Surgery does not improve reoperation risk or patient function compared to nonoperative approaches for common fractures of the clavicle: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: The popularity of surgery for acute displaced midshaft clavicle fractures has been fueled by early randomized controlled trials (RCTs) demonstrating improved radiographic union rates and perceived functional benefits over nonoperative approaches. We performed a meta-analysis to determine the relative effects of operative and nonoperative interventions in treating acute displaced midshaft clavicle fractures on secondary operations, all other complications, and long-term function.

Methods: We search MEDLINE, Embase and the Cochrane Library for reports of relevant RCTs published to March 7th, 2014. Two reviewers assessed the eligibility of potential reports and the risk of bias of included trials. The Grading of Recommendations Assessment, Development and Evaluation approach was used to summarize the quality of evidence for all outcomes.

Results: Fifteen RCTs were included (9 trials comparing operative versus nonoperative, 5 comparing implants for operative treatment, and 1 comparing nonoperative treatments). Nonoperative treatment did not differ from operative treatment in the risk of secondary operations (risk ratio (RR) 1.16, 95% confidence interval (CI) 0.58 to 2.35, p=0.67) or other complications (RR 0.90, 95% CI 0.55 to 1.50, p=0.70). One in four patients suffered a complication regardless of treatment approach. Functional outcome differences, although

smaller than the threshold for minimal important differences at 1 year, favored operatively treated patients (standardized mean difference 0.38, 95% CI 0 to 0.75, p=0.05). Evidence for the type of implant or approach to nonoperative treatment remained inconclusive.

Interpretation: Current evidence does not support routine surgery for displaced midshaft clavicle fractures. Complication rates remain high regardless of treatment approach.

BACKGROUND

Clavicle fractures are common injuries affecting approximately 22,000 Canadians each year and 1.75 million fractures worldwide[1-6]. The vast majority of these fractures are located in the midshaft, accounting for approximately 80% of all clavicle fractures[1,2]. Traditionally closed midshaft clavicle fractures were treated nonoperatively, a practice largely based on previous studies by Neer and Rowe[7,8]. In the last decade, evidence challenged the standard of nonoperative treatment, reporting high rates of nonunion (15-20%), poor early function, and up to 42% of patients experiencing residual sequelae at 6 months following nonoperative management[9]. Small clinical trials that followed have fueled a growing popularity to treat these fractures surgically with plates and screws or intramedullary devices; however, these procedures carry inherent surgical risks for infection, implant failure and hardware irritation requiring subsequent removal[10,11].

We performed a meta-analysis to determine the relative effects of operative and nonoperative interventions in treating acute displaced midshaft clavicle fractures with respect to rates of secondary operations, all other complications, and long-term function. Our study advances prior reviews by including new evidence from randomized controlled trials (RCTs), our focus on major health outcomes such as secondary operations within 1 year, and improved summary of evidence using Grading of Recommendations Assessment, Development, and Evaluation

(GRADE) to rate the quality of evidence available for each patient-focused outcome.

METHODS

We conducted this study according to the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[12]. Our findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[13].

Literature search

We systematically searched MEDLINE, Embase, and the Cochrane Library for articles published up to and including March 7th, 2014 (Appendix 1). MeSH and EMTREE headings were used in various combinations and supplemented with free text (Appendix 1). An RCT filter developed by the Health Information Research Unit (HiRU) at McMaster University[14] was applied to the search. No language or publication date restrictions were applied. Manual review of reference lists of key articles, and use of the "related articles" feature in PubMed were conducted to identify additional studies. We searched conference proceedings (American Academy of Orthopaedic Surgeons, Canadian Orthopaedic Association, Orthopaedic Trauma Association) from the last 5 years and *Clinicaltrials.gov* to identify relevant unpublished studies.

Study selection

We included RCTs comparing any form of operative or nonoperative interventions for acute displaced midshaft clavicle fractures in patients 16 years of age or older. Thus, studies comparing operative versus nonoperative interventions, studies comparing operative implants, as well as studies comparing nonoperative interventions were considered. Two reviewers, both with methodological expertise and one with content expertise independently, in duplicate, screened titles and abstracts of identified citations from the electronic search. Disagreements were carried forward for full text review. The full texts of potentially eligible reports were independently evaluated in duplicate, and disagreements were resolved through a consensus process to determine final eligibility.

Data extraction and quality assessment

The same two reviewers independently extracted data from included studies using a piloted electronic data abstraction form. Authors of included studies were contacted if important data were unclear or not reported. When information was reported by graphical analyses only, the data were derived from the figures using a graph digitizing software (GraphClick, Arizona Software, Switzerland).

