ABSTRACT

BACKGROUND: The treatment of displaced midshaft clavicle fractures remains controversial. These fractures make up 80% of clavicle fractures and clavicle fractures account for 4% of all fractures.

METHODS: We undertook a multi-centre randomised controlled trial evaluating the effectiveness and safety of non-operative management versus open reduction and internal fixation for displaced midshaft clavicle fractures in adults. Randomised patients were followed-up at 6 weeks, 3 months and 9 months from recruitment. 301 eligible adult patients were recruited. The primary outcome was the rate of non-union at 3 months following treatment. Secondary outcomes are the rate of non-union at 9 months, limb function measured using the Constant-Murley Score and Disability Arm Shoulder and Hand (DASH) Score and patient satisfaction.

RESULTS: There was no evidence of a difference in 3-month union between the operative and non-operative groups. The proportion with non-union by 3 months in the surgery group was 28% compared with 27% in the non-operative group. At 9 months there is evidence that the proportion of patients achieving union in the surgery group is significantly greater than in the non-operative group ($p<0.001$) with 11% non-union in the non-operative group compared with 0.8% in the operative group. DASH, Constant-Murley scores and patient satisfaction were all significantly better in the operative group at 6 weeks and 3 months.

CONCLUSIONS: Although up to 3 months from injury there is no evidence of a benefit of surgery in terms of union, non-operative treatment of these fractures leads to an 11% non-union rate at 9 months after injury, and there is an 11% rate of secondary surgical intervention during the study period. Open reduction and internal fixation is a safe and

reliable intervention, with superior early functional outcomes and should be considered for patients who sustain this common injury.

LEVEL OF EVIDENCE: Therapeutic level 1

INTRODUCTION

Rationale for the trial

Clavicle fractures account for around 4% of all fractures[1] and up to 44% of fractures of the shoulder girdle[2,3]. Fractures of the middle third (or midshaft) account for approximately 80% of all clavicle fractures[2,3]. It is not clear whether surgery produces better outcomes than non-surgical management. Traditionally, midshaft clavicular fractures have been managed conservatively, even when substantially displaced[4]. Recent literature has highlighted the high non-union rate in displaced midshaft clavicular fractures, with non-union rate up to 15%[5,6,7]. Furthermore, there is some evidence that conservative management affects the outcome in terms of upper limb function[8,9,10] though this is not universal[11,] and that treatment of non-unions produces inferior results[12,13]. Few comparative studies of operative versus non-operative treatment for midshaft clavicle fractures are available, and contradictory results have been obtained[1,14,15,16].

Two large multicentre, prospective clinical trials have been published, involving 132 and 200 patients[17,18], where patients with a displaced midshaft fracture of the clavicle were randomised to either operative treatment or non-operative treatment. Operative fixation of a displaced fracture of the clavicular shaft resulted in improved functional outcome and a lower rate of mal-union and non-union compared with non-operative treatment at one year of follow-up. Interestingly these two studies reported conflicting recommendations regarding the indication for surgery. A subsequent smaller randomised study in a workers compensation population[19], was supportive of plate fixation in this group of patients.

Two Cochrane reviews have recently been updated[12,20] on the management of middle third clavicle fractures. They concluded that there is insufficient evidence from randomised

controlled trials to determine which methods of conservative[12] and surgical[20] treatment are the most appropriate for middle third clavicle fractures. A further Cochrane review[1] comparing conservative and operative interventions concluded there was little evidence available and that treatment should be selected on an individual patient basis.

MATERIALS AND METHODS

Study Design:

This is a multicentre randomised controlled trial comparing non-operative management versus open reduction and internal fixation of displaced midshaft clavicle fractures. The full trial protocol has been published in Trials BMC[24] thus only the core methodological features and any variation to the trial protocol and analysis during the trial period will be presented in this paper. All variations to the trial protocol were approved by the trial's Ethics Committee.

Setting:

Patients were recruited from 20 acute **hospital**s in England between 2008 and 2014.

Outcomes:

The primary outcome is the rate of non-union at 3 months following fracture. Non-union is defined as lack of radiographic bridging callus between proximal and distal fragments, and / or tenderness and mobility at the fracture site[17,25].

