Upper Limb

Treatment of nonunions in fractures of the humeral shaft according to the Diamond Concept

M. Miska, S. Findeisen, M. Tanner, B. Biglari, S. Studier-Fischer, P. A. Grützner, G. Schmidmaier, A. Moghaddam

From Trauma and Reconstructive Surgery, Center for Orthopedics, Trauma Surgery and Spinal Cord Injury, Heidelberg University Hospital, Heidelberg, Germany

M. Miska, MD, Resident
S. Findeisen, Medical Student
M. Tanner, MD, Consultant
G. Schmidmaier, MD, PhD, Chairman
A. Moghaddam, MD, PhD, Consultant,
Trauma and Orthopaedic Surgery, Trauma and Reconstructive Surgery, Center for Orthopedics, Trauma Surgery and Spinal Cord Injury Heidelberg University Hospital, Schillerbächer Landstraße 200a, 69118 Heidelberg, Germany.
B. Biglari, MD, Consultant
S. Studier-Fischer, MD, Consultant
P. A. Grützner, MD, PhD, Chairman,
Trauma and Orthopaedic Surgery, BG Trauma Center Ludwigshafen, Unfallchirurgische Klinik University of Heidelberg, Ludwig-Guttmann-Straße 13, 67071 Ludwigshafen am Rhein, Germany.

Correspondence should be sent to Dr Med M. Miska; e-mail: matthias.miska@med.uni-heidelberg.de

Methods

Between 2005 and 2012, 50 patients (23 female, 27 male) with nonunion of the humeral shaft were included in this retrospective study. The mean age was 51.3 years (14 to 88). The patients had a mean of 1.5 prior operations (SD 1.2; 1 to 8).

All patients were assessed according to a specific risk score in order to devise an optimal and individual therapy plan consistent with the Diamond Concept. In 32 cases (64%), a change in the osteosynthesis to an angular stable locking compression plate was performed. According to the individual risk an additional bone graft and/or bone morphogenetic protein-7 (BMP-7) were applied.

Results

A successful consolidation of the nonunion was observed in 37 cases (80.4%) with a median healing time of six months (IQR 6). Younger patients showed significantly better consolidation. Four patients were lost to follow-up. Revision was necessary in a total of eight (16%) cases. In the initial treatment, intramedullary nailing was most common.

Discussion

The use of locking compression plates in combination with autologous cancellous bone graft has been shown to be a safe and effective treatment. In more complex cases, the use of the Masquelet technique and BMP-7 may be indicated at the first revision operation.

Take home message: Our results suggest the Diamond Concept is a successful treatment strategy for nonunions of the humeral shaft.

Cite this article: Bone Joint J 2016;98-B:81–7.

Nonunion after fractures most often appears in the leg and is less common in humeral fractures. Despite major advances in operative techniques and the design of implants for osteosynthesis, in humeral fractures, the rate of nonunion of the humeral shaft is still reported to range from 3% to 5% of all operatively treated fractures.1,2 Whilst there may be some consensus on the nature of operative treatment in general, the choice of the fixation device (plate vs nail) is still debated.3 The rate of nonunions after non-operative treatment is higher and described as up to 23% in literature.4,6 There are several local and systemic factors known to disrupt the complex process of bone healing, leading to nonunion, which may include insufficient stabilisation, extensive soft-tissue trauma with compromised vascularisation, high age, comorbidities (diabetes, rheumatoid arthritis, osteoporosis), medication (steroids, NSAIDs) and smoking.7,11 Often there is a multifactorial origin to nonunion.7 In response to the multifactorial origin of nonunion, the Diamond Concept for treatment was developed and described by Giannoudis, Einhorn and Marsh12 and Giannoudis et al.7 The nonunion is evaluated according to the following criteria:

- osteogenic cells,
- osteoconductive scaffolds,
- mechanical environment,
- growth factors,
- vascularity.

By identifying missing factors in each patient, an ideal strategy for treatment may be devised. A reasonable combination of biological and biomechanical approaches may greatly improve outcome.

