Nonunion of the femoral diaphysis

THE INFLUENCE OF REAMING AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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We assessed factors which may affect union in 32 patients with nonunion of a fracture of the diaphysis of the femur and 67 comparable patients whose fracture had united. These included gender, age, smoking habit, the use of non-steroidal anti-inflammatory drugs (NSAIDs) the type of fracture (AO classification), soft-tissue injury (open or closed), the type of nail, the mode of locking, reaming v non-reaming, infection, failure of the implant, distraction at the fracture site, and the time to full weight-bearing. Patients with severe head injuries were excluded. Both groups were comparable with regard to gender, Injury Severity Score and soft-tissue injury.

There was no relationship between the rate of union and the type of implant, mode of locking, reaming, distraction or smoking. There were fewer cases of nonunion in more comminuted fractures (type C) and in patients who were able to bear weight early. There was a marked association between nonunion and the use of NSAIDs after injury ($p = 0.000001$) and delayed healing was noted in patients who took NSAIDs and whose fractures had united.

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Locked intramedullary nailing is the treatment of choice for fixation of fractures of the femoral shaft,^{1,2} allowing early mobilisation with reliable healing and few complications.³ Rates of nonunion of between 1% and 25% have been described.⁴⁻⁹ Curylo and Lindsey¹⁰ reported an increased incidence of nonunion and attributed this to the improved survival of multiply injured patients and current methods of internal fixation.¹⁰ An increase in the rate of nonunion has been reported after the use of thin solid unreamed implants¹¹ and we have previously described a slower healing time when using an unreamed technique.¹²

Other local factors which may predispose to nonunion include the severity of the injury, extensive operative dissection of the soft tissues, inadequate stabilisation and distraction of the fracture and general factors such as weight-bearing, infection, smoking, the use of drugs and a head injury.¹³⁻¹⁶

We have therefore assessed the influence of the technique of unreamed nailing and the thin solid nail on the rate of nonunion and have also attempted to determine the role of other factors which may influence it.

Patients and Methods

We reviewed retrospectively the records of 377 patients treated by intramedullary nailing for fractures of the shaft of the femur (AO 32)¹⁷ between 1991 and 1997 to identify those with nonunion (group 1). Nonunion was defined by routine clinical and radiological criteria, and the need for a further surgical procedure. Of these 377 patients, 170 had been treated by a reamed hollow nail (AO Universal, Gross & Kempf or Russell-Taylor) and 207 by a solid femoral nail (AO, SFN). Nonunion occurred in 32 with a mean time to diagnosis of 11.5 months (7 to 18). There were 26 men and six women with a mean age of 35 years (18 to 85) and a mean Injury Severity Score (ISS) of 11.4 (9 to 32). A control group (group 2) consisted of 67 patients with a mean time to union of six months (3 to 10). There were 41 men and 20 women with a mean age of 38 years (18 to 81) and a mean ISS of 12.5 (9 to 34). There was no significant difference between the groups (Mann-Whitney U test, $p = 0.87$).

All patients were interviewed at the clinic or by telephone, and the following information recorded: age, gen-

der, type of nail, technique (reamed or unreamed), type of fracture (AO classification), soft-tissue injury (open or closed), smoking habits, fracture distraction, mode of locking, time to full weight-bearing, failure of the implant and the postoperative use of non-steroidal anti-inflammatory drugs (NSAIDs). Patients with head injuries were excluded.

Statistical analysis. We tested assumption of normality by a one-sample Kolmogorov-Smirnov test. Between-group comparisons were made using the Student *t*-test with unequal variances and the Mann-Whitney U test as appropriate. The association between union and the type of nail, reaming, smoking and the use of NSAIDs was initially investigated with contingency tables using Fisher's exact and chi-squared tests. Data were then analysed using a logistic regression model. Age, gender and time to full weight-bearing were subsequently dropped from the model as *p* values were greater than 0.05. The software used to generate the model was Stata Release 6.0 (University of Texas, USA).

