Int J Clin Exp Med 2016;9(7):13319-13328
www.ijcem.com /ISSN:1940-5901/IJCEM0024144

Review Article

Operative versus non-operative treatment for complex proximal humeral fractures in the elderly patients: a systematic review of overlapping meta-analyses

Lin Xie, Danmou Xing, Fan Ding, Zhigang Zhao

Department of Orthopedic Surgery, Wuhan Orthopedic Hospital, Wuhan Puai Hospital, Huazhong University of Science and Technology, Wuhan, China

Received January 15, 2016; Accepted May 20, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Background: Proximal humeral fractures are common injuries. Both operative and non-operative treatments have been described and routinely used. Multiple trials have been conducted to compare these treatments. Multiple meta-analyses have been published to compare operative and non-operative treatments for complex proximal humeral fractures (CPHFs) in elderly patients; however, the results remain controversial. The purposes of this study were (1) to perform a systematic review of overlapping meta-analyses comparing operative and non-operative treatments for CPHFs in the elderly patients, (2) to help decision makers critically evaluate the current meta-analyses, and (3) to propose a guide through the best available evidence. Methods: We searched the Cochrane library, PubMed, and EMBASE data bases. Two authors independently scanned titles and abstracts to exclude irrelevant articles and identify meta-analyses that met the eligibility criteria. The methodological quality of the meta-analysis was independently assessed by the two authors using the Oxford Centre for Evidence-based Medicine Levels of Evidence and the Assessment of Multiple Systematic Reviews (AMSTAR) tool. Heterogeneity information of each variable was extracted from the included studies. An I^2 of <60% is accepted in this systematic review. The Jadad algorithm was then applied to determine which of the meta-analyses provided the best evidence. Results: Nine meta-analyses met the inclusion criteria in this study. All studies included RCTs or quasi-RCT and were Level II of evidence. AMSTAR scores varied from 7 to 10. Heterogeneity of each outcome was acceptable. Four authors independently selected the same meta-analysis as providing the highest quality of evidence using the Jadad decision algorithm. Conclusion: This systematic review of overlapping meta-analyses comparing operative and non-operative treatments suggests that compared with non-operative treatment, operative treatment does not result in a better outcome and is likely to result in a greater need for subsequent surgery according to current best available evidence. Hence, treatment should be individualized and operative treatment should be with careful consideration.

Keywords: Operative, non-operative treatment, CPHFs (complex proximal humeral fractures), overlapping meta-analyses

Introduction

Proximal humeral fractures are common injuries, with an overall incidence of 63.0/100,000 per year [1], occurring in patients older than 60 years especially females [2-4]. Nearly 85% proximal humeral fractures are non- or minimally displaced and can be treated conservatively [5]. Many patients could regain shoulder function with non-operative treatment [6]. The remaining 15% displaced fractures which are challenge to surgeons can be treated with operative or non-operative treatment [7]. With recent advancement in technique and implants for fracture surgery, operative treatment has become increasingly popular for these injuries, including internal fixation and humeral head replacement, which increased treatment costs for this fracture [8]. However, the optimal method of this fracture remains a topic of debate.

In particular, a significant body of literature has been devoted to the comparison of operative and non-operative treatment for CPHFs. RCTs comparing operative and non-operative are conflicted as to which treatment is better than the other one [9-18]. In addition, multiple authors [19-29] have conducted meta-analyses