In this study, we present our results from the treatment of nonunions of fractures of the humeral shaft according to the Diamond Concept. The aim of this study was to assess the success of nonunion treatment according to the

©2016 The British Editorial Society of Bone & Joint Surgery
doi:10.1302/0301-620X.98B1.35682 $2.00

Bone Joint J 2016;98-B:81–7
Received 20 December 2014; Accepted after revision 14 August 2015
main observer (AM). Exclusion criteria included patients who were surgically treated for 50 nonunions involving the humeral shaft in two trauma centres from 2005 to 2012, were included in this retrospective study. This study was approved by the institutional review board of Rheinland-Pfalz, “Ethikkommision bei der Landesärztekammer Rheinland-Pfalz,” (No. 837.141.08 (6138)) and the ethics commission of the University of Heidelberg (No. S-532/2011). Patients were considered for the study who had a radiologically detectable nonunion after fracture of the humeral shaft and who developed a nonunion following previous treatment. A nonunion was defined when no healing occurred within six months or strong evidence of therapy failure (e.g., instability, infection) without any signs of improvement or a critical size gap was present independent of a fixed period of time. Radiological criteria of a nonunion were the insufficient bridging of a bone gap, no progress in callus formation and loss of bone alignment. All patients were assessed in the same way, using a standardised study protocol and were supervised and treated by one main observer (AM). Exclusion criteria included patients younger than 18 years, patients unable to give an informed consent for study and patients with a high risk for elective surgical treatment (American Society of Anesthesiologists (ASA) grade > 3). The mean age at operation for trauma was 50.3 years (standard deviation (SD) 18.4; 14 to 87) and 51.3 years (SD 20; 14 to 88) at operation for established nonunion. A total of 33 patients had one prior operation for treatment of the fracture, ten patients had two prior revision procedures, four patients had three prior revisions, one patient had four prior and one patient had eight prior revisions (Table I). These included internal plate fixation (n = 12), antegrade nailing (n = 17), retrograde nailing (n = 14) and closed retrograde bundle nailing (n = 6). One patient underwent initial conservative treatment. In six patients an unsuccessful change of osteosynthesis had been undertaken previously, in three patients with cancellous bone grafting. Four patients underwent revision because of infection.

The mean time period from trauma to nonunion surgery in our clinics was 10.9 months (2 to 53).

In total, two patients had suffered a grade 1 open fracture, one patient a grade 2 open fracture, and one patient a grade 3 open fracture. In all 13 patients had nerve injuries in the affected limb (26.0%), affecting the radial nerve in 12 patients and the median nerve in one. There was a history of current or previous smoking in 14 patients while 36 patients were non-smokers. The mean body mass index (BMI) was 28.8 (20.9 to 43.2). Table II shows the comorbidities of the cohort.

**Table II. Comorbidities in the patient cohort**

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Patients (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Heart diseases</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Back pain</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Gastric diseases</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Thyroid gland disorders</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Renal diseases</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Liver diseases</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Haematological disorders</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* Nonunion operation in our clinics
† Time (mths). Time to heal depends on all patients with consolidated nonunions after our treatment
SD, standard deviation, IQR, interquartile range

**Patients and Methods**

**Patients.** In total, 30 patients (23 female, 27 male) who were surgically treated for 50 nonunions involving the humeral shaft in two trauma centres from 2005 to 2012, were included in this retrospective study. This study was approved by the institutional review board of Rheinland-Pfalz, “Ethikkommision bei der Landesärztekammer Rheinland-Pfalz,” (No. 837.141.08 (6138)) and the ethics commission of the University of Heidelberg (No. S-532/2011). Patients were considered for the study who had a radiologically detectable nonunion after fracture of the humeral shaft and who developed a nonunion following previous treatment. A nonunion was defined when no healing occurred within six months or strong evidence of therapy failure (e.g., instability, infection) without any signs of improvement or a critical size gap was present independent of a fixed period of time. Radiological criteria of a nonunion were the insufficient bridging of a bone gap, no progress in callus formation and loss of bone alignment. All patients were assessed in the same way, using a standardised study protocol and were supervised and treated by one main observer (AM). Exclusion criteria included patients younger than 18 years, patients unable to give an informed consent for study and patients with a high risk for elective surgical treatment (American Society of Anesthesiologists (ASA) grade > 3). The mean age at operation for trauma was 50.3 years (standard deviation (SD) 18.4; 14 to 87) and 51.3 years (SD 20; 14 to 88) at operation for established nonunion. A total of 33 patients had one prior operation for treatment of the fracture, ten patients had two prior revision procedures, four patients had three prior revisions, one patient had four prior and one patient had eight prior revisions (Table I). These included internal plate fixation (n = 12), antegrade nailing (n = 17), retrograde nailing (n = 14) and closed retrograde bundle nailing (n = 6). One patient underwent initial conservative treatment. In six patients an unsuccessful change of osteosynthesis had been undertaken previously, in three patients with cancellous bone grafting. Four patients underwent revision because of infection.

