Injury 52 (2021) 653–663

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Review

ORIF versus MIPO for humeral shaft fractures: a meta-analysis and systematic review of randomized clinical trials and observational studies

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ARTICLE INFO

Article history:
Accepted 5 November 2020

Keywords:
MIPO
ORIF
Humeral shaft fractures

ABSTRACT

Background: There is no consensus on the optimal operative technique for humeral shaft fractures. This meta-analysis aims to compare minimal-invasive plate osteosynthesis (MIPO) with open reduction internal fixation (ORIF) for humeral shaft fractures regarding non-union, re-intervention, radial nerve palsy, time to union, operation duration and functional outcomes.

Methods: PubMed/Medline/Embase/CENTRAL/CINAHL were searched for both randomized clinical trials (RCT) and observational studies comparing MIPO with ORIF for humeral shaft fractures. Effect estimates were pooled across studies using random effects models and presented as weighted odds ratio (OR), risk difference (RD), mean difference (MD) and standardized mean difference (SMD) with corresponding 95% confidence interval (95%CI). Subgroup analysis was performed stratified by study design (RCTs and observational studies).

Results: A total of two RCT's (98 patients) and seven observational studies (263 patients) were included. The effect estimates obtained from observational studies and RCT's were similar in direction and magnitude. MIPO carries a lower risk for non-union (RD: 5%; OR 0.3, 95% CI 0.1-0.9) and secondary radial nerve palsy (RD 5%; OR 0.3, 95%CI 0.1- 0.9). Nerve function eventually restored spontaneously in all patients in both groups. Results were inconclusive regarding re-intervention (RD 7%; OR: 0.7, 95%CI 0.2-1.9), infection (RD 4%; OR 0.4, 95%CI 0.1-1.5), time to union (MD -1 week, 95%CI -3 – 1) and operation duration (MD -13 minutes, 95%CI -38.9 – 11.9). Functional shoulder scores (SMD 0.01, 95%CI -0.3 – 0.3) and elbow scores (SMD 0.01, 95%CI -0.3 – 0.3) were similar for the different operative techniques.

Conclusion: MIPO has a lower risk for non-union than ORIF for the treatment of humeral shaft fractures. Radial nerve palsy secondary to operation is a temporary issue resolving in all patients in both treatment groups. Although both treatment options are viable, the general balance leans towards MIPO having more favorable outcomes.

Introduction

There is a growing interest in minimally invasive plate osteosynthesis (MIPO) in the treatment of humeral shaft fractures [1]. The advantages of MIPO compared to traditional open reduction with plate fixation (ORIF) include less soft tissue damage and preservation of the biological environment of the fracture zone [2]. However, close proximity of neurovascular structures to the humeral bone has raised concerns about the appropriateness of MIPO in this region [3].

To date there is no consensus which operative technique is better. The aim of the present meta-analysis was to compare ORIF to MIPO for patients with humeral shaft fractures with

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https://doi.org/10.1016/j.injury.2020.11.016
0020-1383/

regard to non-union, re-intervention, radial nerve palsy, infection, time-to-union, operation duration, general quality of life, shoulder function, elbow function and total upper extremity function by including both randomized clinical trials and observational studies. Sub-group analyses were performed to compare estimates derived from randomized clinical trials and observational studies.

Methods

This systematic review and meta-analysis was performed and reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist [4,5]. A published protocol for this review does not exist. No ethical committee approval was necessary for this literature review.

Search strategy and selection criteria

The PubMed/Medline, Embase, CENTRAL, and CINAHL database were searched on 24 January 2020, for studies comparing ORIF with MIPO for humeral shaft fractures. The search syntax is described in supplementary material Table 1. Two reviewers (BJMvdW, ND) independently screened title and abstract for eligibility. Both observational studies and randomized clinical trials were included.

The same two reviewers independently performed the full-text screening. Inclusion criteria were humeral shaft fracture, comparison of ORIF with MIPO, age 16 years or older, and reporting on outcomes of interest (non-union, re-intervention, time to union, radial nerve palsy, infection, operation duration, functional outcome). MIPO was defined as obtaining closed reduction under intra-operative fluoroscopy combined with indirect plate fixation through two separate incisions proximal and distal from the fracture line. ORIF was defined as all conventional open approaches (anterolateral or posterior) of the humerus shaft exposing the fracture line followed by direct plating. Exclusion criteria were comparison of nailing to either ORIF or MIPO, pathological fractures, treatment for delayed or non-union, studies with an average follow-up less than 6 months, languages other than English, French, German or Dutch, no availability of full-text, letters, meeting proceedings, and case reports. Disagreements on eligibility of full-text articles were resolved by consensus or by discussion with a third reviewer (FJPB). References of all included studies were screened to identify studies not found in the original literature search.

Data extraction

Two reviewers (BJMvdW, ND) independently performed data extraction using a predefined data extraction sheet. The following baseline characteristics were extracted from the included studies; first author, year of publication, study period, country in which study was performed, study design, number of included patients, type of implant, type of approach in the ORIF group (anterolateral or posterior), gender, age, open/closed fracture, AO/OTA Fracture and Dislocation classification, low- or high energy trauma, and follow-up duration [6].

Quality assessment

Two reviewers (BJMvdW, ND) independently assessed the methodological quality of included studies using the Methodological Index for Non-Randomized Studies (MINORS) [7]. The MINORS is a validated instrument for assessment of methodological quality of cohort studies, resulting in a score between 0 and 24. Disagreements were resolved by consensus. Details on methodological quality assessment are provided in supplementary material Table 2.

Study outcome

Outcome measures included non-union, re-intervention, radial nerve palsy following surgery (secondary radial nerve palsy), infection, operation duration (minutes), time to union (weeks), general quality of life, shoulder and elbow functional scores between 6 and 12 months after ORIF or MIPO. All of these endpoints were considered relevant; hence, no primary endpoint was defined, because we did not consider one of these to be more relevant than the others.

Non-union was defined as absence of fracture consolidation six months after treatment, with the absence of radiological bridging callus at 3 out of 4 cortices [8]. Re-intervention included all surgical procedures performed during follow-up. Infection encompassed both superficial and deep surgical wound infections [9].

General quality of life scores included the Short-Form 36 (SF-36), EuroQol-5D (EQ-5D) and visual analogue scale (VAS) for generic quality of life. Upper extremity functional scores included Disabilities of Arm, Shoulder and Hand (DASH) score. Shoulder functional scores included University of California at Los Angeles (UCLA) Shoulder Score, Constant score, American Shoulder and Elbow Surgeons (ASES) shoulder score, Oxford Shoulder score and Neer score. Elbow functional scores included Oxford elbow score, Mayo elbow performance score and the Broberg-Morrey score. The functional scores were standardized and pooled for each field (general quality of life, upper extremity function, shoulder function, elbow function) separately.

