Parameters for defining efficacy in fracture healing

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Summary

Complications of the bone-healing process, especially in elderly, osteoporotic patients, are cause of important medical and economical burden. At the same time, there is no clinical study today to have shown the efficacy of a pharmacological treatment to enhance fracture repair. The author analyzes the potential criteria that could be used for the evaluation of treatment efficacy to enhance fracture healing in the frame of a clinical study.

KEY WORDS: clinical study, fracture healing, outcome, parameters.

Introduction

Throughout evolution, animals with long bone fractures have almost certainly died. Therefore, having no evolutionary benefit, the healing of long bone fractures has not been optimized by natural selection. Consequently, fracture healing is slow, and is often complicated (2). Fractures in elderly, osteoporotic patients are associated with increased morbidity and mortality. Mortality 5 years after hip or vertebral fracture is about 20% in excess of that expected in a population with no fracture (1). Moreover, healing of fractures is slower and return to normal function occurs later in osteoporotic patients (3). Thus, any positive effect in enhancing consolidation could be considered a breakthrough in the management of fragility fractures, and fractures in general.
The aim of fracture treatment is to restore the biomechanical properties of the fractured bone and to facilitate the return to normal function of the affected limb. Results from pre-clinical studies suggest that strontium ranelate and parathyroid hormone (PTH 1-34) both increase callus tissue and bone volume of healing fractures (4-6). These results in animals warrant further testing in clinical set-up.

Time to fracture healing

The following objectives could be appropriate for a clinical study to assess the effects of a treatment on fracture healing: 1. acceleration of *radiological* fracture union; 2. acceleration of *clinical* healing and 3. *complication rate* (7).
The choice of the patient population (e.g. osteoporotic/general population), the anatomical region (lower/upper extremity), the concerned bone (e.g. tibia/radius), the fracture type (comminuted/simple, dislocated/stable, etc.), and treatment method (conservative/surgical) should be defined in the protocol. In a clinical study with the primary endpoint of "*time to radiological/clinical healing*", it is preferable to study a fracture with a low complication rate. In the lower extremity, weight bearing can be a confounding factor, since weight bearing is dependent on patient-related subjective elements, such as willingness to walk. In the upper extremity, the distal radius has a relatively quick recovery with a low frequency of complications, and it has little soft tissue that can distort the radiograph quality (8). Therefore, non-dislocated, stable, conservatively treated distal radius fractures (Colles' fractures) have been used as a model in several clinical studies (8, 9).
Time to *radiological* and/or *clinical* healing should be (co-)primary endpoints of a clinical study in fracture healing (7, 10). There is no general consensus on the definition of "*clinical healing*", or the criteria for "*return to normal function*". However, there are various clinical healing parameters, such as patient-reported outcome questionnaires and functional tests, which can be endpoints of a clinical study.

Radiographs

Radiographs are the most common objective parameters for the evaluation of outcome after fractures (11). *"Cortical bridging of at least three out of four cortices"* as definition of *radiological healing* was suggested by several working groups (7, 10). In some cases, *bridging of all four cortices* has also been used as primary criterion (9). Either approach can be justified. Therefore, either one is used as primary criterion, the other should be a secondary criterion of the study.
In a fracture healing study there are two options to compare the healing times between the groups. One option is to calculate the *average* time to healing in each group, and compare the two averages. A disadvantage is that a number of patient-visits and radiographs are necessary so that the time of consolidation can be established for each patient. The other option is to look at the ratio of patients who have healed at a pre-defined time point, in each group. The advantage of this approach is that a single visit and a single follow-up radiograph could be sufficient. The difficulty is that the time-point of the visit must fall in the period where a difference between the groups can be detected. Otherwise, this difference can easily be "missed" by the study (Figure 1). Such studies can be planned and performed if credible data has been collected from clinical studies and consequently a well established time-point can be defined, specific for the patient population and the fracture in question.

Patient questionnaires

Parallel to objective outcome parameters, patient-reported outcome questionnaires and functional tests should be used to demonstrate return to normal function (7). Patient questionnaires to be used in clinical studies should be validated in all languages used in the

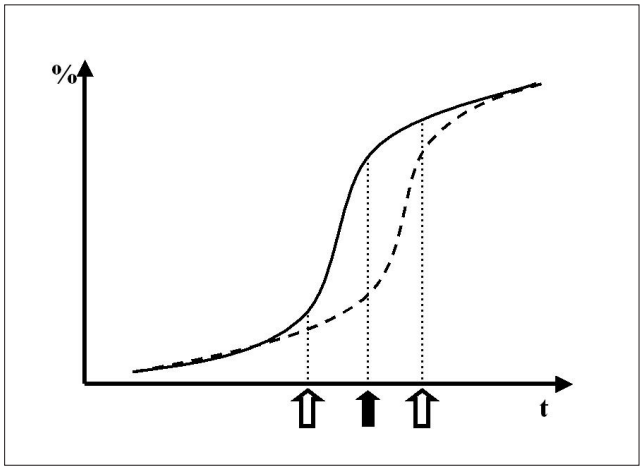

Figure 1 - Per cent of patients healed, in time. If the time of the patient-visit is either too early or too late (white arrows), it is not possible to show significant differences between the groups, even if such differences could be demonstrated at an ideal time-point (black arrow).

study. It may therefore be necessary to perform a validation process of the patient questionnaire prior to the study. Questionnaires should be used specific to the fracture site (e.g. shoulder/wrist), to the broader anatomical region (e.g. lower/upper extremity) and to general health (quality of life).

Functional test

Depending on the fracture site, different functional tests can be used. In the case of lower extremity, a clinically relevant endpoint can be "pain free full weight bearing". Since there are many subjective elements involved, stratification for the centres is necessary. In the upper extremity *hand grip strength test* or *pinch strength test* can be used. Since there are important inter-patient differences for hand grip- and pinch strength (12), the results should be expressed as a per cent value of the contra-lateral (non-fractured) side. Adjustments are also to be made for hand dominance.

Complication rate

In order for "complication rate" to represent the complication rate *related to the fracture*, the definitions should be carefully written in the study protocol. *Surgical intervention* may become necessary due to complications related to soft tissue. Such events should not distort the statistical analysis. The criterion of "*any secondary reduction of the fracture*" may be more precise for the assessment of bone related complications. The rate of "*delayed healing*" is of critical significance in patient-care and should therefore be assessed in clinical set up (7). The definition of *delayed healing* should be carefully chosen, depending on the fracture site and fracture type.

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