Results

In group 1 the distribution of the type of fracture according to the AO classification¹⁷ was 11 type-A injuries, 20 type-B and 1 type-C and in group 2, 26 type-A, 35 type-B and six type-C. The initial intramedullary nails used in group 1 included 23 reamed hollow nails (7 Gross & Kempf, 12 AO Universal (RFN), 4 Russell-Taylor) and 9 solid (unreamed) nails (SFN) and in group 2, 28 reamed hollow nails (3 Gross & Kempf, 19 AO Universal and 6 Russell-Taylor) and 39 solid (SFN) nails. The incidence of distraction at the site of the fracture greater than 5 mm with the nails locked statically was three of 32 in group 1 and three of 67 in group 2. The rate of implant failure was similar in the two groups with two broken distal locking screws in group 1 (one SFN and one R-T) and one broken nail (AO Universal) and two broken distal screws (one SFN and one AO Universal nail) in group 2. Deep infection was present in three cases in group 1 and in none in group 2.

The type of nail used for the initial stabilisation of the fracture is shown in Table I. There was no statistically significant difference in the rate of nonunion in relation to the types (chi-squared test, *p* > 0.05). The effect of a reamed or unreamed technique on the incidence of nonunion is shown in Table II.

The mode of locking used (static or dynamic) was comparable in both groups with 27 (84%) of nails statically locked in group 1 and 52 (77%) in group 2.

The effect of smoking on the incidence of nonunion is shown in Table III; 14 (43.8%) of patients in group 1 were heavy smokers (>20 cigarettes per day) and 17 (25.3%) in group 2.

The mean time to full weight-bearing was 7.8 weeks (3 to 24) in group 1 and 4 weeks (2 to 8) in group 2.

Table I. The types of nail used in both groups (see text)

Group	SFN	RFN(AO)	R-T	GK	Total
1	9	12	4	7	32
2	39	19	6	3	67

Table II. The effect of reaming on the incidence of nonunion

Group	Reaming		Total
	Yes	No	
1	23	9	32
2	39	28	67

Table III. The effect of smoking on the incidence of nonunion

Group	Smoking		Total
	Yes	No	
1	14	18	32
2	17	50	67

Table IV. The effect of NSAIDs on the incidence of nonunion

Group	NSAIDs		Total
	Yes	No	
1	20	12	32
2	9	58	67

Table V. Predictors of primary interest for nonunion

Predictor	Odds ratio (95% CI)	<i>p</i> value
Reaming	1.83 (0.68 to 5.19)	0.275
Smoking	2.29 (0.85 to 6.08)	0.107
NSAIDs	10.74 (3.55 to 33.23)	0.000

The use of NSAIDs is shown in Table IV. The two main drugs were ibuprofen and diclofenac. There was a greater use of these drugs in group 1. A larger number of patients took NSAIDs (62.5% *v* 13.4%) and for a longer time (mean 21.2 weeks *v* 1 week). In addition, the mean time to union was longer (7.5 months; range 6 to 10) in patients in group 2 who took NSAIDs compared with those whose fractures united and did not take these drugs (5.5 months; range 3 to 8). In group 1 four of nine patients on NSAIDs had been treated by the unreamed technique (solid AO nail) and 16 of 23 (70%) by the reamed technique.

The predictors of primary interest derived from the logistic regression model are given in Table V. The model including NSAIDs, reaming and smoking was a good fit to the data (Pearson chi-squared goodness-for-fit statistic, *p* = 0.79).

In the group which took NSAIDs the odds ratio for nonunion was 10.74 (95% confidence interval 3.55 to

33.23; $p = 0.000001$). An increased odds ratio was also noted for nonunion with reaming and smoking but was not statistically significant (Table V).

Discussion

In our series the incidence of nonunion after intramedullary nailing for treatment of fractures of the femoral diaphysis was 8.5%. Boyd, Lipinski and Wiley¹⁸ reported that nonunion of fractures of long bones was more common when the fractures were open, infected, segmental with impaired blood supply, inadequately stabilised, immobilised for an insufficient time, treated by extensive approaches during open reduction and held distracted. These are important factors, but nowadays, modern techniques of trauma management, the development of newer nails and the associated unreamed technique have introduced further considerations in the healing process.