The mean time period from trauma to nonunion surgery in our clinics was 10.9 months (2 to 53).

In total, two patients had suffered a grade 1 open fracture, one patient a grade 2 open fracture, and one patient a grade 3 open fracture. In all 13 patients had nerve injuries in the affected limb (26.0%), affecting the radial nerve in 12 patients and the median nerve in one. There was a history of current or previous smoking in 14 patients while 36 patients were non-smokers. The mean body mass index (BMI) was 28.8 (20.9 to 43.2). Table II shows the comorbidities of the cohort.

**Estimation of individual risk scores.** The individual risk for developing a nonunion was estimated using the score developed by Moghaddam et al. The score gathers specific parameters regarding the localisation of the fracture with accompanying injuries of the nerves and soft tissues and additional patient related risk factors. Risk factors taken into account are medication like NSAIDs and bisphosphonates, the presence of diabetes and, with high impact, the smoker status. These parameters add to a total point value leading to a risk classification of the patients, divided in low risk patients with < 10 points, medium risk patients with 10 to 20 points and high-risk patients with > 20 points. In 22 patients (44.0%) a low risk score (type 1) applied, 17 patients (34.0%) had a medium risk (type 2), and 11 patients (22.0%) a high risk (type 3). The median individual risk score in the patient cohort was ten points (6 to 31) (Table II).
Surgical treatment of nonunions. Each fracture was evaluated for individual risk, indications for revision surgery, and the need for osteoinductive and/or osteogenic additives according to the Diamond Concept (Fig. 1). In fractures with insufficient stability at the primary osteosynthesis but were considered either low risk or moderate risk, a single revision of the osteosynthesis was made (Fig. 2). Cancellous bone grafting was performed to fill bone defects after...
debridement of the nonunion. In large defects where no shortening was possible (> 2 cm), and especially when devitalised tissue could be detected, bone morphogenetic protein-7 (BMP-7) (OP-1, Osigraft, Olympus Biotech, Lyon, France) was applied. Complex cases with infection and osteitis underwent a two-stage Masquelet-procedure\textsuperscript{16,17} to debride the necrotic bone and induce a vascularised membrane (Fig. 3). BMP-7 was used in high risk patients and in patients after one previous failed attempted treatment of the nonunion.

The nature of the techniques applied for each nonunion are outlined in Table III. Revision of the existing osteosynthesis was performed in 45 patients (90.0%), with conversion to locking compression plates (LCP, Johnson & Johnson, New Brunswick, New Jersey) in 32 patients (64%). Whenever possible, broad 4.5 mm LCP with at least three angular stable screws in the proximal and distal fragment were applied. Cancellous bone was taken from the iliac crest or via reaming/aspiration of the femoral shaft (Reamer Irrigator Aspirator (RIA) system, Johnson & Johnson, New Brunswick, New Jersey). In larger defects, synthetic bone substitutes were used to increase the volume of the graft to enabling adequate filling of the defect.

The mean Moghaddam risk score\textsuperscript{15} in the group of nine patients (18.0%) treated with BMP-7 was 16.5 points (SD 9.5). Patients treated without BMP-7 (82.0%) had a mean individual risk score of 12.6 points (SD 6.9).

**Follow-up.** Regular follow-up examinations were performed six weeks, three, six, and 12 months after discharge from hospital and included a clinical examination and plain radiographs in two planes. If necessary, follow-up examinations were continued for longer than 12 months. CT-scans were performed, when bone bridging could not clearly be detected via radiographs. A fracture was defined as successfully healed when fusion with bone bridging was observed in three-quarters of the circumference of cortical bone, and the patient reported they could load the affected limb without pain. When no progress in bone healing could be detected over a period of one year after surgery or complications occurred, revision surgery was performed.