The primary outcomes for this review were secondary operations, all other complications, and long-term function (1 year or longer). Routine hardware removal was not included as a secondary operation; only those that had an indication for removal such as, infection, irritation or implant failure were counted.

Complications included symptomatic malunion, symptomatic nonunion, loss of primary reduction, hardware irritation, infection, neurologic symptoms, or other issues requiring surgical treatment. The selected complications were chosen as they are considered to be patient-focused outcomes or were commonly reported in the identified primary studies.

For the assessment of methodological quality, both reviewers independently assessed the risk of bias of included trials using the Cochrane Risk of Bias tool[12]. They evaluated the quality of evidence in included trials using the GRADE approach[15]. Data from RCTs were considered high-quality evidence, but could have been rated down according to risk of bias, inconsistency, imprecision, indirectness, or publication bias.

Data synthesis

Studies comparing operative implants, as well as studies comparing nonoperative interventions were summarized quantitatively using risk ratios (RRs) for secondary operations and all other complications. Mean differences (MDs) were calculated for functional outcome scores.

Operative versus nonoperative trials were pooled in a meta-analysis. We pooled data on secondary operations and all other complications from only trials that completely reported these outcomes, and calculated RRs using the Mantel-Haenszel method and a random effects model[12]. We performed a ‘none has

event' analysis, a variation of 'analysis-as-randomized'[16]. All patients randomized comprised the denominator but those that were lost to follow-up (LTFU) were assumed to not have had an event[16]. We performed two sensitivity analyses to investigate the effects of dropouts and exclusions: 1) complete-case analyses and 2) arm-level assumption analyses, where the relative incidence among those with missing data was assigned the same incidence as those followed-up in the same arm ($RI_{LTFU/FU} = 1$)[16].

A complete case analysis was performed for long-term function and was summarized using Standard Mean Differences (SMDs). The SMDs were weighted according to the inverse variance method and pooled with a random-effects model[12,17,18]. Minimal important differences (MIDs) were incorporated to aid the interpretation of treatment effects. The MID describes the smallest effect that an informed patient would perceive as beneficial enough to justify a change in management[19-23]. The MID for the DASH questionnaire is estimated to be 10.2 points[24,25], which was converted to units of SD using the DASH median SD for each comparison[26]. A zone of clinical equivalence based on the converted MID was projected onto the forest plot to aid interpretability of the pooled SMDs.

We quantified heterogeneity using the X^2 test for heterogeneity and the I^2 statistic[12]. We developed a priori hypotheses to explain potentially high heterogeneity in treatment effects across trials between intramedullary and plate fixation, between immediate and delayed (1-4 weeks) surgical intervention,

between two fragment and comminuted fractures, and between the presence or absence of selection and/or detection bias.

The Cohen κ (kappa) coefficient was used to evaluate agreement between the two reviewers for full text screening and a weighted κ coefficient was used to evaluate inter-observer agreement between the two reviewers for the risk of bias assessment[27,28]; all coefficients were calculated using SPSS software (version 21.0; SPSS Inc.). All tests of significance were 2-tailed, and p values of less than 0.05 were considered significant. To assess for publication bias, we visually inspected a funnel plot for the outcome of long-term function[12]. The forest plots and funnel plot were generated using Review Manager software (RevMan version 5.2; Nordic Cochrane Centre, Cochrane Collaboration, 2012).

RESULTS

Included Studies

The electronic literature search identified 422 potentially relevant citations. Fifteen of these studies proved eligible for inclusion (Figure 1). The overall agreement between reviewers for final eligibility was excellent (κ = 0.94, 95% CI 0.84 to 1).

Study Characteristics

All fifteen studies included in this review were published between 2007 and 2013 (Table 1). Nine studies compared operative with nonoperative treatment. Five

studies compared different operative implants[29-33]. One placebo-controlled trial managed all fractures nonoperatively[34]. Twelve studies were reported in English. The three studies that were not in English were translated by reviewers with methodological expertise[30,35,36]. Eight studies were considered to be at *low* risk for attrition bias, six were classified as *high* risk, and one was judged as unclear (Figure 2). Agreement between reviewers in the assessment of study methodological quality was excellent, weighted κ = 0.85. The funnel plot did not suggest publication bias (Figure 3); however, the sample of only eight studies[5,10,35,37-41] limits interpretability[12].