Statistical analysis

Information about continuous variables was presented as means with standard deviation (SD) or range, or information was converted to mean and SD using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [10]. Dichotomous variables were presented as counts and percentages. Effects of treatment options on binary outcomes were pooled using the (random effects) Mantel-Haenszel method and presented as odds ratio (OR), risk difference (RD), mean difference (MD) and standardized mean difference (SMD) each with a 95% confidence interval (95%CI). Hereafter the terms weighted OR, weighted RD, weighted MD and weighted SMD are used for brevity. In case of zero-cell counts in one of the two treatment groups, 0.5 was added to all cells of the contingency table of treatment and outcome of those studies in which this occurred. Effects of treatment options on continuous outcomes were pooled using the (random effects) inverse variance weighting method and presented as mean difference (time-to-union, operation duration) or standardized mean difference (functional scores) with 95%CI. None of the observational studies corrected for confounding. Therefore, the estimated relations between treatment and outcome presented for these studies are unadjusted for possible confounding.

Heterogeneity between studies was assessed for all OR's by visual inspection of forest plots and by the I^2 statistic for heterogeneity. All analyses were stratified according to study design, i.e., randomized clinical trials or observational studies. Differences in effect estimates between the two groups of studies were assessed using the χ^2-test as described in the Cochrane Handbook for Systematic Reviews of Interventions. A p-value below 0.05 was considered statistically significant. Publication bias was assessed by visual inspection of funnel plots, which are presented for each outcome separately in the Supplementary materials. Review Manager (RevMan, version 5.3.5) was used for all statistical analysis.

Sensitivity analysis

A sensitivity analysis was performed on the outcome re-intervention. The effect estimate of the primary meta-analysis on re-intervention for all indications (including non-union) was compared to the risk estimates of re-intervention for indications other than non-union.

Additional sensitivity analyses were performed for all other outcomes on high quality studies, studies published after 2015, studies employing LCP only for fixation, and studies including patients with open fractures. High quality studies were defined as studies with a MINORS score of 16 or higher (range 0-24). The cut-point of 2015 was chosen based on the median publication year of included studies. Sensitivity analysis was only performed when two or more studies were available for pooled analysis.

Results

Literature search

Fig. 1 presents the flowchart summarizing the literature search and study selection. In total, nine articles were included for analysis; two randomized clinical trials and seven observational studies [11–19].

Baseline study characteristics

The nine studies included 461 patients; 240 were treated with ORIF and 221 with MIPO. Table 1 shows the baseline characteristics of all studies including implant type, type of approach in the ORIF group, AO/OTA Fracture and Dislocation classification, open fractures and energy of trauma. The length of the incisions used in the MIPO group varied between 3 and 5 cm. The overall weighted mean age was 39.5 (range 16-88) years. Among the studies that reported mean stratified by surgical intervention group, the mean age was 40.2 years in the ORIF group and 40.0 years in MIPO group; for these studies, the overall weighted mean age was 40.1. Of the patients included in the studies, 344 (74.6%) were male. The mean follow-up ranged from 6 to 48 months across studies.

The two randomized clinical trials included 98 patients of whom 47 were treated with ORIF [14,15]. In the studies that reported mean age per intervention group, the overall mean age was 41.0 (range 16 – 86) years; 41.8 years in the ORIF and 40.3 years in the MIPO group, respectively. Only one trial reported on type of plate used for both ORIF and MIPO and included locking compression plates (LCP).

The seven observational studies – three prospective and four retrospective studies – included 363 patients, of whom 193 were treated with ORIF [11–13,16–19]. In the studies that reported mean age per intervention group, the mean weighted age was 39.7 years (range 16 – 88); 39.6 years in the ORIF and 39.8 years in the MIPO group, respectively. Five studies reported on type of plates used for both ORIF and MIPO and included dynamic compression plates (DCP) and LCP.

Quality assessment

The details and distribution of the MINORS scores are described in Table 2. The overall mean MINORS score was 18 (range 13 - 22); this was 22 for the two randomized clinical trials and 17 for the seven observational studies.

Non-union

Non-union rate was reported in eight studies; two randomized clinical trials and six observational studies [11–16,18,19]. Non-union occurred in 8.5% of patients treated with ORIF and 2.0%

Table 1
Characteristics of studies included in systematic review of ORIF versus MIPO for humeral shaft fractures.

Author	Year	Country	Design	Study period	Comparison	Surgical approach ORIF	Plate type	Total number of patients		Gender male/female		Mean age (SD)		Open fracture		AO (A|B|C)		HET		Follow-up (mean and/or range)
								ORIF	MIPO	ORIF	MIPO	ORIF	MIPO	ORIF	MIPO	ORIF	MIPO	ORIF	MIPO	
Randomized clinical trials																				
Kim	2015	Korea	RCT	2010-2011	plate (ORIF)| MIPO	Anterolateral	LCP	32	36	18|14	19|17	44 (16.8)	41 (17.8)	1	3	21|11|0	19|17|0	NR	NR	6 months
Hadhoud	2019	Egypt	RCT	2012-2014	plate (ORIF)|MIPO	Anterolateral,posterior	NR	15	15	11|4	9|6	36 (12.8)	40 (12.7)	NR	NR	10|4|1	9|3|3	NR	NR	>6 months
Observational studies																				
An	2010	China	retro	2004-2006	plate (ORIF)|MIPO	Anterolateral,posterior	DCP	16	17	9|7	12|5	37 (11.4)	38 (9.2)	0	0	NR		12	12	28 months (range 14-48)
Oh	2012	Korea	pros	2003-2009	plate (ORIF)|MIPO	Anterolateral,posterior	LCP	30	29	16|14	16|13	42 (16.3)	40 (16.7)	5	3	15|8|7	11|11|7	21	19	18 months
Esmailiejah	2015	Iran	pros	2008-2011	plate (ORIF)|MIPO	Anterolateral,posterior	DCP	33	32	24|9	24|8	35 (12.1)	33 (10.6)	0	0	12|10|11	10|9|13	12	11	NR
Wang	2015	China	pros	2008-2009	plate (ORIF)|MIPO	Anterolateral,posterior	LCP	23	22	16|7	14|8	36 (10.9)	39 (10.1)	0	0	5|12|6	5|8|9	NR	NR	12 months
Lee	2016	Korea	retro	2010-2012	plate (ORIF)|MIPO	NR	LCP 5.0, 3.5mm	28	24	18|10	15|9	48 (13.8)	51 (18.3)	NR	NR	NR		NR	NR	24 months (range 6-40)
Kulkarni	2017	India	retro	2014-2016	plate (ORIF)|MIPO	Anterolateral,posterior	NR	34	34	83|29	40 (13.0)	3	2	24|8|2	18|10|6	NR	NR	>6 months		
Goncalves	2018	Brazil	retro	2014-2016	plate (ORIF)|MIPO	NR	NR	29	12	40|11	35 (13.5)	NR	NR	34|7|10	35	12 months				

NR: not reported
Retro: retrospective study
Pros: prospective study
RCT: randomized clinical trial