**Statistical analysis.** Descriptive statistics for normally distributed variables are reported as mean and SD, otherwise medians and interquartile ranges (IQR) have been calculated. Data analyses were performed with Microsoft Excel 2003 (Microsoft, Redmond, Washington) and SigmaPlot 12 (Systat Software, Chicago, Illinois) using the Rank Sum Test for comparison of groups regarding patients’ age and risk score. A p-value of < 0.05 was considered statistically significant.
ing nonunion. Therefore no further surgery was performed because of the patient’s age. One patient showed successful healing following a second revision with humeral shortening. The remaining five patients with nonunion did not pursue further treatment under our care.

Discussion

By following the Diamond Concept for treatment, we have seen a bone healing rate of 80.4%. The advantage of the study was the inclusion of a large number of patients and applying a standardised treatment concept for all patients. Treatment of nonunions, especially in patients with large and complex defects and disturbed biology, remains a major challenge in orthopaedic and trauma surgery. A limitation of the study was the inhomogeneity of the patients. Each fracture presented with a specific risk profile and biomechanical situation, requiring individualised treatment within the therapeutic concept, making comparisons difficult. Further limitations were the lack of a control group, no randomisation and the absence of functional outcome scores. However, to the knowledge of the authors, this is the first documentation of a larger number of patients treated for nonunions of fractures of the humeral shaft with standardised data collection and analysis.

Although the overall risk of nonunion dramatically increases in the presence of several risk factors, it is possible to avoid the influence of adverse mechanical factors on bone healing. Commencing with a simple avoidable mechanical problem that leads to initial failure, a high number of frustrated operative treatments and complications such as infections may lead to a difficult local environment with disturbed biology. In our series we observed a rate of nonunions of 63% after intramedullary nailing vs. 24% after internal plate fixation for initial treatment. Bhandari et al. did not find a difference in their meta-analysis regarding randomised trials, but in non-randomised studies it could be shown that plate fixation had a lower relative risk for revision surgery. Other authors clearly prefer the use of plate fixation over the intramedullary nailing. However, larger randomised trials are necessary to clarify if this is truly the case.

Borus et al. reported good results in the treatment of refractory nonunion after revision with a cancellous bone graft and rigid compression plating in a case series of seven patients. McKee et al. also described better results after plating and cancellous bone grafting in nonunions after nailing of a fracture of the humeral shaft in comparison to a closed procedure with a simple change of the device to a locking nail in 21 cases. These reports seem to reflect our observations, with angular stable plating proving to be a reliable treatment in nonunions of the humeral shaft and providing a stable biomechanical environment. Successful treatment has been described using circular external fixators in 16 patients with a nonunion of the humeral shaft. Although this technique provided a good outcome, treatment with an external fixator for at least three and up to 17 months is very demanding for the patients.

Results

Successful healing could be detected in 37 patients after a median time period of six months (1 to 23). In nine patients, there was no healing of the fracture after a minimum observation period of 12 months. Four patients were lost to follow up. Median follow-up time was 12 months (11 to 29). The rate of healed fractures from those who attended follow-up was 80.4%. In the group of patients who received BMP-7 (n = 9), one patient was lost to follow-up. For the remaining eight patients, consolidation was observed in six fractures. In the other two patients, one needed revision surgery after post-operative formation of a haematoma, and one (a high risk patient) progressed to a shoulder joint arthroplasty. This represents a successful rate of healing of 75% (6/8) in the BMP-7 group.

Patients with successful bone healing were significantly younger (mean 46.6 years; SD 17.5 years) than patients with persisting nonunion (mean 62.4 years; SD 16.5) (p = 0.031) (Fig. 4). There was no significant difference between the two groups regarding the risk score (p = 0.83). The mean risk in patients with consolidated nonunions was slightly higher (15.1 points; SD 10.6) than in patients without bone union (13.9; SD 7.8).

Revision surgery was necessary in eight patients (16%). Major complications were implant breakage in three cases, plate cut-out in two cases, post-operative haematoma in two patients, and re-infection in one case. Of the patients with revision surgery three healed at subsequent follow-up after replacement of the broken or cut-out implant (Table IV). Overall, in two patients, a prosthesis was used at revision. One older patient (87 years) showed no union but a stable reconstruction with the current plate despite persisting nonunion. Therefore no further surgery was performed.