OPERATIVE VERSUS NONOPERATIVE MANAGEMENT

Secondary Procedures

Nonoperative treatment did not confer a greater risk of secondary operations across 8 trials involving 685 patients (RR 1.16, 95% CI 0.58 to 2.35, p = 0.67; heterogeneity p = 0.08, I^2 = 50%) (Figure 4). Subgroup analyses suggested an interaction between the type of operative implants (plate versus intramedullary fixation) and the need for secondary operation (p = 0.05). These findings were robust to sensitivity testing (complete-case and $RI_{LTFU/FU}$ = 1 analyses) for those trials with missing data. Reoperations in the operative group commonly included hardware irritation (54.8%), infection (19%) and implant failure/refracture (19%). Common indications for secondary procedures in nonoperatively managed patients were symptomatic nonunion (57.1%) and symptomatic malunion (28.6%).

All Complications

Across eight studies, there were 77 (23%) complications in 340 operatively treated patients and 88 (26%) complications in 345 nonoperatively treated patients (Table 2). Operative and nonoperative treatments did not differ in complication risk (RR 0.90, 95% CI 0.55 to 1.50, p = 0.70; heterogeneity p = 0.01, I^2 = 63%) (Figure 5). Between trial heterogeneity was not explained by subgroup analysis for type of operative implant (p = 0.15). Sensitivity testing (complete-case and $RI_{LTFU/FU}$ = 1 analyses) for those trials with missing data conferred a similar result.

Functional scores

All studies in the pooled analysis evaluated function at 1-year with the exception of one trial[40], which assessed shoulder function at 2 years. Long-term function favored operatively treated patients (SMD 0.38, 95% CI 0.00 to 0.75, p = 0.05; heterogeneity p = 0.0001, I^2 = 79%) (Figure 6); however, the pooled estimate did not exceed the threshold of ±1.33 SD for the MID. Subgroup analyses to assess the potential risk of selection bias and attrition bias for overall function at one year or more did not differ appreciably from the prior analysis.

OPERATIVE INTERVENTIONS

Comparison of surgical implants with respect to indications for reoperations, all other complications and long-term function have been summarized in Table 3.

The functional outcome at 1-year was similar between groups in all trials, demonstrating no significant difference irrespective of the implant used for internal fixation.

NONOPERATIVE TREATMENTS

The available evidence for conservative treatment of acute displaced midshaft clavicle fractures from a placebo-controlled trial of high methodological quality found no differences in clinical fracture healing between LIPUS and placebo[34]. The study reported nine (4 placebo, 5 active) out of 101 (8.9%) patients who completed the study underwent subsequent operative treatment with open reduction and internal fixation (ORIF) for fractures that did not heal according to the patients.

INTERPRETATION

Key Findings

This meta-analysis assessing the relative effects of operative versus nonoperative intervention for acute displaced midshaft clavicle fractures suggested that the incidence of secondary operations and all other complications were similar in both the operative and nonoperative groups. There was modest functional improvement at 1 year in operatively treated patients, however this finding did not reach clinical significance. Based on the GRADE criteria (Table 4), the current systematic review and meta-analysis found a lack of high-quality

evidence to inform the management of acute displaced midshaft clavicle fractures.

A previous systematic review captured secondary procedures[1] and reported a pooled estimate of effect reported as a RR of 0.38, 95% CI 0.15 to 0.99, favoring the operative group, a finding that is inconsistent with our review. Our review added a recent RCT and increased the pooled sample size by over one third, likely explaining, in part, the inconsistency. This discrepancy may be further explained by the fact that our review captured hardware irritation and infection as indications for non-routine secondary procedures, whereas Lenza et al., 2013[1] did not.

Limitations

While our population was homogenous in terms of major demographic characteristics, heterogeneity was identified across our key outcomes (I^2 of 50% - 79%). Although operative treatment with plates and screws, and intramedullary devices are technically distinct from each other, pooling them separately did not explain the high heterogeneity seen in the primary analyses. Seven out of the fifteen trials included in this review had inadequately addressed those patients who were lost to follow-up. Markedly, a greater number of patients lost to follow-up were in the nonoperative group of the trials comparing operative to nonoperative treatment, which may limit the precision of our estimates of treatment effects and thus overall generalizability.

Implications for practice

Adopting a policy of routine internal fixation for acute displaced midshaft clavicle fractures is contentious, as surgery carries the burden of greater hospital expenditures, as well as inherent surgical complications, including deep or superficial wound infection, hardware irritation, hardware failure or migration, and poor cosmesis of a surgical scar[9,41]. A recent retrospective population-based study conducted in Ontario, Canada of 1350 patients treated with ORIF for a closed isolated midshaft clavicle fracture conducted by Leroux et al., 2014 reported a reoperation rate (24.6%), which is approximately twice as high as our findings[42]. Fifty percent of patients had their hardware removed after 12 months (median 12, months; IQR, 5.8 to 16.1 months), whereas more than half of the trials included in this meta-analysis had a follow-up period of only 12 months. The inclusion of data from non-academic institutions and longer follow-up in this retrospective analysis could potentially explain the higher reoperation rate compared to the RCTs included in this study, and nonetheless could have profound clinical implications.