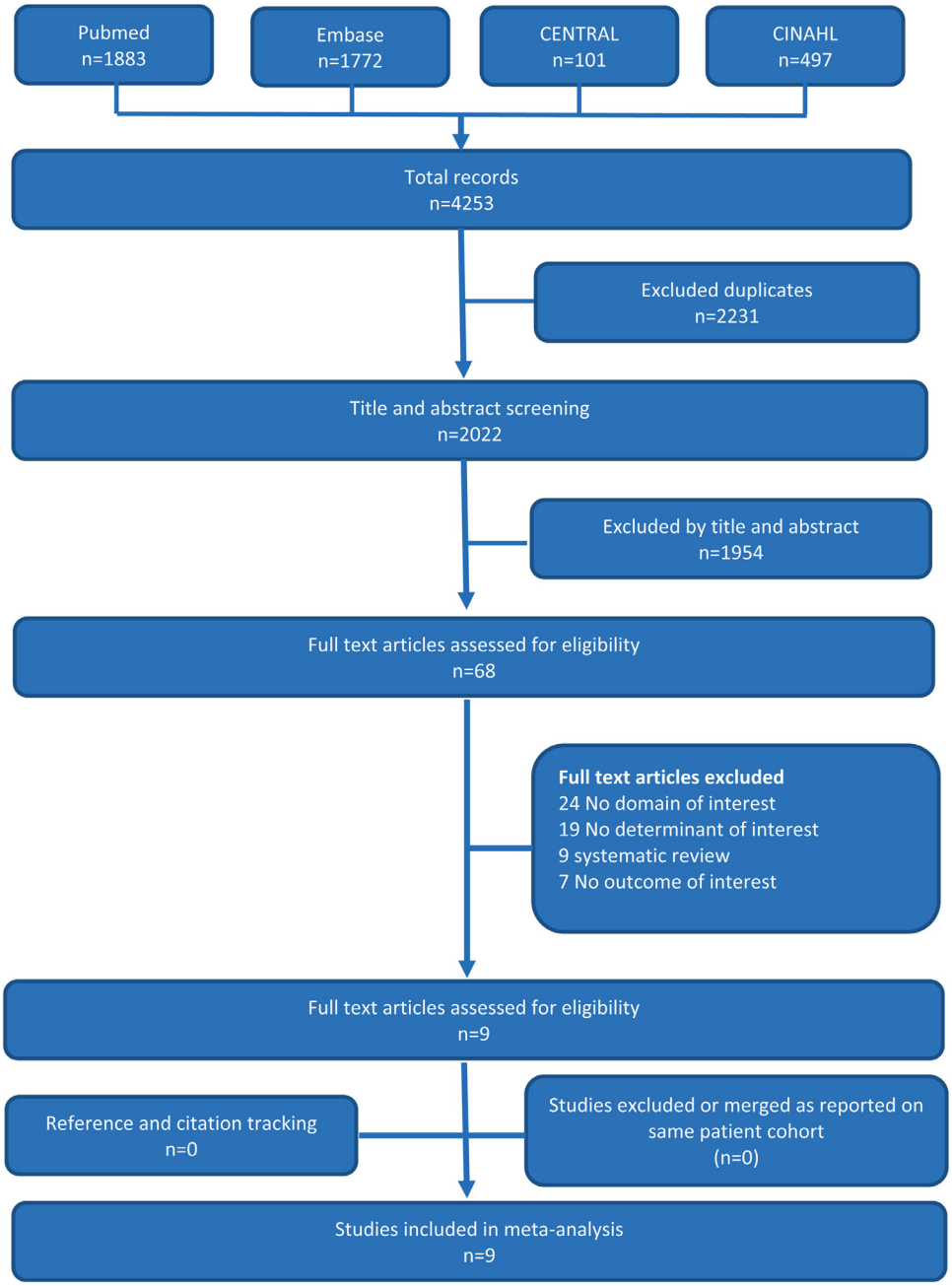

Fig. 1. Flow diagram of search and selection of studies ORIF versus MIPO for humeral shaft fractures.

treated with MIPO (weighted RD 5%, 95%CI 1%-9%). The risk of non-union was lower in patients treated with MIPO than in patients treated with ORIF (weighted OR 0.3 95%CI 0.1 – 0.9; I^2=0%) (Fig. 2). The effect estimates were similar between RCT's (weighted OR 0.3, 95%CI 0.3 – 3.0; I^2=0%) and observational studies (weighted OR 0.4, 95%CI 0.1 – 1.1; I^2=0%) (test for subgroup difference: p-value 0.91; I^2=0%).

Re-intervention

Re-intervention was reported in six studies; two randomized clinical trials and four observational studies [11,14–16,18,19]. Re-intervention was required in 9.4% of patients after ORIF and in 6.1% treated with MIPO (weighted RD 2%, 95%CI 0% - 4 %). The most frequent indication for re-intervention among patients treated with ORIF was due to non-union (n=4). Noteworthy, further management of patients with non-unions who did not underwent re-intervention, was not reported in the included studies, except one patient who refused further treatment. The most frequent indication for re-intervention for patients treated with MIPO was implant irritation (n=5). All indications for re-interventions are listed in Supplementary material Table 3.

No difference was observed in re-intervention risk between treatment groups (weighted OR 0.7, 95%CI 0.2 – 1.9; I^2=6%) (Fig. 3) and this was consistent across study designs; for RCTs weighted OR 0.3 (95%CI 0 – 8.3; I^2=not applicable) and for observational studies weighted OR 0.7 (95%CI 0.2 – 2.8; I^2=33%) (test for subgroup difference: p-value 0.64; I^2=0%).

Time to union

Five studies reported on mean time to union – 2 randomized clinical trials and 3 observational studies [11,13–15,17]. The weighted mean time to union in the ORIF group was 16.3 weeks