Secondary outcomes are the rate of non-union at nine months and limb function measured using the Constant-Murley Score[26] and Disability Arm Shoulder and Hand (DASH) Score[27] measured at 6 weeks, 3 months and 9 months post-randomisation. The 6-week clinical assessment was added early in the trial period to improve the longitudinal assessment of clinical recovery.

Ethical Considerations:

Ethical Approval was obtained from the UK National Research Ethics Service, Charing Cross Hospital Ethics Committee (for multicentre trials) Reference number 06/Q0411/82 prior to commencement of this study. Local Ethics Committee approval for each unit involved in the trial was also obtained. Lay advice was obtained from the non-medical members of the steering committee and the patient representative members of the Ethics Committee. The protocol includes the requirement for patient feedback.

Consent & recruitment Procedures:

Patients were identified from accident and emergency department referral and attendance at fracture clinic. Informed consent was obtained from all patients prior to randomisation with written patient information and a reflective period as defined by the protocol.

Inclusion criteria:

- Age 18- 65 years
- Displaced midshaft fracture of clavicle within 2 weeks of injury
- Robinson Classification 2B1 and 2B2[28]
- Medically fit to undergo surgery (ASA grade 1-3)

Exclusion criteria

- Patient refusal
- Medically unfit (ASA Grade 4/5)
- All other clavicle fractures
- Established non-union from previous fracture

- Previous fractures around the clavicle
- Previous operations to shoulder or clavicle
- Metabolic bone disease
- Significant neuro-muscular upper limb disability.

Operative Details:

All procedures were performed under antibiotic cover according to local microbiology protocols in each centre. General anaesthetic was used for all patients with or without supplementary interscalene blockade. All surgical procedures were performed by one of the orthopaedic consultants named in the protocol or by their specialist registrar / research fellow under consultant supervision. All the patients enrolled in the study were treated in a standardised way: An infraclavicular incision was used and a myo-periosteal flap elevated from the fracture segments. Fixation was performed using the Acumed clavicle fixation system (Hillsboro, Oregon), consisting of a pre-contoured titanium plate. Following wound closure the affected arm was placed in an arm sling. Pendulum and elbow exercises were allowed the first day post-operatively and subsequent mobilisation and rehabilitation protocol was the same as the non-operative group (see below).

Non-operative Treatment

The arm on the fractured side was immobilised in a sling at the side in internal rotation up to 6 weeks or until clinical and/or radiological union. Patients were allowed to remove the sling for short periods to wash, dress, write, eat and use a keyboard as soon as comfort allows. Active assisted range of motion was permitted from 2 weeks as comfort allowe**d**. Full

active mobilisation, resistance exercises and cross-arm adduction commenced after 6 weeks.

Allocation to groups

Computer generated randomisation lists were produced stratified by centre using random permuted blocks and equal allocation to the operative and non-operative groups. To conceal allocation each centre was provided with a set of sequentially number sealed envelopes which were opened with the patient after recruitment.

Assessment:

Trial assessments took place in clinic at baseline (first orthopaedic consultation), 6 weeks, 3 months and between 9 and 12 months after randomisation at routine outpatient consultations.

Baseline data were collected for all eligible patients before consent to randomisation. If patients did not consent to the trial reasons for declining were recorded where possible.

For all subjects, radiographs were performed at the 6 week and 3 month follow-up. Radiological union was assessed by the principle investigator at each site. Clinical data of union including fracture mobility, tenderness and pain was also obtained at the 3-month follow-up. The x-rays of the first 40 subjects were reviewed by an independent, blinded radiologist, once the principal investigator had judged the fracture to have united or be un-united. There was a discrepancy of opinion greater than 2% (1 patient) and therefore as per the trial protocol the radiographs were reviewed by the Chief Investigator for all trial

patients. For those radiographs where there was a discrepancy of opinion between the Chief Investigator and the treating unit, the case was reviewed and a majority consensus opinion was gained from 2 Principal Investigators and a musculoskeletal radiologist who were blinded to the previous opinions.

The Constant-Murley[26], Disability Arm, Shoulder and Hand score (DASH)[27] including the Work and Sport and Music modules, and patient satisfaction questionnaires were collected at the 6 week, 3 month and 9 month reviews. An independent research trained health practitioner not involved in patient's surgical care or rehabilitation program administered these assessment tools.

Patient satisfaction was ascertained from a single item question about satisfaction with treatment with response categories; excellent, good, satisfactory and poor.