Risk Score according to patients’ age. The boxes represent the patients within the lower and upper quartile (enclosing the middle half of the sample) and the sample median, as the horizontal line. The whiskers represent the sample maximum and minimum, excluding outliers represented by the black dots (patients with the values between 1.5 and 3 x interquartile range from the 75th or 25th percentile). Patients who remained ununited healing after our treatment had a significantly higher age (p = 0.031).
In addition to biomechanical problems, another reason for developing a nonunion is the individual risk of the affected patient. In the applied risk score we classified the patients according to the type of fracture, soft-tissue damage and specific risk factors. Only 11 patients (22%) were in the high risk group at initial trauma vs 39 patients (78%) in the low and middle risk group. Furthermore, we were not able to show any significant difference in distribution of risk scores between patients who progressed to union and patients whose fracture remained ununited. This may be due to the small number of patients with nonunions but may also suggest that mechanical stabilisation is a more important factor in fractures of the humeral shaft than was initially thought.

Despite the small number of patients in the nonunion group, the patients’ age was significantly associated with outcome (p = 0.031). While young patients with good general healing potential showed high rates of consolidation, older patients showed higher rates of nonunion independent of their risk score. These findings are in line with the results of previous studies.

**Outcome after nonunion treatment.** In 37 fractures, we saw successful healing after multimodal treatment for nonunions. The rate of union was 80%, which is a very encouraging when considering the patients’ long history. We saw a moderate rate of complications with eight patients having to undergo revision surgery. This may seem high but the cohort itself mainly included cases with previous revision operations, most of them multiple in nature, and many complex cases. In these, bone regeneration was complicated not only by local factors like scar tissue and insufficient vascularisation but also by systemic factors, comorbidities and low bone quality, and decreased stability of the osteosynthesis. Patients were generally over 50 years old, representing an age when biologically some limitations of bone regeneration are present. We also observed post-operative hyperthermia and flushing at the application site approximately five days after the use of BMP-7. This local reaction is in accordance with previously described findings and seems to the result of an aseptic inflammatory reaction with the protein. The median interval from nonunion therapy to consolidation of the fracture was six months. Possibly this reflects the difficult vascular environment in nonunion. Large defects, especially in high risk patients, obviously need longer to heal than simple fractures.

**Combination of autologous bone graft and BMP-7.** In Germany, the clinical application of BMP-7 as a drug (Op-1, Osigraft,) has been approved for tibial shaft nonunions since 2001. Its use in other sites is ‘off label’ and is considered the responsibility of the attending surgeon. BMP-7 requires adequate blood perfusion and a vital bone structure to enable complete expression of the bone growth factor. Accordingly adequate surgical debridement and resection of the necrotic and devitalised tissue at the nonunion are essential. The use of cancellous bone grafts to fill larger defect gaps increases primary stability. Additionally, cancellous bone serves as a rich cellular environment for BMP-7 and is assumed to increase the local adhesion of BMP-7 in the bone defect. The osteoinductive effect of BMP-7 has been shown in several studies. Latterly we have preferred the use of RIA as a source for autologous bone rich in mesenchymal stem cells from reaming material with a higher osteogenic potency than cells obtained from the iliac crest. In some humeri we combined autologous bone with synthetic bone replacement material to augment the volume of larger defects. However a large multi-centre randomised trial would be needed to determine any superiority in outcome after use of BMP-7 in the treatment of nonunions compared with a control group.

In conclusion, in our series the use of angular stable locking compression plates in combination with an autologous cancellous bone graft has been shown to be a safe and effective treatment method for nonunion of the humeral shaft. The Masquelet technique in combination with BMP-7 provided good results in more complex cases. The analysis of the individual risk profile and missing factors for each patient is probably the most important consideration in defining the optimal treatment. The Diamond Concept seems to be a successful way to define treatment for nonunions of the humeral shaft.

**Supplementary material**

A table showing the score to estimate the individual risk of patients for delayed union of long bone fractures is available alongside the online version of this article at www.bjj.boneandjoint.org.uk

**Author contributions:**

M. Miska: Writing the paper, Performed surgeries, Patient recruitment, Data collection, Data analysis.

S. Findeisen: Writing the paper, Patient recruitment, Data collection, Data analysis.

M. Tanner: Performed surgeries, Patient recruitment, Paper correction.

B. Biglari: Patient recruitment, Data collection.

S. Studier-Fischer: Performed surgeries, Patient recruitment, Data collection, Data analysis.

A. Moghaddam: Study design, Performed surgeries, Writing the paper, Patient recruitment, Data collection, Data analysis.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

This article was primarily edited by G. Scott

**References**