Implications for research

If long-term function is seemingly similar between treatment groups then further investigation should aim to determine if early functional improvements (<6 months) in operatively treated patients significantly differ from those patients treated nonoperatively. The most recent RCT included in our review evaluated

absence from work, and found that although the timing of return to work was dependent on the nature of the patients' work, no significant differences were found between the two groups in terms of total time off work following injury (p = 0.7)[5].

The trials included in our review did not provide sufficient evidence to suggest which patients would benefit most from surgical treatment. It still remains unclear whether certain fracture characteristics such as shortening, displacement or comminution can reliably predict patient-focused functional outcomes[43]. A reliability study amongst fellowship-trained shoulder and sports medicine orthopedic surgeons demonstrated moderate to strong agreement for both degree of displacement and comminution; however, standard plain unilateral radiographs of the clavicle were insufficient to reliably determine the degree of shortening of clavicle fractures and the need for surgery among this cohort[44]. Further investigations are required to develop better criteria to avoid under- or overestimating fracture severity. Thereby, focusing the utilization of surgical resources on appropriate candidates and preventing under-treatment of the injury nonoperatively.

CONCLUSIONS

Routine use of internal fixation for the treatment of these injuries may not be entirely consistent with current best evidence. Evidence for the type of implant or

approach to nonoperative treatment remains inconclusive and complication rates high regardless of the management approach.

Conflict of Interests: There was no funding for this study.

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Appendix 1. Example search strategy – MEDLINE via OVID

1. Clavicle/
2. clavic*.mp.
3. collarbone*.mp.
4. or/1-3
5. exp Fractures, Bone/
6. exp Fracture Healing/
7. exp Fracture Fixation/
8. fracture*.mp.
9. Surgical Procedures, Operative/
10. exp Orthopedic Procedures/
11. Surgery.fs.
12. Orthopedic Fixation Devices/
13. surgical.mp.
14. surger*.mp.
15. operative.mp.
16. intramedullary.mp.
17. open reduction.mp.
18. internal fixation.mp.
19. plate*.mp.
20. nonoperative.mp.
21. non-operative.mp.
22. conservative.mp.
23. sling*.mp.
24. or/5-23
25. 4 and 24
26. randomized controlled trial.pt.
27. randomized.mp.
28. placebo.mp.
29. or/26-28
30. 25 and 29
31. limit 30 to animals
32. limit 31 to humans
33. 31 not 32
34. 30 not 33

