# Investigation of smoking effects on percutaneous autologous bone marrow injection for nonunion patients

Taher Abd Elsattar Aid[1], Adel Ibrahim Alseedy[1], Ahmed F. Shams[1], Ahmed Abd Elfattah Khalil[2].

[1]Department of Orthopedic Surgery, Faculty of Medicine, Menufiya University, Egypt
[2]Department of Orthopedic Surgery, Al-Menshawy Hospital, Tanta, Egypt
midoorthopedics@yahoo.com

**Abstract:** Regarding the effects of smoking on fracture healing and post-operative infection after long-bone fracture surgery, there is little reported analysis. Our study aimed to report the smoking effect on percutaneous autologous bone marrow injection for nonunion patients. Twenty patients, 10 smokers and 10 nonsmokers, were referred to us with a nonunion of the tibia and femur after number of previous interventions on bone to procure healing at the time of fracture. A total of 40–80 mL of bone marrow aspirated from the anterior iliac crest and injected in and around the nonunion site under fluoroscopic guidance. The overall success rate obtained from the operation was 70.0% (14/20), but there was a significant difference between the success rates of smokers and non-smokers [50.0% (5/10) vs 90.0% (9/10)]. Generally, smoking was associated with increased nonunion for all fractures. Additionally, smokers trended towards longer mean healing times.

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**Key Words:** nonunion, bone marrow, injection, smoking

## 1.Introduction:

Bone healing is a complex process that is influenced by biological, mechanical and systemic factors (1). There is growing evidence that smoking delays or inhibits bone healing after surgery or trauma. This evidence has largely been derived from animal studies and human studies focusing on spinal fusion (2-5).

Causes of nonunion may be related either to the fracture (type and site of fracture, degree of comminution, infection, instability, vascular injury) or to systemic factors including diabetes (6), peripheral vascular disease (7), and non-steroidal anti-inflammatory drugs (NSAiDS) (8). Smoking has a well documented negative effect on the cardiac and respiratory systems. Moreover, there is little reported analysis regarding the effects of smoking on fracture healing and post-operative infection after long bone fracture surgery (9). The current study tries to bring in arguments for a similar negative effect on bone healing. There are 4000 chemicals found in cigarettes (10). Nicotine, carbon monoxide and hydrogen cyanide are often cited as the causes of adverse effects. However the exact mechanism and effect of smoking on fracture healing has yet to be established (11).

Bone marrow contains osteoprogenitor cells capable of forming bone (12,13). Percutaneous bone marrow grafting involves harvesting autogenous bone marrow from the anterior or posterior iliac crest using a trochar needle (13). The technique is minimally invasive, has low morbidity (13- 15). Percutaneous bone marrow injection has been reported with favorable results as a clinical treatment for diaphyseal fracture nonunions in humans in the upper extremity (16), femur (17), and tibia (14,18). Giannoudis (19) described a “diamond concept of requirements” for fracture healing to occur successfully: osteogenic cells, osteoconductive scaffold, mechanical stability and adequate growth factors. Whilst it is unlikely that smoking affects the mechanical stability, it may have effects on the other three aspects of the diamond.

This study looks specifically at the effect of smoking on the outcome of bone marrow injection for the nonunited long bone fractures.

## 2. Patients and Methods

A total of randomized 20 prospective patients were admitted to Menufiya University hospital and El Menshawy Hospital, Egypt, from November 2009 and February 2013. Out of 20 patients, 10 patients were smokers and the remaining patients were non smokers, with nonunion were treated with bone marrow injection. The patient's age ranged between 20-63 years.

Selection criteria for treatment with percutaneous autogenous bone marrow injection in patients were described by Willkins (20) as follows: established nonunion more than six months after injury with no evidence of healing for the previous three months, no evidence of motion seen at nonunion site, no intervention in past three months, no evidence of active infection, no smoking for last six weeks, no pre-existing angular deformity or shortening. Additionally, the hardware components seemed to be intact by radiographic evaluation, and there was no apparent or compelling reason to remove the hardware (e.g, poorly oriented or

inappropriate for the injury). Also, the injury site was mechanically stable by clinical examination.