We have considered a number of aspects. Contrary to common belief, our data suggest that the more severe, multifragmentary fracture (type C) may heal more reliably than the 'simpler' type-A or type-B fractures. This may explain in part the difference in the healing time after unreamed nailing reported by ourselves¹⁹ and others.^{20,21} We note that our patients (mean ISS 12, no head injuries) appear to be drawn from a different population than both of these previous studies^{20,21} in which the patients were severely injured (mean ISS 41) with probably more severe femoral fractures and a high incidence of head injuries. Kyro et al¹⁵ reported a longer time to union after fracture of the tibia in smokers but this difference was not significant in our patients (odds ratio 2.29; 95% CI 0.85 to 6.08; $p = 0.1$). Similarly, we could not demonstrate a difference in the rate of nonunion with respect to dynamic or static locking, as also reported by Brumback et al,²² or distraction at the fracture site. Early weight-bearing is associated with increased bone formation.²³⁻²⁵ We noted that delay in full weight-bearing was linked with a higher incidence of nonunion. This is, however, difficult to analyse retrospectively since the pain associated with failure of union will lead to a delay in weight-bearing and an increased requirement for analgesia.

We have previously reported the osteogenic effect of reaming and a slightly longer time to union in patients in whom the unreamed technique had been used,^{12,19} but other authors found less good results using newer designs of nail without reaming.^{11,12,21} In this larger study we have been unable to find an association between nonunion and the unreamed technique, but our results agree with those of Hammacher, Van Meeteren and van der Werken²⁶ who noted that the incidence of nonunion after unreamed femoral nailing is comparable with that of reamed nailing. In a contrasting study¹¹ the unreamed technique was abandoned because of a high rate of failure of the implant, which may represent failure of a specific nail (thin and hollow) and not of the technique. Clearly, the technique and the type of nail

should be considered independently either in a study or when deciding on surgical treatment. Unfortunately, the association between the use of the unreamed technique and the thin solid nail makes this difficult in practice.

The most significant predictor in our study is the striking correlation between the use of NSAIDs, especially for longer than four weeks, and the incidence of nonunion. The short-term use of NSAIDs in group 2 was also associated with a prolonged time to union. Although the inhibitory effect of NSAIDs on the osteoblastic activity of bone is well documented²⁷⁻³³ and they have been used for prophylactic treatment for heterotopic ossification after hip arthroplasty³⁴⁻³⁶ and trauma,^{19,37} little is known of their effect in acutely injured patients in whom they are used for the management of pain. When this factor was considered together with the nailing technique used, we noted that 70% of patients with reamed nonunions had taken NSAIDs in contrast to 44% of those with unreamed nonunion. These findings agree with those of Butcher and Marsh³⁸ who reported a delay in the healing of tibial fractures associated with the use of NSAIDs. Khan³⁹ noted a similar association with clavicular nonunion.

Dimar et al⁴⁰ reported an inhibitory effect of NSAIDs in patients undergoing spinal fusion, while Altman et al⁴¹ found that, in animals, indomethacin and ibuprofen given continuously throughout a 12-week period induced a significant delay in the healing of fractures, as determined both by mechanical and histological criteria. The mechanism of action of NSAIDs on the healing of injured tissue remains unknown. Most anti-inflammatory drugs appear to act on mechanisms which are common to inflammation of different causes. In addition to the inhibition of the synthesis of prostaglandin they include activation of neutrophils, migration, chemotaxis and phagocytosis.^{42,43}

Our findings suggest that the technique of unreamed femoral nailing and the use of a thin solid nail are not associated with a higher incidence of nonunion of fractures of the femur and indeed give comparable results with those of reamed nailing. While there are many factors involved in bone healing, the main feature of our study is the association of non- and delayed union with the use of NSAIDs. We now exclude these from clinical use in our patients with diaphyseal fractures.

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