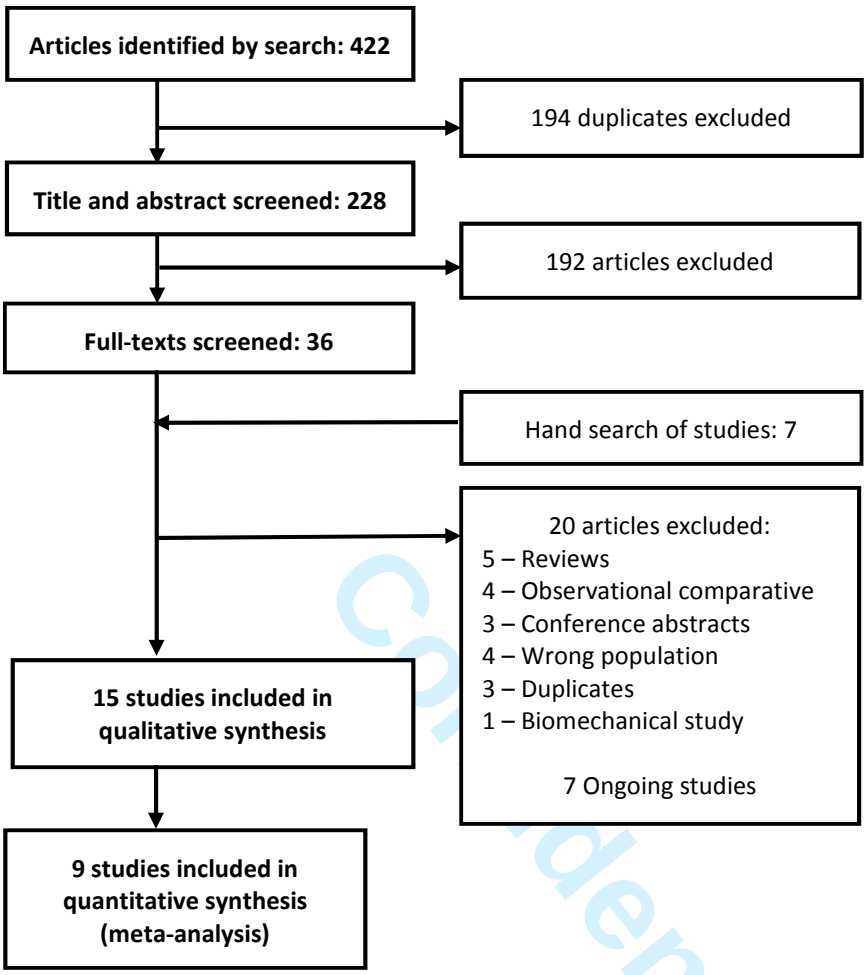

Figure 1. Study flow diagram

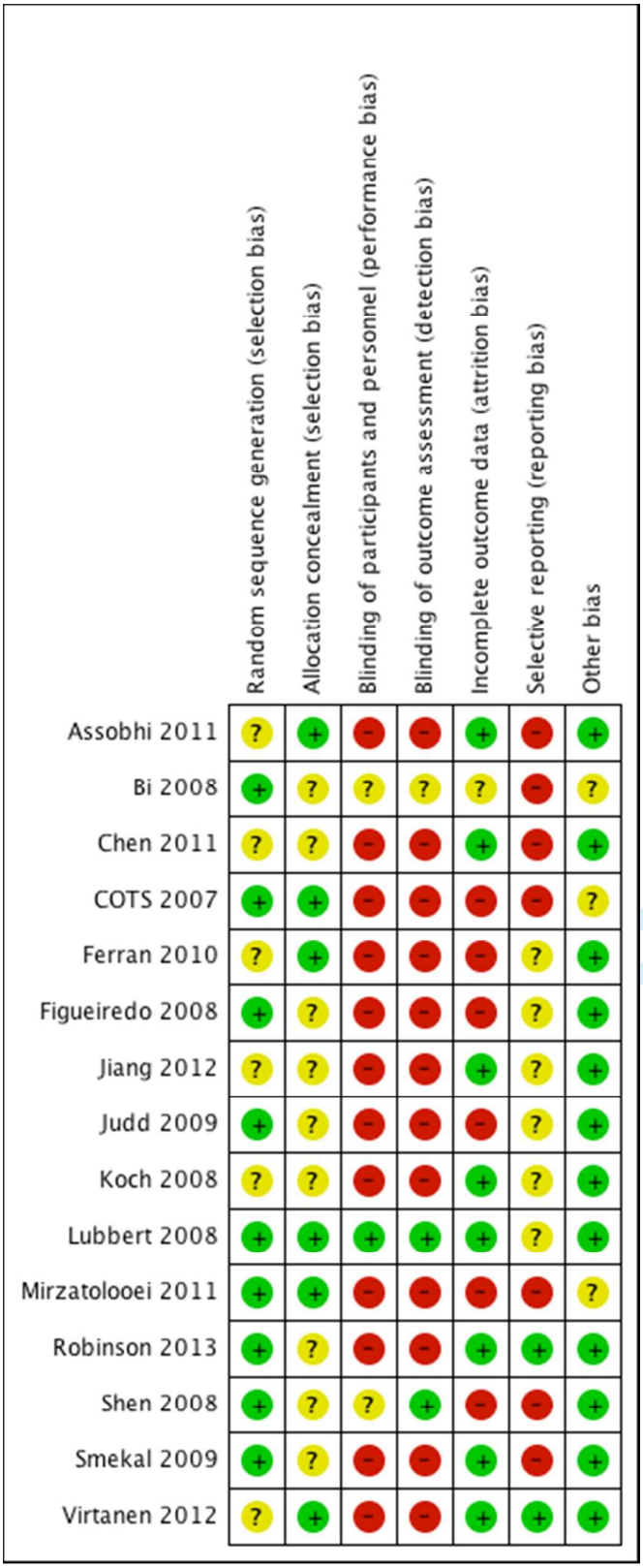

Figure 2. Risk-of-bias assessment of randomized controlled trials in the meta-analysis