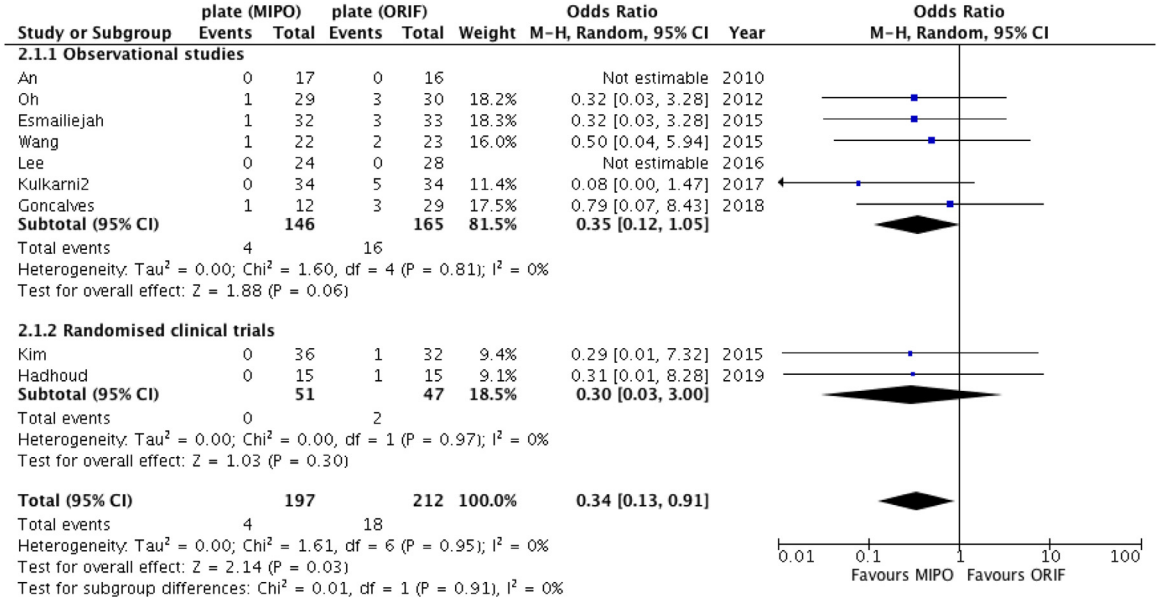

Fig. 2. Forest plot of non-union rate after ORIF versus MIPO for humeral shaft fractures.

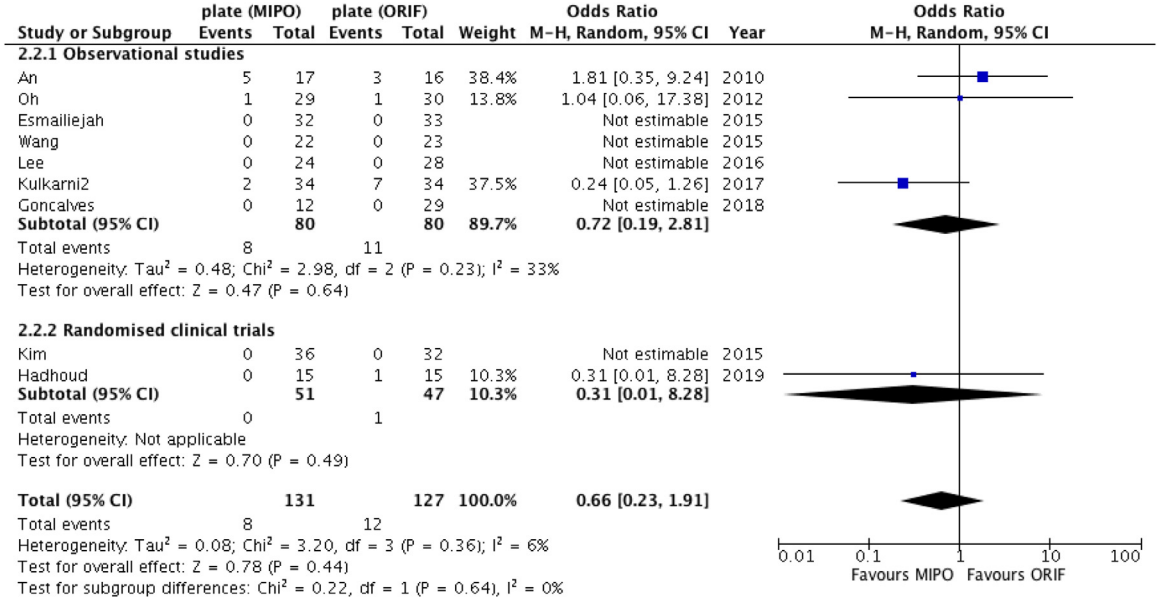

Fig. 3. Forest plot of re-intervention rate after ORIF versus MIPO for humeral shaft fractures.

versus 15.2 weeks in the MIPO group. There was no significant difference in time to union between both treatment groups (weighted MD -0.7 weeks, 95%CI -2.8 – 1.4; I^2=25%) (Fig. 4). The effect estimates of RCT's (weighted MD -0.5 weeks, 95%CI -4.8–3.8) and observational studies (weighted MD -0.5, 95%CI -4.8–3.8) were similar (test for subgroup difference: p-value 0.80; I^2=0%).

Secondary radial nerve palsy

Secondary radial nerve palsy was reported in all studies [11–19]. Secondary radial nerve palsy occurred in 8.3% of patients treated with ORIF versus 2.3% in the MIPO group (weighted RD 5.0%, 95%CI 0% – 10%). In all patients the nerve function recovered spontaneously. The risk of radial nerve palsy secondary to operation was lower among patients treated with MIPO than among patients treated with ORIF (weighted OR 0.3, 95% CI 0.1 – 0.9; I^2=0%) (Fig. 5). The effect estimates in randomized clinical trials (weighted OR 0.4, 95%CI 0.1 – 2.8; I^2=0%) and observational studies (weighted OR 0.3, 95%CI 0.1 – 0.9; I^2=0%) were similar (test for subgroup difference: p-value 0.86; I^2=0%).

Infection

Infection was reported in eight studies; two randomized clinical trials and six observational studies [11–16,18,19]. Infection occurred in 3.3% of patients after ORIF and in 1.0% treated with MIPO (weighted RD 1%, 95%CI 0% - 4%). No difference was observed in risk of infection between treatment groups (weighted OR: 0.4, 95%CI 0.1 – 1.5; I^2=0%). The effect estimates of randomized clinical trials (weighted OR 0.3, 95%CI 0.0 – 8.3; I^2= not applicable) and observational studies (OR 0.4, 95%CI 0.1 – 1.8; I^2=0%) were similar (test for subgroup difference: p-value 0.85; I^2=0%) (Fig. 6).

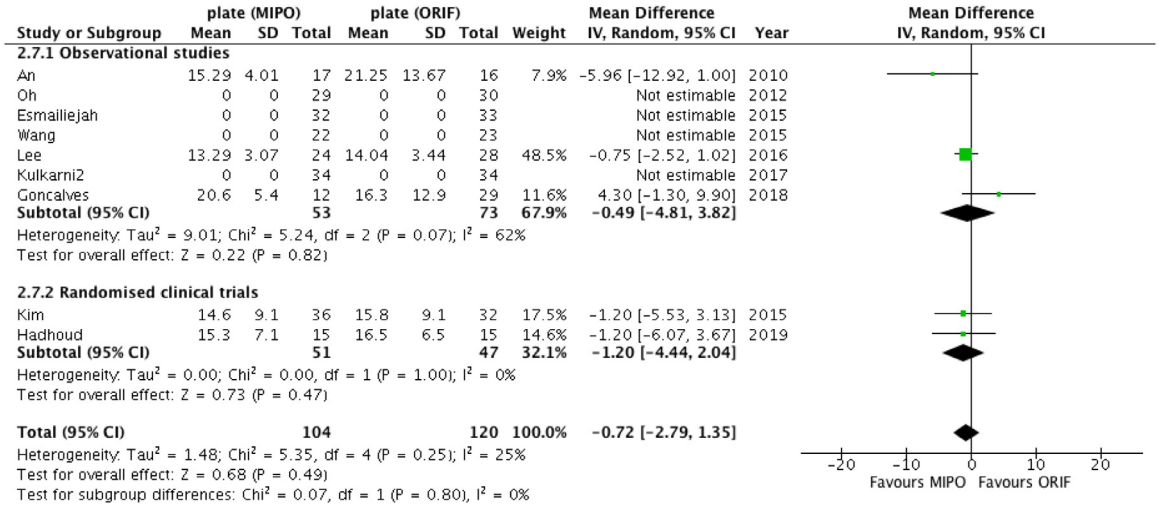

Fig. 4. Forest plot of time to union (weeks) ORIF versus MIPO for humeral shaft fractures.