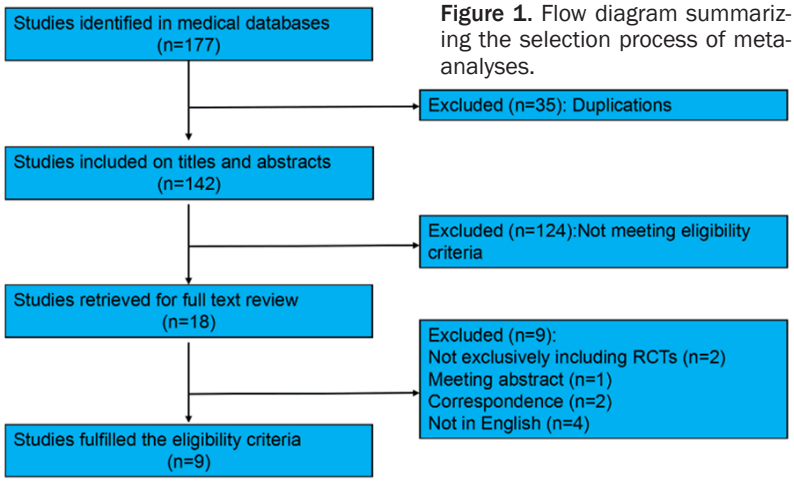

Figure 1. Flow diagram summarizing the selection process of meta-analyses.

comparing operative and non-operative treatments. However, the results of the meta-analyses have been discordant in their findings. For example, a meta-analysis by Fu, T [21] and Song, JQ [27] showed operative treatment leads to a higher risk of complications. However, Jia, Z [22] and Mao, Z [23] concluded that both operative and conservative treatments can achieve a similar incidence of complications. Debate continues in the literature and both treatment continue to be used frequently in practice.

The purposes of this study were: (1) to perform a systematic review of overlapping meta-analyses comparing operative and non-operative treatment for CPHFs in the elderly patients, (2) to help decision makers critically evaluate the current meta-analyses, and (3) to propose a guide through the best available evidence.

Materials and methods

This systematic review was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses [30]. Ethical approval and informed patient consent were not required, as this study was a literature review and had no direct patient contact or influence on patient care.

Study search

We searched the Cochrane library, PubMed, and EMBASE. The following search terms were used: humeral or humerus; proximal; fracture; and meta-analyses or systematic review. The search was limited to articles written in English. All reviewed articles were then manually cross-referenced to ensure that all potential studies were included. The search was performed on November, 2015.

Eligibility criteria

The study inclusion criteria were: (1) meta-analyses exclusively including RCTs; (2) meta-analyses comparing operative with non-operative treatment for proximal humeral fractures; (3) meta-analyses reported at least 1 variable. The exclusion criteria were: (1) meta-analyses including non-RCTs; (2) non-English language articles; and (3) meetings abstract. Full manuscripts were obtained for those studies that met both the inclusion and exclusion criteria. The references for each of these citations were then manually screened to ensure that no studies were missed.

Selection of meta-analyses

Two authors (DM.X, F.D) independently checked titles and abstracts from the searches to identify potentially eligible studies. The authors were not blinded to the names of original researchers, journals, or institutions. They independently retrieved and reviewed full-text articles for the purpose of applying eligibility criteria. When there were disagreements between authors, a consensus was reached through discussion or a third author (ZG.Z) was consulted.

Data extraction

Two authors (L.X, F.D) independently extracted the data of each study. The following informations of the meta-analyses were extracted: journal, date of literature search, search database, date of publication, number of included trials, software use, and I^2 statistic value. When there were disagreements between authors, a third author (ZG.Z) was consulted.

Quality assessment

Methodological quality for each included meta-analyses was assessed using the Oxford Levels of Evidence [31] and AMSTAR [32]. AMSTAR uses 11 items to assess which review methods

Table 1. General Description of the Characteristics of Each Meta-analyses

Authors	Journal	Date of last literature search	Date of publication	No of included RCTs
Li, Y et al 2013	PLoS One	October, 2012	September, 2013	3
Fu, T et al 2014	Int J Clin Exp Med	June, 2013	December, 2014	6
Jia, Z et al 2014	Orthopedics	November, 2012	June, 2014	6
Mao, Z et al 2014	Orthopedics	March, 2013	May, 2014	6
Mao, F et al 2015	J Invest Surg	October, 2013	January, 2015	5
Song, J.Q et al 2015	Acta Orthop Traumatol Turc	December, 2012	January, 2015	6
Xie, L et al 2015	Springerplus	July, 2015	November, 2015	7
Rabi, S et al 2015	World J Orthop	February, 2014	November, 2015	6
Handoll, H.H et al 2015	Cochrane Database Syst Rev	November, 2014	November, 2015	8