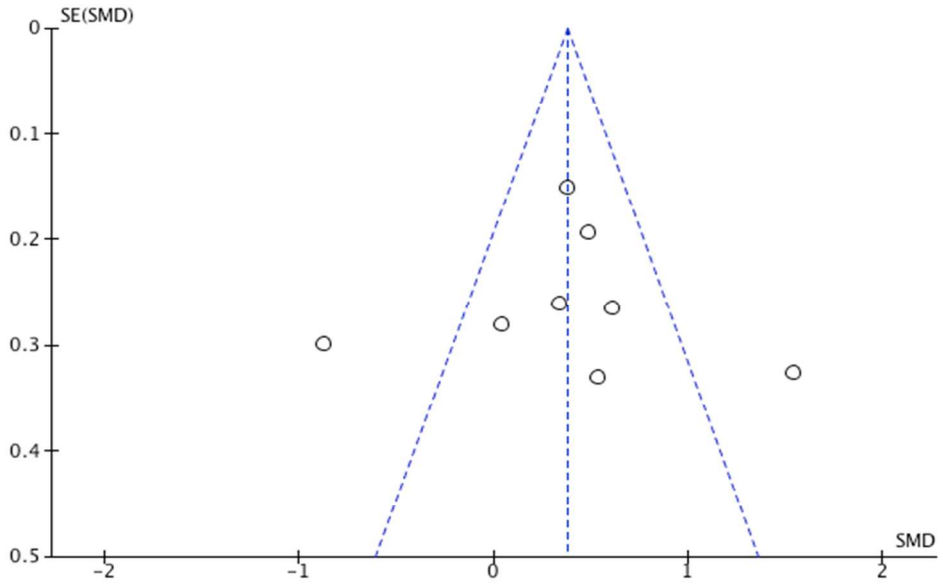

Figure 3. Funnel Plot of long-term function in trials of operative versus non-operative treatment

Note: SMD = standardized mean difference

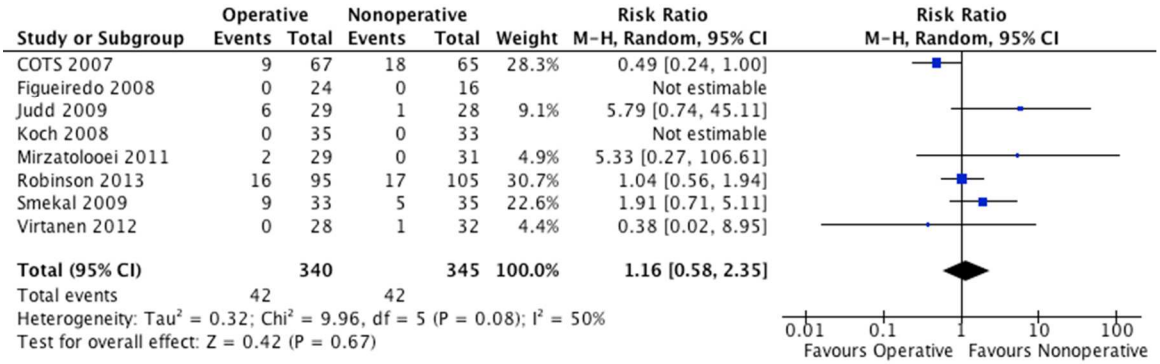

Figure 4. Pooled estimates of secondary surgery between operative and nonoperative groups

Note: Figueiredo et al., 2008; n =24 (operative), n=16 (nonoperative) are number completed for this study, and not the number initially randomized. CI = confidence interval

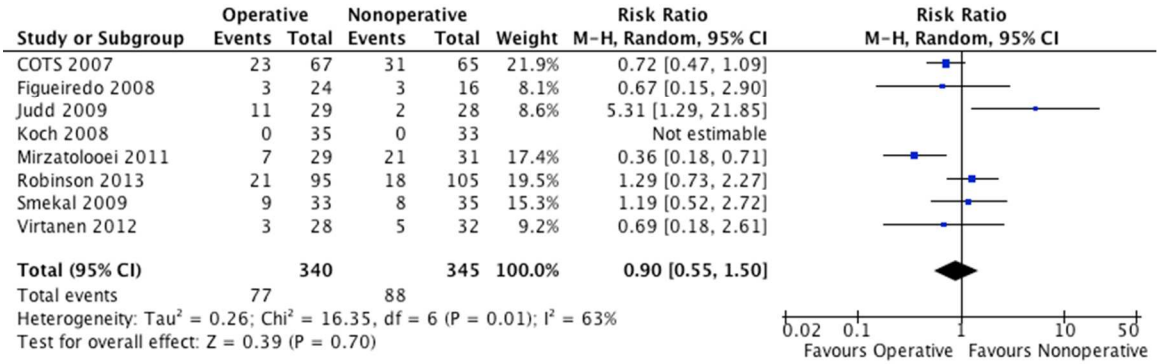

Figure 5. Pooled estimates of all other complications between operative and nonoperative groups

Note: Figueiredo et al., 2008; n =24 (operative), n=16 (nonoperative) are number completed for this study, and not the number initially randomized. CI = confidence interval