Adverse event or complications were defined as any event that necessitates another operative procedure or additional medical treatment. Occurrences of Non-union, Symptomatic mal-union and Complex regional pain syndrome were recorded throughout follow up.

Details about the surgery were recorded for those in the intervention group including peri-operative complications and deviations from the standard technique. These included surgeon grade, antibiotic use and dose, plate length, locking screws, number of cortices fixation, duration of operation, use of X-ray control, complications and satisfaction with reduction.

For patients who withdrew or dropped out from the trial, information was collected on the date of withdrawal/dropout and where possible the reason.

Sample size:

Based on a comparison of the proportions of patients with a non-union at 3 months following treatment, it was estimated that 141 patients would be required in each treatment group in order to detect at least a reduction in proportions from 15%[6] to 5% with 80% power and a significance level of 5%. For the purposes of the power calculation we used 5% as a maximum acceptable clinical failure rate. To allow for drop out the study aimed to randomise 300 patients (150 per group).

Data Analysis:

The proportions of patients with non-union by 3 months were compared between the randomised groups using a chi squared test reported alongside an estimate of the difference in proportions and odds ratio both with 95% confidence intervals. In additional analyses we allowed for a possible centre effect using a random effects logistic regression model and also made adjustments for predefined baseline factors thought to be related to outcome (age at injury, gender, fracture classification and ASA grade).

We carried out all analyses by intention to treat but excluded those with missing information about union at 3 months. To consider the impact of this missing data on our conclusions we examined characteristics of those with missing values and used logistic regression to identify factors associated with missingness.

We applied similar approaches for analyses of the secondary outcomes. For the 9 month non-union outcome we used exact methods and carried out only unadjusted analyses

because of small numbers. For the continuous Constant and Dash scores we used quantile regression to estimate treatment effects as differences in medians with 95% confidence intervals since both outcomes had highly skewed distributions. Robustified standard errors were used to allow for centre clustering (J.M.C. Silva, Robust covariance estimation for quantile regression. UK stata users group, 2015). In addition we extended models to allow for the repeated measurements at 6 weeks, 3 months and 9 months and to investigate treatment by time interactions. For patient satisfaction outcomes we used ordered logistic regression to estimate odds ratios with 95% confidence intervals.

All statistical analyses followed a predefined analysis plan and were carried out using STATA version 14.

TRIAL REGISTRY

United Kingdom Clinical Research Network. ID: 8665

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RESULTS

Figure 1 shows the recruitment and flow of participants in the trial. Of the 533 patients eligible for the study, 302 (57%) consented to take part; the remainder had a preference for surgery or no surgery, opted to be treated privately or did not want to be randomised. One randomised patient was later found to be ineligible. Table 1 compares the known details of

those who consented and those who did not and shows that the study sample had good external validity. Overall, 154 (51%) eligible participants were randomised to the surgery group and 147 (49%) to no surgery. The randomised groups were well balanced for baseline characteristics (table 2).

In the operative group three patients withdrew and 9 patients were lost to follow up before 3 months. 11 did not have surgery, of which 6 patients subsequently decided they did not want surgical intervention, 2 patients were not fit for anaesthesia, 1 patient had no pain, 1 patient was uncontactable, and in 1 patient surgery was delayed beyond the trial protocol period for surgery. In the non-operative group there were 4 withdrawals and 11 lost to follow up. 7 patients had surgery before 3 months, all were a clinical choice due to excessive pain and / or deformity judged by the surgeon or patient.

The outcome in terms of non-union are shown in Table 3. The proportion of patients not achieving union by 3 months were similar in the two groups: 28% in the operative group and 27% in the non-operative group and analyses showed no evidence of a difference between the groups (difference in proportions 0.9% (95% confidence interval -9.8% to 11.5%) P=0.87).

At 9 months the proportion of patients with non-union in the non-operative group was 11%, compared with less than 1 % in the operative group. This difference is statistically significant (difference in proportions -9.8% (95% CI -16.3 to -4.3) P<0.001) (table 3).