Table 2. Primary Studies Included in Meta-analyses

Authors	Stableforth 1984	Kristiansen 1988	Zyto K, 1997	Fjalestad T, 2011	Olerud P, 2011 a	Olerud P, 2011 b	Boons 2012	Rangan 2015
Li, Y et al 2013			+	+	+			
Fu, T et al 2014	+		+	+	+	+	+	
Jia, Z et al 2014	+		+	+	+	+	+	
Mao, Z et al 2014	+		+	+	+	+	+	
Mao, F et al 2015			+	+	+	+	+	
Song, J.Q et al 2015	+		+	+	+	+	+	
Xie, L et al 2015	+		+	+	+	+	+	+
Rabi, S et al 2015	+		+	+	+	+	+	
Handoll, H.H et al 2015	+	+	+	+	+	+	+	+

are unbiased and are extensively applied. Both authors independently assessed methodological quality. Then the scores for every meta-analyses were calculated.

Assessment of heterogeneity

Heterogeneity information of each variable was extracted for the included studies. We explored whether the studies evaluated possible sources of heterogeneity across studies and whether the investigators performed a sensitivity analysis. According to the Cochrane Handbook, heterogeneity is considered not important between 0% and 40%; moderate between 30% and 60%; substantial between 50% and 90%, and considerable between 75% and 100%. Therefore, an I^2 of less than 60% is accepted in this systematic review.

Application of jadad decision algorithm

Four authors (L.X, DM.X, ZG.Z, F.D) independently applied the Jadad algorithm [33] and arrived at a consensus as to which of the systematic reviews provided the best currently available evidence. This methodology determines the source of discordance between systematic reviews from the following six reasons: (1) clinical question, (2) inclusion and exclusion criteria, (3) data extraction, (4) quality assessment, (5) data pooling, and (6) statistical analysis [33].

Results

Search results

A flow diagram that depicts the search process can be found in **Figure 1**. One hundred and seventy-seven titles were found initially. Nine studies [19-27] met the inclusion criteria. Two studies were excluded because they did not exclusively include RCTs [28, 29]. A general description of the characteristics of each meta-analyses is provided in **Table 1**. These studies were published between 2013 and 2015, and all nine performed a meta-analysis. The number of primary studies varied widely from 3 in those studies published in 2013 [20] to 8 for 1 study published in 2015 [24] (**Table 2**).

Table 3. Databases used by each study in their literature searches

Authors	PubMed	Medline	Springer Link	Web of Knowledge	Embase	Cochrane Library	OVID	Google scholar	Others
Li, Y et al 2013	+					+			
Fu, T et al 2014	+				+	+			
Jia, Z et al 2014	+	+		+	+	+	+	+	+
Mao, Z et al 2014	+				+	+			
Mao, F et al 2015		+			+	+		+	+
Song, J.Q et al 2015		+			+	+	+		+
Xie, L et al 2015	+	+			+	+	+	+	+
Rabi, S et al 2015		+		+	+	+	+		+
Handoll, H.H et al 2015	+	+			+	+	+	+	+

Table 4. Methodological Information for Each Included Study

Authors	Included study design	Level of evidence	Software	GRADE use	Sensitivity Analysis
Li, Y et al 2013	RCT	Level II	Revman	No	Yes
Fu, T et al 2014	RCT	Level II	Stata	No	Yes
Jia, Z et al 2014	RCT	Level II	Stata	No	Yes
Mao, Z et al 2014	RCT	Level II	Revman	No	No
Mao, F et al 2015	RCT	Level II	Revman	No	Yes
Song, J.Q et al 2015	RCT	Level II	Revman	No	Yes
Xie, L et al 2015	RCT	Level II	Revman	No	No
Rabi, S et al 2015	RCT	Level II	Revman	Yes	Yes
Handoll, H.H et al 2015	RCT	Level II	Revman	Yes	Yes

Search methodology

Most studies comprehensively searched databases. All of the included studies searched Cochrane Library and PubMed. There was heterogeneity as to whether studies also included searches of Embase, OVID, and Google scholar. **Table 3** gives details regarding search methodology used by each included study

Methodological quality

All studies included RCTs or quasi-RCTs and were Level II of evidence (**Table 4**). AMSTAR results for each question from each meta-analysis are shown in **Table 5**. AMSTAR scores varied from 7 to 10.