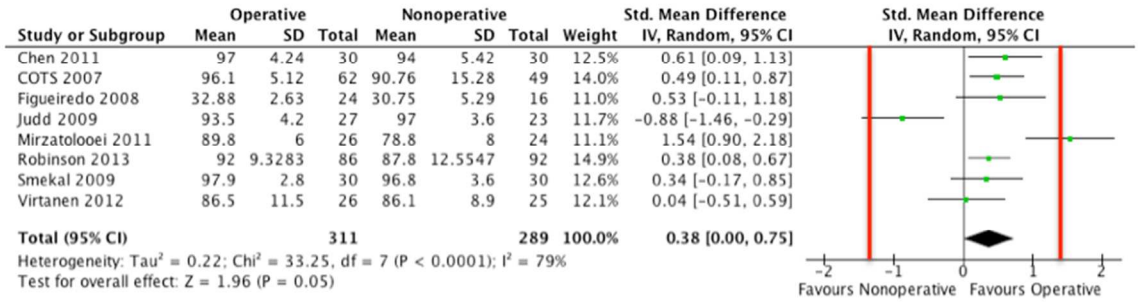

Figure 6. Pooled long-term (≥ 1 year) function following operative and non-operative treatment

Note: Red lines show a zone of clinical equivalence based on a minimal important difference of 10.2 points on the DASH questionnaire. Standardized mean differences greater than zero favor operative treatment. CI = confidence interval

Table 1. Characteristics of included studies

Study	Country	Sample size	Males (%)	Age (mean)	Length of Follow-up ‡	Intervention	Comparison
Chen et al., 2011[37]	China	60	53	38.7	15 (10-20)	TEN	Sling
COTS 2007[10]	Canada	132	78	33.5	12*	Open reduction plate fixation†	Sling
Figueiredo et al., 2008[35]	Brazil	50	78	30.2	24	DCP AI plate	Sling
Judd et al., 2009[38]	United States	57	91	26.5	12	Modified Hagie pin	Sling
Koch et al., 2008[36]	Germany	68	66	35.4	19.1 (8-26)	Intramedullary pin	Figure of 8 dressing
Mirzatolooei 2011[39]§	Iran	60	82	35.6	12	Reconstruction plate on superior surface	Sling
Robinson et al., 2013[5]	United Kingdom	200	88	32.4	12	Locking plate	Collar and Cuff
Smekal et al., 2009[40]	Austria	68	87	37.7	24	TEN	Sling
Virtanen et al., 2012[41]	Finland	60	87	36.7	12	Reconstruction plate on anterior surface	Sling
Assobhi et al., 2011[29]	Egypt	38	87	31.5	12	AI reconstruction plate	RTEN
Bi et al., 2008[30]	China	201	72	39.8	10.6 (4-21)	Retrograde percutaneous pin	Kirshner pin
Ferran et al., 2010[31]	United Kingdom	133	84	29.2	12	LCDCP	Rockwood pin
Jiang et al., 2012[32]§	China	64	63	42.5	24	LCP	MIPPO
Shen et al., 2008[33]	China	32	56	44.2	12	Superior reconstruction plate	3D contoured cortical plate
Lubbert et al., 2008[34]	Netherlands	120	84	NR	12	LIPUS	Placebo

Note: NR = Not reported, TEN = Titanum elastic nail, DCP AI = Dynamic compression plate in antero-inferior position, N/A = Not applicable, AI = antero-inferior surface, RTEN = retrograde titanium elastic nail, LCP = locking compression plate, MIPPO = minimally invasive percutaneous plate osteosynthesis, LCDCP = limited contact dynamic compression plate

§ Only enrolled patients with comminuted fractures (3 or more fragments)

† Open reduction and plate fixation (44 patients with limited contact dynamic compression plates; 15 with 3.5 mm reconstruction plates; four with pre-contoured plates, and four with other plates

‡ Longest follow-up; Chen et al., 2011, Koch et al., 2008, Bi et al., 2008 reported as mean (range)

*Data for two years in a subsequent publication (Schemitsch et al., 2011)

