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Effect of different statistical methods on union or time to union in a published study about clavicular fractures

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Background: Time to union is a suspect measure for comparing treatments given the absence of a consensus definition of union, the limited reliability of diagnostic tests, and inconsistency in evaluation times. The purpose of this study was to quantify the variations in union and time to union according to different statistical methods and different approaches to missing data.

Materials and methods: Data from a published multicenter, randomized trial comparing operative and nonoperative treatment of clavicular fractures were reanalyzed. Two main types of missing data were encountered: (1) lost to follow-up or died before union and (2) missed appointment. We studied the effect of four statistical methods—comparison of means, comparison of medians, χ^2, and Kaplan-Meier curves—for comparing union or time to union between cohorts for the following scenarios: strict intention-to-treat, intention-to-treat with exclusion of patients with less than 12 months of follow-up, as-treated analysis, and four different imputation methods for missing data.

Results: Mean and median time to union varied up to 17%, but comparative statistics consistently demonstrated shorter time to union among operatively treated patients. There were significant differences in the odds ratio, χ^2 values, and the number needed to treat (8%-62%) of union vs nonunion for the three principal analyses.

Conclusion: Different strategies for handling missed evaluations seem to influence categoric results (eg, union or nonunion) more than continuous measures such as time to union.

Level of evidence: Basic Science Study, Analysis of Study Methodology.

Keywords: Clavicle; fracture; intention-to-treat; time to union; union

Time to union is often used to evaluate fracture treatment. There is no consensus definition of union, and there is no consensus reference standard for the diagnosis of union.[4] This, combined with the limited reliability of radiologic diagnosis of union for many fractures, decreases confidence that time to union is a useful measure of treatment success. Add to that that even with best efforts in prospective research, radiographic evaluations are spaced unevenly as well as inconsistently and patients often miss appointments (missing outcome).[5]

Given the complexity of measuring time to union, we were interested in quantifying the variations that would occur according to different ways of measuring and comparing time to union and different methods of handling missing evaluations. In this study, we analyzed these variations using data from a published multicenter, randomized

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trial comparing operative and nonoperative treatment of clavicular fractures.[3]

Materials and methods

The Canadian Orthopaedic Trauma Society study

A multicenter randomized clinical trial, Nonoperative Treatment Compared with Plate Fixation of Displaced Midshaft Clavicular Fractures, was conducted by the Canadian Orthopaedic Trauma Society (COTS) between 2001 and 2004 and published in January 2007.[3] The inclusion criteria were: (1) completely displaced midshaft fracture of the clavicle (no cortical contact between the main proximal and distal fragments); (2) a fracture in the middle third of the clavicle (a fracture amenable to plate fixation with a minimum of 3 screws in each proximal and distal fragment); (3) age between 16 and 60 years; (4) no medical contraindications to general anesthesia; and (5) provided informed consent.

The study enrolled 132 patients. Randomization was made by the research nurse using a sequentially numbered envelope to nonoperative care (a sling) or open reduction and plate fixation in a 1:1 ratio. Intention-to-treat principles were applied, and 111 patients with a 1-year follow-up analyzed. The protocol specified that patients would have radiographs of the clavicle at 6, 12, 24, and 52 weeks after injury. The study definition of radiographic union was ''complete cortical bridging between proximal and distal fragments on both radiographs as determined by the treating surgeon.'' Time to union was recorded as time from injury to the appointment where union was noted radiographically, regardless of whether previous appointments had been missed.

Present study

The COTS provided us with deidentified data of 132 patients documenting treatment assignment, the dates of injury and of each follow-up visit, the diagnosis of union or nonunion at each assessment, missing data, and sex and smoking status. One patient randomized to operative treatment declined surgery (crossover of treatment). One patient randomized to nonoperative treatment insisted on operative repair and was later lost to follow-up. Two nonoperatively treated patients received operative treatment for an impending open fracture (crossover of treatment). Two main types of missing data were encountered: (1) lost to follow-up or died before union and (2) missed appointment (Fig. 1).

Statistical analysis

Treatment allocated vs treatment received

We used 3 methods of addressing differences between treatment allocation and actual treatment (Fig. 1):

1. Strict intention-to-treat analysis, where patients were analyzed by treatment assigned regardless of whether they crossed over to another treatment group or were lost to follow-up;
2. Intention-to-treat analysis with exclusion of patients with less than 12 months of follow-up, corresponding to the published COTS data and was the reference for comparing mean values; and
3. As-treated analysis, in which patients with a follow-up of at least 12 months were studied according to their actual treatment (operative vs nonoperative), independent of the initial randomization.

Missing data (time to union)

Twelve patients were lost to follow-up or died before union. We analyzed 4 different methods for handling lost or dead patients before union (Fig. 1): (1) mean imputation; (2) median imputation; (3) multivariate imputation, in which the missing time to union was imputed by a regression model based on 3 covariates (treatment group, sex, and smoking status); and (4) best outcome, in which we assumed that the patient would have union at the next appointment if not lost to follow-up.

Seven patients missed the appointment before the appointment where union was noted. We analyzed two different methods for handling missed appointments: (1) use the appointment where union was noted, or (2) union was assumed to have been present at the missed visit.

Handling of nonunions

Nine fractures did not heal after the initial treatment (2 operative, 7 nonoperative). After 1 year and additional surgeries in 7 patients, only 2 nonunions remained. We used 2 different methods for handling these patients: (1) we used the time to union even after secondary procedures in 7 and excluded the 2 persistent nonunions; and (2) we excluded the 9 patients from time-to-union calculations.

Time-to-union comparisons

Time to union (operative vs nonoperative) was compared in 4 different ways:

1. mean time to union was compared using the Student *t* test;
2. median time to union was compared using Mann-Whitney *U* test;
3. the Pearson χ^2 test and the Fisher exact test (if the expected cell frequency was less than 5) were used to compare 2 categoric variables (union vs nonunion and operative vs nonoperative) at 6 weeks and at 3, 6, and 12 months; number needed to treat (NNT) was determined at the same point of time (the operative group was the experimental group and union was the event)[1]; and
4. Kaplan-Meier analysis, in which nonunions and lost to follow-up or death before union, if not imputed, were right-censored and marked as vertical ticks in the Kaplan-Meier curves.

The mean times to union of the different scenarios and analysis strategies were compared with the paired-sample and 1-sample *t* test. The test value (reference standard) was the mean time to union of the intention-to-treat analysis, as published in the COTS study.

Results

Similar results

The hypothetically calculated mean and median time to union varied up to 17% from the reference standard