Heterogeneity assessment

The I^2 statistic value was calculated to assess study heterogeneity as a measure for determining the inter-study variability in all meta-analyses. Heterogeneity of each outcome was acceptable (<60%) in those meta-analyses pooled results (**Table 6**). Of the 9 meta-analyses, 7 meta-analyses conducted sensitivity analyses based on publication status or methodological quality (**Table 4**).

Results of jadad decision algorithm

The Jadad decision algorithm was applied to determine which of the included studies provided the best available evidence [33]. The results of all included meta-analyses were summarized in **Table 7**. Given that the selection criteria were not accordant among included meta-analyses, the Jadad algorithm suggests that the highest-quality review should be selected based on the publication characteristics of the primary trials, the methodology of the primary trials, the language restrictions, and whether analysis of data on individual patients was included in the study. As a result, we selected a high-quality Cochrane review [24] (**Figure 2**). Study suggested that operative treatment provides a lower rates of nonunion and severe pain, but is associated with more additional surgery, penetration of implant into joint rate, metalwork problems and infection. Hence, treatment should be individualized, with careful consideration of the advantages and disadvantages of each treatment method and of patient preferences (**Table 7**).

Discussion

A number of RCTs have attempted to compare operative and non-operative treatment with CPHFs [9-18]. Systematic reviews or meta-anal-

Table 5. AMSTAR Criteria for Each Included Study

Items	Li, Y et al 2013	Fu, T et al 2014	Jia, Z et al 2014	Mao, Z et al 2014	Mao, F et al 2015	Song, J.Q et al 2015	Xie, L et al 2015	Rabi, S et al 2015	Handoll, H.H et al 2015
Was an a priori design provided?	0	0	0	0	0	0	0	0	1
Was there duplicate study selection and data extraction?	1	1	1	1	1	1	1	1	1
Was a comprehensive literature search performed?	1	1	1	1	1	1	1	1	1
Was the status of publication (ie, grey literature) uesd as an inclusion criterion?	1	1	1	1	0	0	0	0	1
Was a list of studies (included and excluded) provided?	0	0	0	0	1	0	1	1	1
Were the characteristics of the included studies provided?	1	1	1	1	1	1	1	1	1
Was the scientific quality of the included studies assessed and documented?	1	1	1	1	1	1	1	1	1
Was the scientific quality of the included studies used appropritely in formulating conclusions?	1	1	1	1	1	1	1	1	1
Were the methods used to combine the findings of studies approprite?	1	1	1	1	1	1	1	1	1
Was the likelihood of publicaton bias assessed?	0	0	0	0	0	0	0	1	0
Was the conflict of interest stated?	1	1	1	1	0	1	1	1	1
Total scores	8	8	8	8	7	7	8	9	10