DASH and Constant scores measured at 6 weeks were significantly different between randomised groups, indicating improved scores for the operative group in adjusted and unadjusted analyses (table 4) and these are graphically represented in figure 2 and figure 3. Improvements in scores for operative patients were also evident at 3 months. Patients with non-union at nine months had worse clinical scores even if they had subsequently

undergone surgery **with an average DASH of 11.3 (range 4.1-56.2) and 1.6 (0-5.8) respectively**. At 9 month follow up there was no evidence of a statistical difference overall between groups for either score. Results for patient satisfaction at the 3 time points shows strong evidence of greater patient satisfaction in the operative compared with the non-operative groups at 6 weeks and 3 months (table 5).

The DASH score sport/music and work supplementary modules were significantly better for the operative group at 6 weeks, but not at 3 or 9 months.

Subgroup analysis for smoking and fracture comminution showed no differences at 3 months and at 9 months in the operative group, but there was a non-significant trend to higher non-union rates in the non-operative group at 9 months in smokers (25% vs 7%) and patients with fracture comminution (13% vs 4%).

Complications are presented in table 6. There was one reoperation for loss of fixation in the operative group, who went on to unite. There were no surgical site infections in this study. No patients who received an operation went on to non-union.

The operative technique was followed in all cases. 1 patient received a plate from an alternative manufacturer due to non-availability at the time of surgery. 87% of procedures utilised locking and non-locking screws, 13% non-locking only, and 92% achieved 6 cortex medial and lateral fixation. The median operative time was 60 minutes and the median plate length 8 holes.

DISCUSSION

The union rate of midshaft clavicle fractures at three months is low, at around 70%, regardless of whether the treatment is operative or not. This however does not correlate well to the clinical status of the patient, which in general demonstrates a good functional recovery at this time point. However, when these fractures are assessed at 9 months from injury the rate of union is statistically different with a very low non-union rate in surgically treated patients, but a persistently high non-union rate in non-surgically treated patients at 11%. Including patients already treated for non-union by 9 months this rate rises to 15%, and in total 12 patients initially treated non-operatively had undergone or were due surgery for non-union at the end of the trial period.

At the early time points objective and patient reported scores were significantly better in the operative group, but at 9 months were equivalent. Equally patient satisfaction was greater at the early time points but approaching the same by 9 months.

Importantly, the risk of complications in both treatment groups is low, if one excludes treatment for non-union. The clinical outcome is also good in both treatment groups if union is achieved.

The strengths of this randomised controlled trial include the **balance of** representative demographics of the trial population compared with the screened patients, and the consistency between the treatment arms. Patients were recruited from a range of hospital provider types, and wide geographic distribution. A single implant and standardised technique was used for the operatively treated patients, and the rehabilitation protocol was the same for both treatment groups. Follow-up was performed by independent assessors, and for a surgical RCT high follow up rates were achieved for the primary outcome at 89.4%.

Weaknesses of the study were that the assessors were not blinded to the treatment groups, the follow-up rate was lower in the non-operatively treated group, and there was higher than anticipated cross over between groups. The completeness of the 9 month outcome scores were also lower than the union data, particularly for the Constant score.

Other randomised trials[17,18] have demonstrated similar results, but were smaller and less controlled, and came to conflicting conclusions. One area of debate is the definition of non-union, as well as the timing and modality of its assessment. Computerised tomography (CT) at 6 months was used in one study[18] but this is not usual clinical practice. Most other published randomised trials are comparisons of different surgical or non-surgical techniques.

Our conclusion is that the outcome of a united midshaft clavicle fracture is good, whether operatively or non-operatively treated. Both treatment modalities are safe with few significant complications demonstrated in this study population. The rate of non-union is significantly reduced by surgical intervention, and functional recovery and patient satisfaction is better in this group at both 6 weeks and 3 months. There is also a high rate of secondary surgical intervention in non-operatively treated patients. Overall we feel that surgical treatment for displaced midshaft clavicle fracture should be offered to patients, and this paper can provide the clear and robust data to inform patients to make their choice.

Further research is required to demonstrate the longer term outcome of those patients that were awaiting treatment for non-union. The relative safety and success of secondary surgical intervention for non-union is also not well documented, and **as recently described,** may be poorer than that of acute surgery[30]. The rate of secondary surgical intervention for metalwork removal will require a long term longitudinal study to clarify.

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FIGURE LEGENDS

Figure 1

Consort Flow Diagram

Figure 2

Medians (SE bar) over time for Constant score by randomised group

Figure 3

Medians (SE bars) over time for DASH score by randomised group