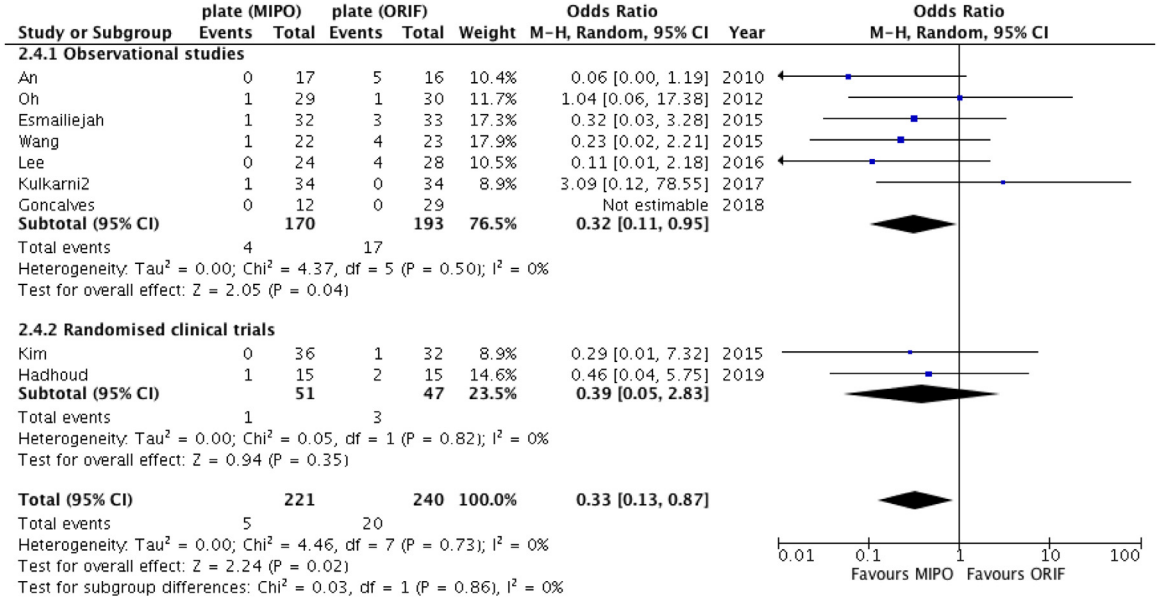

Fig. 5. Forest plot of secondary radial nerve palsy after ORIF versus MIPO for humeral shaft fractures.

Operation duration

Five studies reported on operation duration; two randomized clinical trials and three observational studies [11,12,14,15,19]. The weighted mean operation duration in the ORIF group was 113 minutes versus 104 minutes in the MIPO group. There was no significant difference in mean operation duration between both groups (weighted MD -13 minutes, 95%CI -39 – 12; I^2=95%) (Fig. 7). The effect estimates of randomized clinical trials (weighted MD -28 minutes, 95%CI -60 – 4; I^2=95%) and observational studies (weighted MD -2 minutes, 95%CI -20 – 17; I^2=70%) were similar (test for subgroup difference: p-value 0.17; I^2=47.8%).

Functional shoulder scores

Five studies reported on functional shoulder scores, measured 6 to 12 months after surgery; two randomized clinical trials and three observational studies [11,12,14,15,19]. There was no significance difference in scores between ORIF and MIPO (weighted SMD 0.0, 95%CI -0.3 – 0.3; I^2=28%) (Fig. 8). The estimates of randomized clinical trials (weighted SMD 0.0, 95%CI -0.6 – 0.7; I^2=56%) and observational studies (weighted SMD 0.1, 95%CI –0.3 – 0.5; I^2=33%) were similar (test for subgroup difference: p-value 0.87; I^2=0%).

Functional elbow scores

Four studies reported on functional elbow scores, measured 6 to 12 months after surgery; two randomized clinical trials and two observational studies [12,14,15,17]. There was no significance difference in scores between ORIF and MIPO (weighted SMD 0.0, 95%CI -0.3 – 0.3; I^2=0%) (Fig. 9). The estimates of randomized clinical trials (weighted SMD 0.1, 95%CI -0.3 – 0.5; I^2=0%) and observational studies (weighted SMD -0.1, 95%CI –0.5 – 0.3; I^2=0%) were similar (test for subgroup difference: p-value 0.43; I^2=0%).

Other outcome measures

No studies reported on general quality of life, measured 6 to 12 months after surgery. Also, no studies reported on functional scores of the total upper extremity, measured 6 to 12 months after surgery.

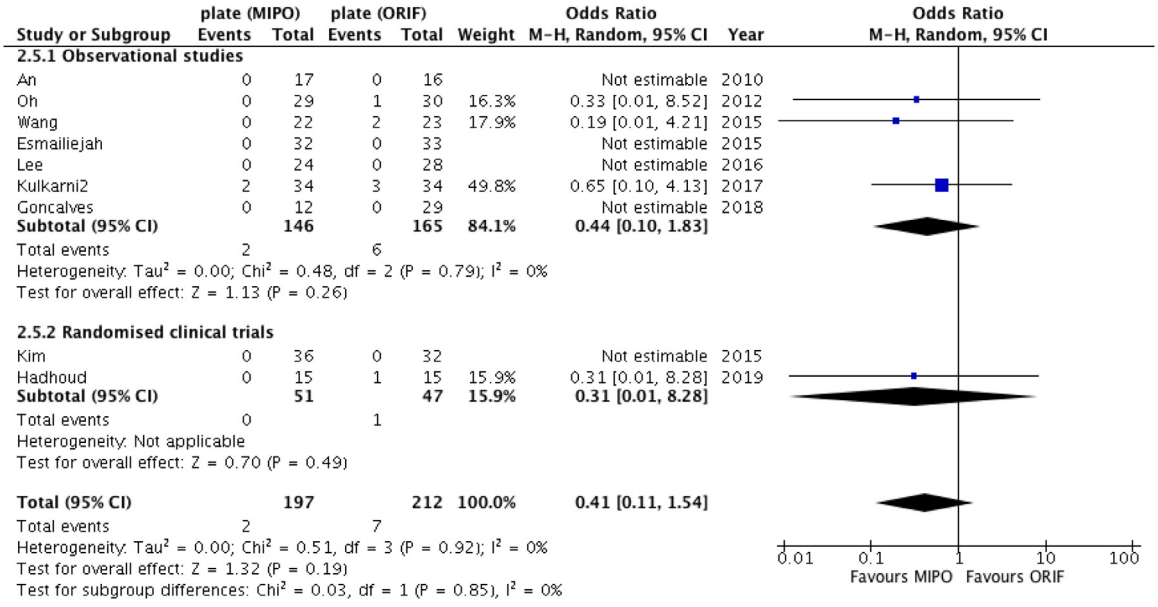

Fig. 6. Forest plot of infection after ORIF versus MIPO for humeral shaft fractures.