Table 6. I^2 Statistic Value of Each Variable in Each Meta-analysis

Outcome	Li, Y et al 2013	Fu, T et al 2014	Jia, Z et al 2014	Mao, Z et al 2014	Mao, F et al 2015	Song, J.Q et al 2015	Xie, L et al 2015	Rabi, S et al 2015	Handoll, H.H et al 2015
CS scores at 4 mo	-	-	-	-	-	-	-	-	42%
CS scores at 12 mo	-	0%	0%	0%	0%	0%	0%	0%	0%
CS scores at 24 mo	0%	-	0%	0%	-	-	0%	-	0%
CS scores at 50 mo	-	-	NA	-	-	-	-	-	NA
DASH scores at 4 mo	-	-	-	-	-	-	-	-	0%
DASH scores at 12 mo	-	-	0%	0%	-	-	0%	-	0%
DASH scores at 24 mo	-	0%	0%	0%	-	0%	0%	-	0%
ASES score at 6 mo	-	-	NA	NA	-	-	NA	-	NA
ASES score at 12 mo	-	-	NA	NA	-	-	NA	-	NA
ASES score at 24 mo	-	-	-	-	-	-	-	-	NA
OSS	-	-	-	-	-	-	NA	-	NA
SST at 3 mo	-	-	NA	-	-	-	-	-	NA
SST at 12 mo	-	-	NA	-	-	-	-	-	NA
SF-12 physical component score	-	-	-	-	-	-	NA	-	NA
SF-12 mental component score	-	-	-	-	-	-	NA	-	NA
total complication rates	-	8%	0%	0%	-	61%	0%	-	0%
Additional surgery rate	-	-	0%	3.8%	-	0%	13%	0%	0%
Mortality	-	-	-	0%	-	-	0%	0%	0%
Infection	-	NA	-	0%	NA	-	0%	-	0%
Avascular necrosis	0%	NA	-	41.9%	NA	-	16%	-	0%
Osteoarthritis	13%	NA	-	52%	NA	-	13%	-	25%
Nerve injury	-	NA	-	-	NA	-	0%	-	
Nonunion	0%	NA	-	0%	NA	-	10%	-	0%
Impingement	-	-	-	-	-	-	0%	-	0%
Redisplacement	-	NA	-	0%	-	-	48%	-	0%
Refracture	-	-	-	-	-	-	-	-	NA
Dislocatioin	-	-	-	60%	NA	-	-	-	NA
Penetration of implant into joint rate	-	NA	-	0%	NA	-	-	-	0%
Symptomatic malunion	-	-	-	-	-	-	-	-	NA
Metalwork problems	-	-	-	-	-	-	-	-	NA
Wire penetration	-	-	-	-	NA	-	-	-	NA
Implant-related failure	-	-	-	-	-	-	-	-	0%
Post-traumatic stiffness	-	NA	-	-	-	-	-	-	NA
Rotator cuff tear	-	-	-	-	-	-	-	-	0%
Severe pain	-	NA	-	-	-	-	-	-	NA
Heterotopic ossification	-	-	-	-	-	-	-	-	NA
Dependent in activities of daily living	-	-	-	-	-	-	-	-	NA
Bone resorption	-	NA	-	-	-	-	-	-	
Haematomata	-	NA	-	-	-	-	-	-	
Pulmonary embolism	-	NA	-	-	-	-	-	-	
EQ-5D at 4 mo	-	-	0%	-	-	-	-	-	22%
EQ-5D at 6 mo	-	-	-	-	-	-	-	-	0%
EQ-5D at 12 mo	-	-	0%	0%	0%	-	0%	-	6%
EQ-5D at 24 mo	-	3.1%	0%	0%	-	0%	0%	-	56%
15D at 3 mo	-	-	NA	-	-	-	-	-	NA
15D at 6 mo	-	-	NA	NA	-	-	-	-	NA
15D at 12 mo	-	-	NA	-	-	-	NA	-	NA
15D at 24 mo	-	-	-	-	-	-	NA	-	NA

yses are considered the highest level of scientific evidence [34]. Multiple meta-analyses [19-27] have been published for the treatment of displaced proximal humeral fractures, they still reached different conclusions. These discordances complicate surgeons, patients, and