Exclusion criteria for treatment with percutaneous autogenous bone marrow injection in patients were as follows: infection, skin lesions, coagulopathy, anemia, large fracture gap, persistent fracture mobility.

Between November 2009 and February 2013, 20 consecutive patients meeting these inclusion criteria were referred to Menoufia University Hospitals and Al-Menshawy Hospital and were included in the current study.

Marrow aspiration and injection needles were used in this study. C-arm was used for detection of the nonunited fracture site and insertion of those needles into their proper position. The first we have to do trimming and refreshing of the fracture edges closed under guidance of C-arm by needles. Then aspiration of bone marrow from anterior superior iliac spine with another needle and the aspirated marrow was injected simultaneously into the injection needles inserted into the non union site. Postoperatively, the patients were admitted for an overnight hospital stay with the surgical leg supported in a horizontal position to maintain the injected marrow at the nonunion or delayed union site. The patients were instructed to ambulate non weight and were begun on progressive weight bearing as tolerated starting at 6 weeks postoperative. Patients were evaluated by clinical examination and radiological assessment.

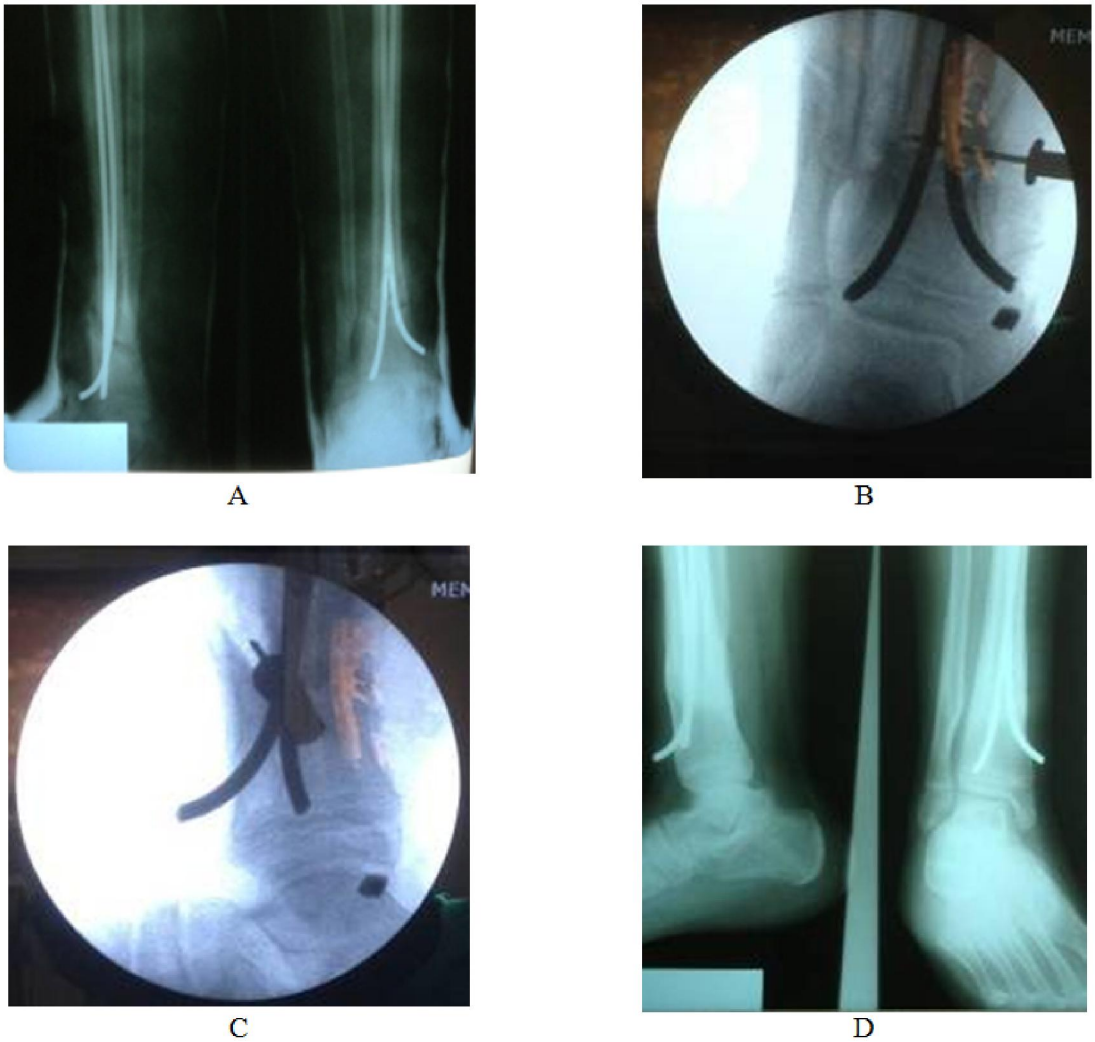


Figure 1. A 15-year-old man, 5.9 months after road traffic accident and a open distal tibia–fibula fracture treated intramedullary flexiable nails fixation. At presentation in our facility, the Pre-operative anteroposterior radiograph (A) and Immediate intra-operative radiograph by C-arm (B, C) showed a nonunion at the fracture site with 0% cross-sectional healing. At 6 months after the percutaneous autologous bone marrow injection, the patient's radiograph (D) showed solid bony union. At final follow-up 12 months after marrow injection, the patient reported large improvements in pain (13/50 according to Calori et al (1). nonunion scoring system).