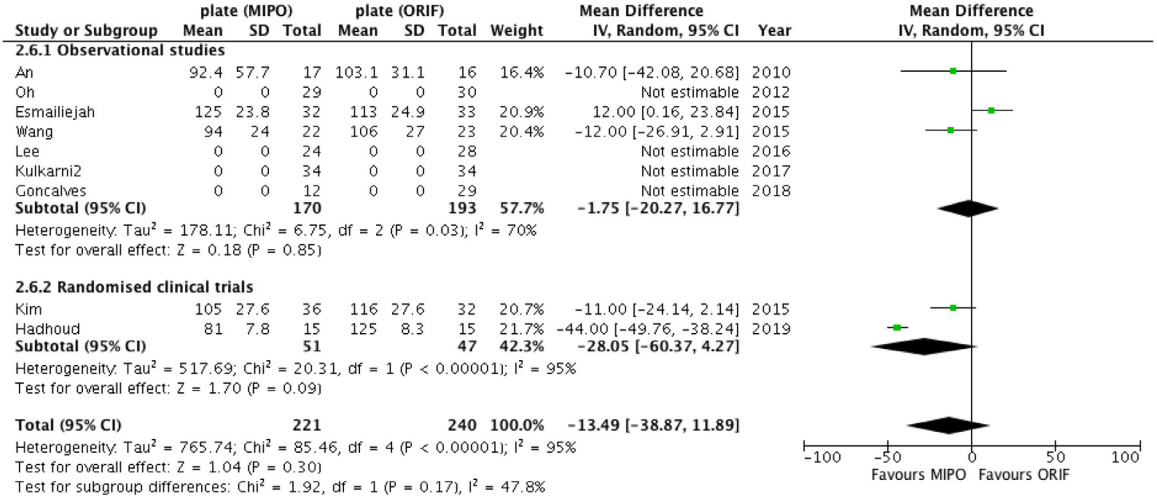

Fig. 7. Forest plot of operation duration (minutes) after ORIF versus MIPO for humeral shaft fractures.

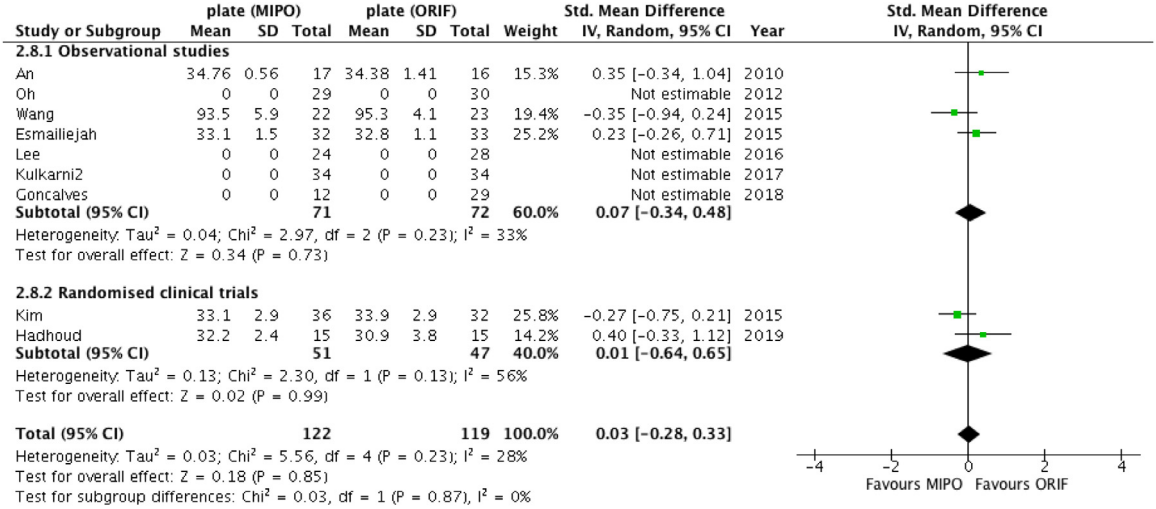

Fig. 8. Forest plot of standardised mean difference in functional shoulder scores after ORIF versus MIPO for humeral shaft fractures.

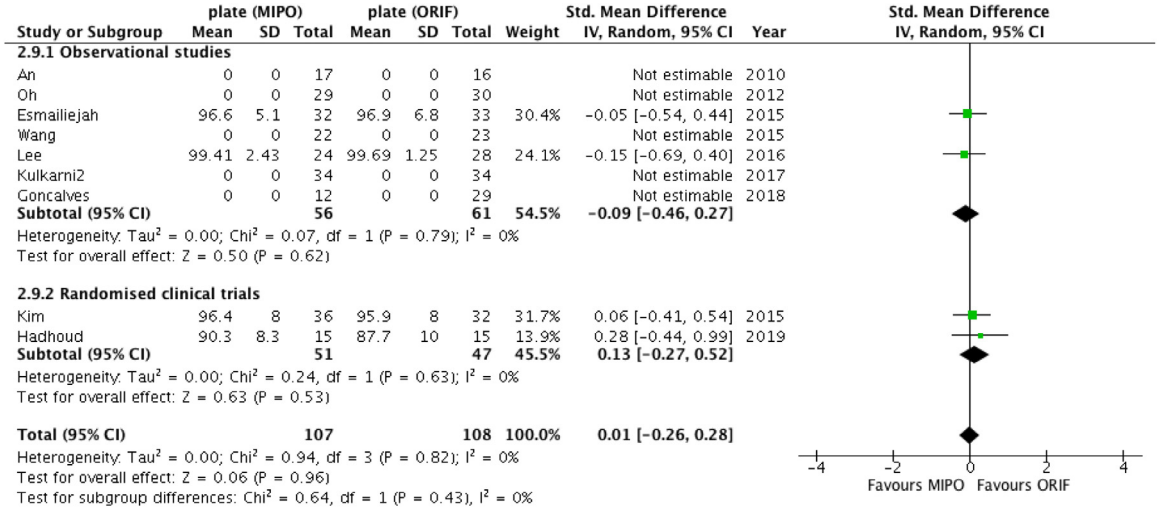

Fig. 9. Forest plot of standardised mean difference in functional elbow scores after ORIF versus MIPO for humeral shaft fractures.