Table 7. Results of each included meta-analysis

Outcome	Li, Y et al 2013	Fu, T et al 2014	Jia, Z et al 2014	Mao, Z et al 2014	Mao, F et al 2015	Song, J.Q et al 2015	Xie, L et al 2015	Rabi, S et al 2015	Handoll, H.H et al 2015
CS scores at 4 mo									3
CS scores at 12 mo		5	NA	4		5	4	5	4
CS scores at 24 mo	3		NA	3			4		3
CS scores at 50 mo			NA						1
DASH scores at 4 mo									2
DASH scores at 12 mo			NA	2			2		2
DASH scores at 24 mo		2	NA	2		2	2		2
ASES score at 6 mo			NA	1			1		1
ASES score at 12 mo			NA	1			1		1
ASES score at 24 mo									1
OSS							1		1
SST at 3 mo			NA						1
SST at 12 mo			NA						1
SF-12 physical component score							1		1
SF-12 mental component score							1		1
total complication rates		6	6	6		6	7		1
Additional surgery rate			6	5		6	6	5	7
Mortality				2			4	5	6
Infection				3	5		4		8
Avascular necrosis	3			5	5		6		7
Osteoarthritis	2			2	4		2		4
Nerve injury					4		2		4
Nonunion	3			5	5		4		7
Impingement							2		2
Redisplacement		3		3			3		2
Refracture									1
Dislocatioin				4	5				1
Penetration of implant into joint rate		4		4	5				3
Symptomatic malunion									1
Metalwork problems									1
Wire penetration					5				1
Implant-related failure									2
Post-traumatic stiffness									1
Rotator cuff tear									2
Severe pain									1
Heterotopic ossification									1
Dependent in activities of daily living									1
Bone resorption		2							
Haematomata		1							
Pulmonary embolism		1							
EQ-5D at 12 mo			2	2	2		2		4
EQ-5D at 24 mo		3	2	2		2	2		4
15D at 3 mo			NA						1
15D at 6 mo			NA	1					1
15D at 12 mo			NA				1		1
15D at 24 mo							1		1

Red means favoring operative treatment; green means no difference; yellow means not reporting; and blue means favoring non-operative treatment. Arabic numerals mean the number of included randomized clinical trials.

policymakers. and our study has thus attempted to determine which of these studies represents the highest level of evidence on this topic to date.

Jadad [33] summarized the potential sources of discordance among meta-analyses including the clinical question (population of patients, interventions, outcome measures, and setting),

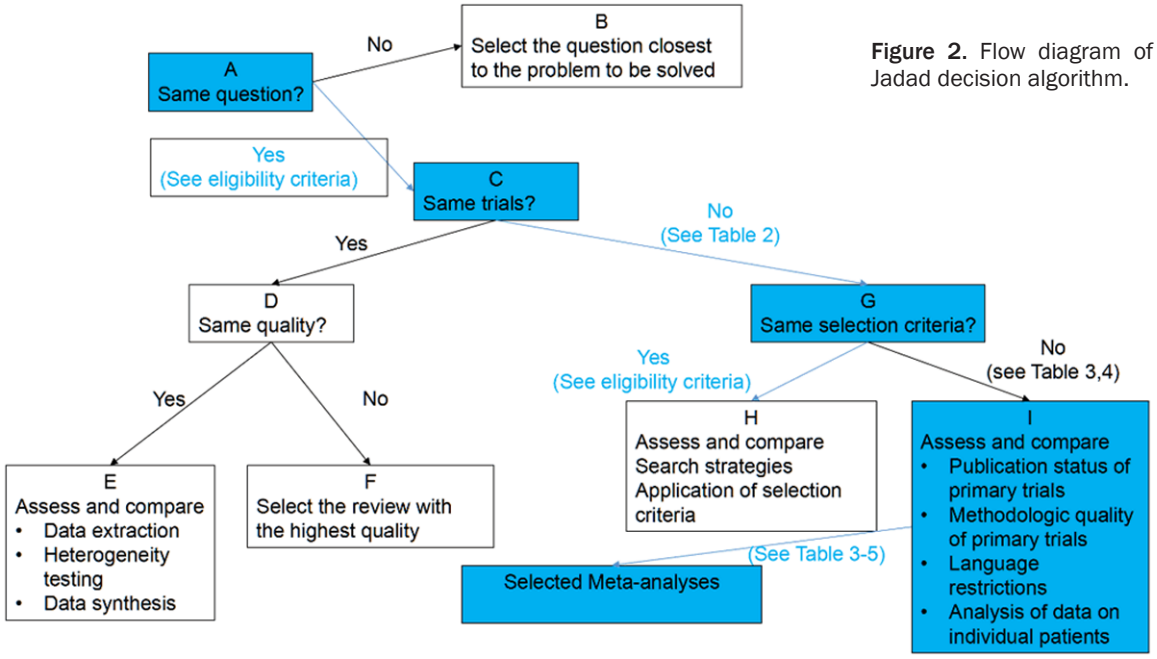

Figure 2. Flow diagram of Jadad decision algorithm.