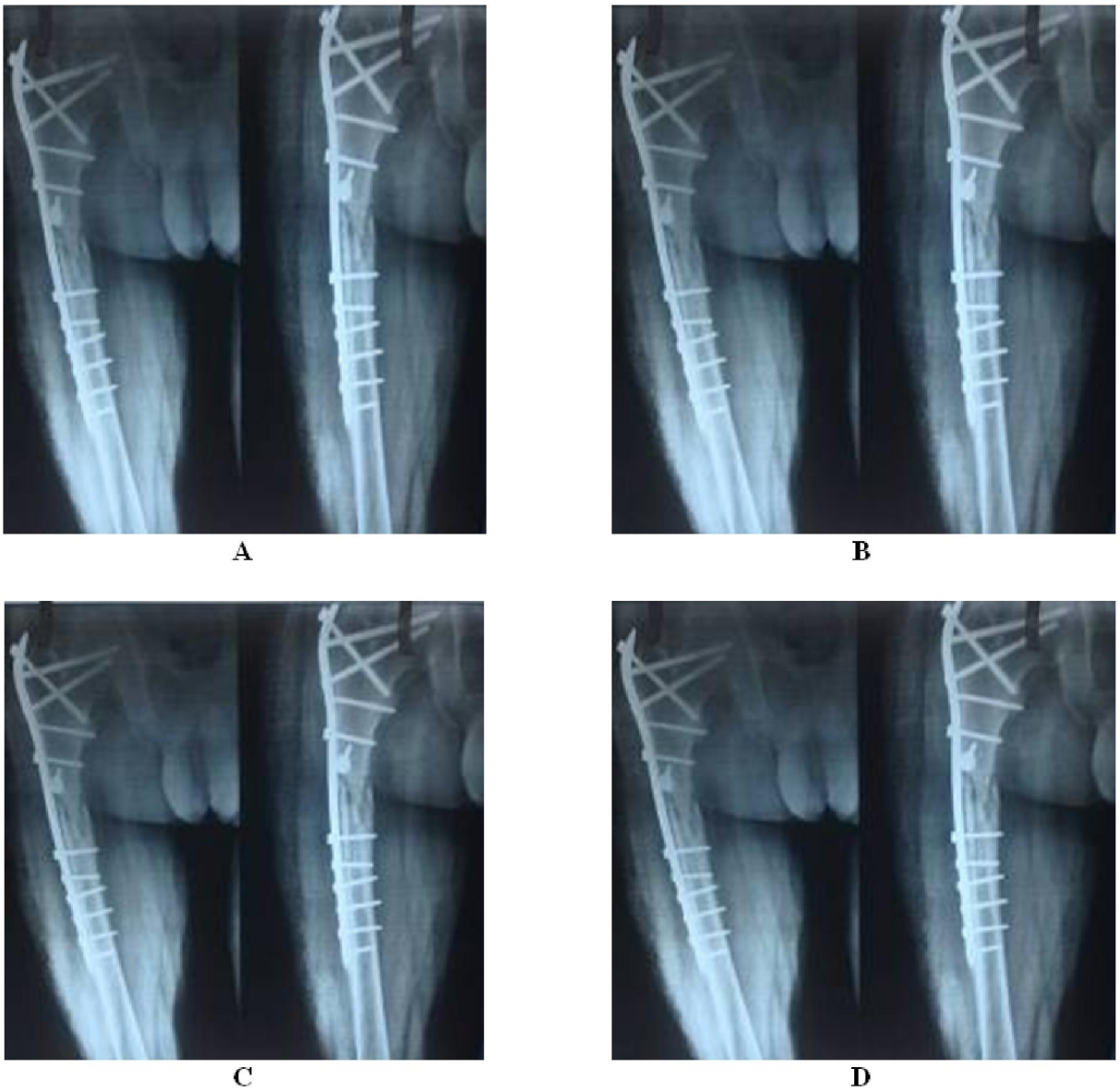


Figure 2. A 26-year-old man, 15.0 months after road traffic accident and closed subtrochantric fracture right femur treated immediately by proximal femoral plate and bicortical bone grafting. At presentation in our facility, the Pre-operative anteroposterior radiograph (A), three weeks after first bone marrow injection (B) and radiograph after third time of bone marrow injections (C). After the fourth time percutaneous autologous bone marrow injection, the patient's radiograph (D) showed nonunion. At final follow-up 15 months after marrow injection, the patient reported (38/50 according to Calori et al. (1) nonunion scoring system).

**Table (1). The relation between the age and the number of injections for healed and non healed patients**

| No. of injections | No. of patients injected | Healed | | Not Healed | |
|---|---|---|---|---|---|
| | | Mean of patients age ± SD | No. of patients (%) | Mean of patients age ± SD | No. of patients (%) |
| 2 | 2 | 23.0 ± 11.34 | 2 (100) | 0.0 ± 0.0 | 0 (0) |