Table 2. All other complications

Study	Operative Group (N = 340 Patients)	Nonoperative group (N = 345 Patients)
COTS 2007[10]	9 operative procedures 2 symptomatic nonunions 8 neurologic symptoms 2 abnormality of the AC or SC joint 2 other (not described)	18 operative procedures 7 neurologic symptoms 1 complex regional pain syndrome 3 abnormality of the AC or CV joint 2 other (not described)
Figueiredo et al., 2008[35]	2 symptomatic nonunions 1 implant failure	1 symptompatic nonunion 2 adhesive capsulitis
Judd et al., 2009[38]	6 operative procedures 1 refracture 3 wound infections 1 neurologic symptoms	1 operative procedure 1 refracutre
Koch et al., 2008[36]	NR	NR
Mirzatolooei 2011[39]	2 operative procedures 4 symptomatic malunions 1 early mechanical failure	19 symptomatic malunions 2 neurologic symptoms
Robinson et al., 2013[5]	16 operative procedures 2 wound infections 1 wound dehiscence 2 rotator cuff impingement	17 operative procedures 1 rotator cuff impingement
Smekal et al., 2009[40]	9 operative procedures	5 operative procedures 3 neurologic symptoms
Virtanen et al., 2012[41]	1 refracture 1 early mechanical failure 1 hardware irritation	1 operative procedure 2 symptomatic malunions 2 refractures
Total Complications	77	88

Note: NR = Not reported, AC = Acromioclavicular, SC = Sternoclavicular

Table 3. Summary of secondary operation and complication rates, and functional outcome for trials comparing operative interventions

Study	Secondary Operations	RR (95% CI)	Complications not requiring surgical intervention	RR (95% CI)	Functional Outcome: Constant Score (1 year)	MD (95% CI)
Assobhi et al., 2011[29]						
AI reconstruction plate (n = 19)	1 nonunion 1 wound infection and implant loosening	0.67 (0.13 to 3.55)	1 nonunion	1.00 (0.23 to 4.34)	89.8 (11.3)	-5.60 (-11.21 to 0.01)
RTEN (n = 19)	3 prominent nails		NR		95.5 (5.3)	
Bi et al., 2011[30]						
Retrograde percutaneous pin (n = 101)	NR	NA	NR	0.11 (0.01 to 2.02)	NR	NA
Kirshner pin (n = 100)	NR		4 nonunions		NR	
Ferran et al., 2010[31]						
Rockwood pin (n = 17)	1 implant loosening	0.22 (0.06 to 0.88)	NR	0.22 (0.06 to 0.88)	92.1 (6)*	3.4 (-2.02 to 8.82)
LCDCP (n = 15)	3 superficial infections 1 persistent pain 4 hardware irritation		NR		88.7 (9.1)*	
Jiang et al., 2012[32]						
MIPPO (n = 32)	NR	NA	NR	NA	96†	0.30 (-4.70 to 5.30)
LCP (n = 32)	NR		NR		95.7†	
Shen et al., 2008[33]						
3D contoured cortical plate (n = 67)	1 delayed union	0.12 (0.02 to 0.96)	3 'symptomatic patients'	0.20 (0.06 to 0.65)	NR	NA
Superior reconstruction plate (n = 66)	8 delayed unions		15 'symptomatic patients'			

Note: NR = Not reported, NA = Not applicable, AI = antero-inferior surface, RTEN = retrograde titanium elastic nail, LCP = locking compression plate, MIPPO = minimally invasive percutaneous plate osteosynthesis, LCDCP = limited contact dynamic compression plate
*Unclear as to whether or not this was at 1-year assessment
†No standard deviation reported; means were abstracted from graphical analyses

Table 4. GRADE summary of findings for operative compared with nonoperative treatment for acute displaced midshaft clavicle fractures

Patient or population: patients with an acute displaced midshaft clavicle fracture
Intervention: Operative treatment (plate or intramedullary device)
Comparison: Nonoperative treatment (standard sling, figure of eight dressing, or a collar and cuff)
Outcomes: Secondary operations, all other complications, long-term function

Outcomes	No. of participants (studies)	Anticipated effects, risk with operative treatment (95% CI)	GRADE quality of evidence
Secondary operations Follow-up: 12 months	685 (8)	Evidence suggested higher incidence of secondary surgery (RR 1.16, 95% CI 0.58 to 2.35) in the operative group, but this was not statistically significant	⊕⊕⊖⊖ **low*‡**
All other complications Follow-up: 12 months	685 (8)	Evidence suggested a slightly lower number of complications (RR 0.9, 95% CI 0.55 to 1.5) in the operative group, but this was not statistically significant	⊕⊕⊖⊖ **low*‡**
Long-term function Follow-up: (≥ 1 year)	611 (8)	Mean long-term shoulder function was 0.38 SDs higher (0.22 lower to 0.54 higher)†	⊕⊖⊖⊖ **very low***§

Note: CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, RR = risk ratio, SMD = standardized mean difference, SD = standard deviation, MID = minimal important difference
*Downgraded because of risk of bias (lack of blinding study personnel, unclear reporting of allocation concealment and sequence generation)
†Effect failed to exceed minimal important difference (smallest effect that an informed patient would perceive as beneficial enough to justify a change in management)
‡Downgraded because of fragility of few events
§Downgraded for imprecision and inconsistency

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	21
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

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