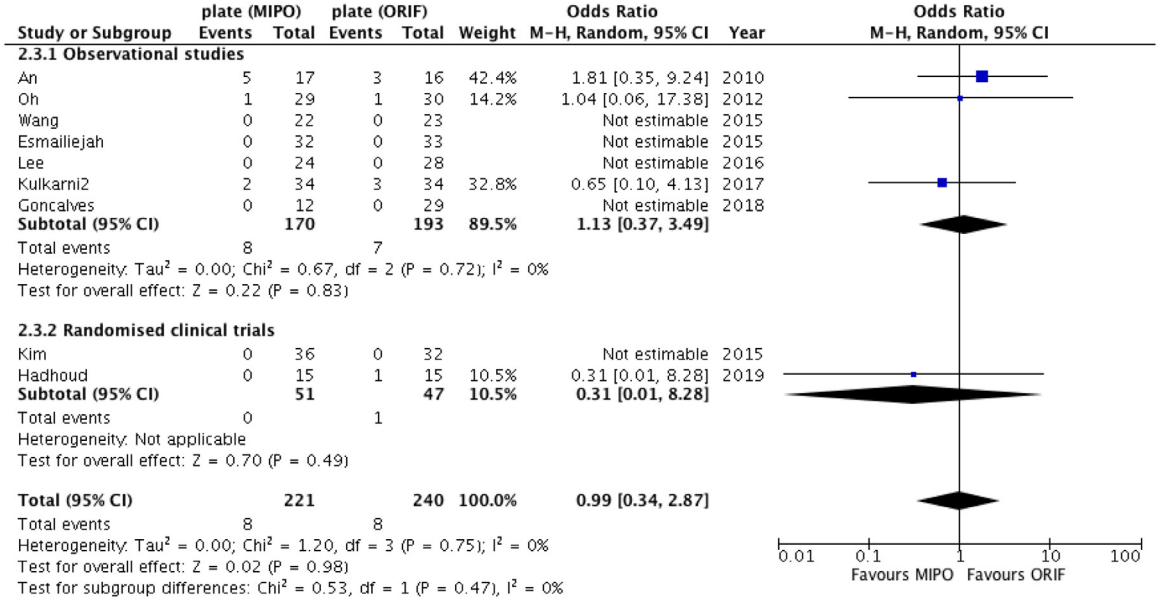

Fig. 10. Forest plot of re-intervention rate (other indications than non-union) after ORIF versus MIPO for humeral shaft fractures.

Sensitivity analysis

Re-intervention for indications other than non-union was reported in six studies; two randomized clinical trials and four observational studies [11,14–16,18]. Re-intervention for indications other than non-union occurred in 3.3% of patients after ORIF and in 6.6% treated with MIPO (weighted RD 0%, 95%CI 0% - 3%). The pooled analysis showed no significant difference between treatment groups (weighted OR 1.0, 95%CI 0.3 – 2.9; I^2=0%) and the effect estimates of randomized clinical trials and observational studies were similar (test for subgroup difference: p-value 0.85; I^2=0%) (Fig. 10).

Table 3 shows the results of the sensitivity analysis on all other outcomes with regard to high quality studies, studies published after 2013, using LCP only for fixation and studies including open fractures as well. No significant differences were found between the main analyses and these sensitivity analyses.

Discussion

This systematic review and meta-analysis of nine studies, including randomized clinical trials as well as observational studies, compared open reduction and plate fixation (ORIF) with minimally invasive plate fixation (MIPO) in patients with humeral shaft fractures. MIPO carries a lower risk for non-union and secondary radial nerve palsy. There appears to be no significant difference in risk for re-intervention and infection, time to union, operation duration and functional elbow and shoulder scores. The effect estimates from randomized clinical trials and observational studies were similar for all outcomes.

Comparison with previous findings

To date five meta-analyses have been published on the role of MIPO in the treatment of humeral shaft fractures. Two meta-analyses compared MIPO to a control group consisting of ORIF and nailing combined [2,20]. As a result, the pure difference between

Table 2
Quality assessment of studies included in systematic review of ORIF versus MIPO for humeral shaft fractures.

	Randomized clinical trials	Hadhoud 2019	Kim 2015	observational studies	Goncalves 2018	Kulkarni 2017	Lee 2016	Wang et al 2015	Esmailiejah 2015	Oh 2012	An 2010
Clearly stated aim		2	2		1	2	2	2	2	2	2
Inclusion of consecutive patients		2	2		2	2	2	2	2	2	2
Prospective data collection		2	2		0	0	0	2	2	2	0
Appropriate endpoints		2	2		1	2	2	2	2	2	2
Unbiased assessment endpoints		1	1		0	0	0	0	0	0	0
Appropriate follow-up (>1year)		1	1		2	1	2	2	0	2	2
Loss-to-follow-up <5%		2	2		1	0	2	1	0	2	0
Prospective calculation study size		1	2		0	0	0	2	0	0	0
Adequate control group		2	2		1	2	2	2	2	2	2
Contemporary groups		2	2		2	2	2	2	2	1	2
Baseline equivalence of groups		2	2		1	2	2	2	2	2	2
Adequate statistical analysis		2	2		2	2	2	2	2	2	2
Total		21	22		13	15	18	21	16	19	16

Table 3
Sensitivity analysis of all outcomes for ORIF versus MIPO for humeral shaft fractures.

	Non-union	Re-intervention	Secondary radial nerve palsy	Time to union (weeks)	Infection	Operation duration (minutes)	Functional shoulder scores	Functional elbow scores
	OR (95%CI)	OR (95%CI)	OR (95%CI)	MD (95%CI)	OR (95%CI)	MD (95%CI)	SMD (95%CI)	SMD (95%CI)
All studies	0.3 (0.1-0.9)	0.7 (0.2-1.9)	0.3 (0.1-0.9)	-0.7 (-2.8-1.4)	0.4 (0.1-1.5)	-13 (-39-12)	0.0 (-0.3-0.3)	0.0 (-0.3-0.3)
High quality studies	0.4 (0.1-1.1)	1.2 (0.3-4.5)	0.3 (0.1-0.7)	-1.1 (-2.6-0.4)	0.3 (0-1.7)	-13 (-39-12)	0.0 (-0.3-0.3)	0.0 (-0.3-0.3)
Low quality studies	0.3 (0.0-2.9)	NC	NC	NC	NC	NC	NC	NC
Studies after 2015	0.3 (0.1-1.6)	0.3 (0.1-1.1)	0.5 (0.1-2.8)	0.0 (-2.6-2.6)	0.5 (0.1-2.7)	NC	0.4 (-0.3-1.1)	0.0 (-0.4-0.4)
Studies 2015 and before	0.4 (0.1-1.5)	1.6 (0.4-6.5)	0.3 (0.1-0.9)	NC	0.3 (0.0-2.3)	-4 (-18- 9)	0 (-0.4-0.3)	0.0 (-0.3-0.4)
Studies using LCP only	0.4 (0.1-1.7)	1.0 (0.1-17.4)	0.3 (0.1-1.2)	-0.8 (-2.5-0.8)	0.3 (0-2.3)	-11 (-21- -2)	-0.3 (-0.7-0.1)	-0.0 (-0.4-0.3)
Studies using DCP only	NC	NC	0.2 (0-1.1)	NC	NC	5 (-15-26)	0.3 (-0.1-0.7)	NC
Studies with open and closed fractures	0.2 (0.0-1.0)	0.4 (0.1-1.5)	0.6 (0.1-5.0)	NC	0.6 (0.1-2.8)	NC	NC	NC
Studies with only closed fractures	0.4 (0.1-2.2)	NC	0.2 (0.1-0.8)	NC	NC	-2 (-20-17)	0.1 (-0.3-0.5)	NC

OR – odds ratio
MD – mean difference
SMD – standardised mean difference
95%CI – 95% confidence interval
NC – not calculable (less than 2 studies available)

MIPO and ORIF could not be adequately appreciated. Yu et al. published a meta-analysis of five studies conducted before 2016 demonstrating only a difference in secondary radial nerve palsy in favor of MIPO [3].