| 3 | 8 | 31.9 ± 11.6 | 7 (87.5) | 49.0 ± 0.0 | 1 (12,5) |
| 4 | 10 | 41.2 ± 15.56 | 5 (50) | 15.56 ± 12.36 | 5 (50) |
| All | 20 | 30.92 ± 10.88 | 14 (70) | 47.33 ± 7.47 | 6 (30) |
| T value | | 10.629*** | | 15. 512*** | |

** Significant at ($P$ 0.05 – 0.001).
*** Highly significant at ($P \leq 0.001$).

**Table 2: Comparison of smokers and non-smokers undergoing bone marrow injections for long bone non-union**

| Parameter | | Smokers | Non-smokers |
|---|---|---|---|
| Number | | 10 | 10 |
| Age (years) | Mean | 42.2 | 28.5 |
| | Range | 32.0–60.0 | 15.0–54.0 |
| Fracture location | Femur | 4 | 2 |
| | Tibia | 6 | 8 |
| Fixation type | Plate & screws | 2 | 2 |
| | Intra-medullary fixation | 4 | 4 |
| | External fixators | 3 | 2 |
| | P.O.P Cast fixation | 1 | 2 |
| Time between injury and operation (months) | Median | 12.6 | 11.4 |
| | Range | 9.0–24.0 | 7.0–24.0 |
| Post-operative time in plaster cast (weeks) | Mean | 14.2 | 7.4 |
| | Range | 9.0–22.0 | 5.3–17.4 |
| Final outcome | United | 5 | 9 |
| | Not united | 5 | 1 |
| | Union rate | 50.0% | 90.0% |

