A.Z.; Formal Analysis: A.C. and A.P.; Investigation: A. S., N. B., A. C.; Writing – Original Draft Preparation: A.S., N. B., A.C.; Writing – Review & Editing: A.P.; Supervision: G. M.

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