Qui et al. (2016) as well as Zhao et al. (2017) compared MIPO, ORIF, and nailing with each other using a network meta-analysis of randomized clinical trials and observational studies [21,22]. A network analysis uses an entire body of evidence with all available direct and indirect comparisons to create a ranking among the investigated treatment modalities. It has the advantage of comparing more than two treatment modalities with each other in contrast to traditional meta-analyses which typically compare two, such as in the present study. However, both did not perform subgroup analysis stratified by study design and therefore did not take into account that there might be a difference in estimates between randomized clinical trials and observational studies. Functional results were also not included. Our traditional meta-analysis complements their studies, as it addresses both issues. In accordance with their findings, the present study supports that MIPO has a lower risk of radial nerve palsy and that there is no significant difference in time to union and infection rate. This meta-analysis, however, did detect a difference in non-union in favor of MIPO. It might have been possible that the effect estimates in the studies of Qui and Zhao have been diluted by the estimates yielded from the indirect comparisons in their network-analysis. In contrast to Qui and Zhao, the present meta-analysis also investigated shoulder and elbow function for which we did not detect a significant difference.

Interpretation of results

The main difference between MIPO and ORIF is the occurrence of non-union as demonstrated by a pooled risk difference of 5%. Secondary radial nerve palsy following surgery is indeed more frequent among patients treated with ORIF, however, this is a temporary issue and resolved spontaneously in all patients of included studies.

Interestingly, a closer look reveals that MIPO showed more favorable results compared to ORIF in practically all pooled outcomes including infection, time to union, re-intervention and operation duration, although, differences were not statistically significant. It is difficult to determine whether these non-significant differences were the result of underpowering of the meta-analysis or the fact that there truly is no difference between both treatment groups. It should, however, be acknowledged that the individual studies included in the pooled analysis pointed in the same direction favoring MIPO for, particularly, the outcomes infection, time to union and operation duration. This, combined with the fact that the general ranking for MIPO in previous network meta-analyses was better than ORIF, makes it probable that MIPO leads to better results on more than just the field of non-union.

The functional shoulder and elbow outcomes were similar for MIPO and ORIF-treated patients. It is plausible that the underlying cause for this is that the two techniques only differ in type of approach and stability (absolute or relative). The shoulder or elbow joint are not involved, such as is the case with for example nail fixation [23].

Implications for future research

Minimally invasive techniques cause less damage to soft tissue and disturbance of the fracture zone [2]. It is therefore expected to reduce complications and lead to faster healing, as suggested by the findings of this meta-analysis. However, MIPO is a fairly young technique, first described in 1996 and gaining popularity since 2009 (Fig. 11) [24]. As a result, not many studies have been performed on the application of this technique in patients with a humeral shaft fracture. More studies are needed to confirm these, in our view, clinically relevant differences. In addition, it would be of interest to relate MIPO vs. ORIF-treatment with return to work and daily pain scores. None of the studies reported on these outcomes.

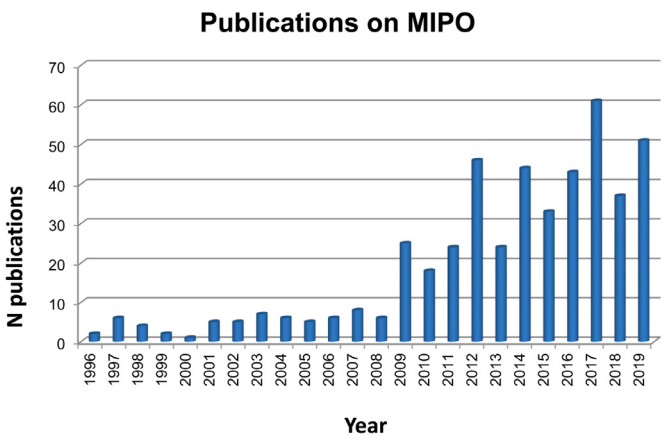

Fig. 11. Number of publications on minimally invasive plate osteosynthesis (MIPO) throughout the years.

Limitations

Several limitations have to be considered. Firstly, as previously mentioned, a relatively small number of studies was available for pooled analysis of which particularly the number randomized clinical trials was small. Furthermore, not all studies reported on every outcome of interest. Secondly, there was considerable heterogeneity in the pooled analysis for operation duration and consequently results for that outcome are less accurate. Thirdly, the observational studies included in this meta-analysis may potentially suffer from confounding. However, previous meta-analyses comparing operation techniques suggest that groups of patients treated with comparable operation techniques tend to be very similar [25–29]. This was also observed in this meta-analysis, where the treatment groups in the observational studies appeared to be very similar regarding age, sex, high energy trauma, type of open approach, open/closed fractures and AO classification. We acknowledge that unmeasured confounding cannot be ruled out.

With regard to generalizability, it is important to understand that the results of this meta-analysis are applicable to the average population with humeral shaft fractures. Every individual patient has their own specific subset of characteristics/risk factors. There are several known risk factors for non-union including high age, smoking, alcohol abuse, liver disease, and fracture location for which we could not perform subgroup analysis to investigate what their effect is on healing [30,31]. Choice of treatment should therefore always be individualised taking these risk factors, the local expertise and evidence at hand, into account.

Conclusion

This meta-analysis showed that the risk of non-union in patients with humeral shaft fractures is lower when they are treated with MIPO than when treated with ORIF. Also, secondary radial nerve palsy was found to occur less frequently after MIPO. The latter, however, was temporary and nerve function resolved spontaneously in all patients in both treatment groups. Evidence was inconclusive regarding risk of infection, re-intervention, time to union, and operation duration, be it that all these outcome results were all in the direction favoring MIPO. Functional shoulder and elbow scores did not differ, most likely, as a result of the fact that

both joints are not involved in either of the two treatment modalities. Both treatment options seem viable. However, the general balance tips in favor of MIPO.

Declaration of Competing Interest

None.

Acknowledgement

No funding received.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2020.11.016.

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