Anteroposterior and lateral radiographs were obtained and evaluated to assess healing at the injury site. The Calori et al. (1) nonunion scoring system used in this work depends on three "core" factors being bone, soft tissues status and patient. Each factor is ranged from 0 up to 6 and the total score represents the summation of points of three factors (50 points). The statistical analysis was conducted using SPSS version 16.0 (SPSS Inc., Chicago, IL). A *P* value of <0.05 was considered to be statistically significant.

## 3. Results

Out of the 20 patients, 14 (70.0%) achieved bony union in an average of 4.1 months (range, 1.7–6.4 months) as represented in Case 1(Fig 1). Six patients failed to achieve bony union, with no signs of healing at 3 months after marrow injection as represented in Case 2 (Fig 2). One of these patients was non smoker and the other five patients were smokers as illustrated in Table (1). Noticeably, smokers patients were received more bone marrow injections than non smoker patients.

Smoker and non-smoker sub-groups were comparable in terms of fracture location, delay to operation, implant used and duration of post-operative immobilization (Table 2). The overall success rate of the operation was 70.0% (14/20), but there was a significant difference between the success rates of smokers and non-smokers [50.0% (5/10) vs 90.0% (9/10)]. The relative rate of smokers having a persistent non-union was 3.4 (0.60/0.176) compared to smokers.

## 4. Discussion

The effect of smoking on bony healing has been investigated mainly in long-bone fractures. Smoking impairs bony healing in tibial fractures, whether treated operatively (21) or non-operatively (22). However, in established nonunion of femoral fractures, one study found that the operative intervention was sufficient to overcome the effect of smoking on bone healing (23).

This study found association between failure of operative treatment of established nonunion and a history of smoking. Bone marrow injections had a lower success rate in smokers than in non-smokers (50.0% vs 90.0%). However, this study has several limitations. Firstly, it is quite a small study, with only 20 cases. Also, its retrospective nature does not allow for confounding factors. Nevertheless, as shown in Table 2, factors such as delay to surgery, age at operation, fracture location and duration of post-operative immobilisation were similar among smokers and non-smokers. Our results agree with the study of Kyrö et al. (22) who showed a total of 135 patients with a fresh tibial shaft fracture who underwent primary conservative treatment. The smokers were found to have a significantly longer mean time to clinical union (23.7 weeks versus 19.1 weeks) and a higher incidence of nonunion: 50% versus 32%. In addition, McKee et al. (24) retrospectively reviewed 84 patients who underwent 86 Ilizarov reconstructions. There was a higher incidence of nonunion in the smoking group: 10 versus 2. Seven of eight patients with persisting infection were smokers. All five amputations were in smokers. There were significantly more poor results in the smoking group than in the non -smoking group (18/47, 38% versus 4/39, 10%). Four studies (25-27) compared the healing time of tibial fractures in smokers and nonsmokers: the difference was about 2 months.

## Conclusion

This study found a significant association between smoking and failure of bone marrow injections in treatment of nonunion. The persistent nonunion rate was over four-times higher in smokers

than non smokers. We recommend that patients should attempt smoking cessation therapy before consideration for elective orthopaedic treatment.

**Corresponding author:**
Ahmed Abd Elfattah Khalil,
Orthopedic Department, El Menshawy Hospital,
Tanta, Egypt,
Email: midoorthopedics@yahoo.com

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