study selection and inclusion (selection criteria, application of selection criteria, strategies used to search the literature), data extraction (methods used to measure outcomes, end points, human error), assessment of study quality (methods used to assess quality, interpretations of quality assessments, methods used to incorporate quality assessments in review), assessment of the ability to combine studies (statistical methods, clinical criteria used to judge the ability to combine studies), and statistical methods for data synthesis. Jadad [33] also provided a decision tool (decision algorithm) to help decision-makers select from among discordant reviews. It is a useful tool for differentiating between overlapping reviews and was widely used, as shown in the present study. Using the Jadad algorithm [33], 4 authors independently arrived at the conclusion that the review provided by Handoll, H.H [24] provides the current highest level of evidence and it concludes that the differences between operative treatment and non-operative treatment were not significant in function score, total complication rates, mortality, avascular necrosis, osteoarthritis, nerve injury, impingement, re-displacement, re-fracture, dislocation, symptomatic malunion, wire penetration, implant-related failure, post-traumatic stiffness, rotator cuff tear, heterotopic ossification, dependent in activities of daily living and quality of life. But operative treatment provides a lower rate of nonunion and severe pain. While operative treatment is associated with more additional surgery rate, infection, metalwork problems and penetration of implant into joint rate. Handoll, H.H [24] concluded that operative treatment does not result in a better outcome for the majority of people with displaced proximal humeral fractures and is likely to result in a greater need for subsequent surgery. Treatment should be individualized, with careful consideration of the relative advantages and disadvantages of each intervention and of patient preferences.

There are numerous limitations to our study. First, our search strategy was limited by the exclusion of non-English literature that might have met our inclusion criteria, although we searched for as many meta-analyses as possible. Second, although only the meta-analyses exclusively including RCT design were assessed to ensure the high quality of this systematic review, all meta-analyses were Level II evidence. And none of them was Level I evidence.

Conclusions

In this systematic review of overlapping meta-analyses comparing operative and non-operative treatment for displaced proximal humeral fractures involving the humeral neck suggested that according to current best available evidence, compared with non-operative treat-

ment, operative treatment does not result in a better outcome and is likely to result in a greater need for subsequent surgery. Hence, treatment should be individualized and operative treatment should be with careful consideration.

Disclosure of conflict of interest

None.

Address correspondence to: Zhigang Zhao, Department of Orthopedic Surgery, Wuhan Orthopedic Hospital, Wuhan Puai Hospital, Huazhong University of Science and Technology, Hanzheng Street 473#, Wuhan 430033, Hubei Province, China. Tel: +8618051183772; Fax: +8688337786; E-mail: dr_zhaozhigang@163.com

References

[1] Baron JA, Karagas M, Barrett J, Kniffin W, Malenka D, Mayor M and Keller RB. Basic epidemiology of fractures of the upper and lower limb among Americans over 65 years of age. Epidemiology 1996; 7: 612-618.

[2] Horak J and Nilsson BE. Epidemiology of fracture of the upper end of the humerus. Clin Orthop Relat Res 1975; 250-253.

[3] Bengner U, Johnell O and Redlund johnell I. Changes in the incidence of fracture of the upper end of the humerus during a 30-year period. A study of 2125 fractures. Clin Orthop Relat Res 1988; 179-182.

[4] Roux A, Decroocq L, El Batti S, Bonnevialle N, Moineau G, Trojani C, Boileau P and de Peretti F. Epidemiology of proximal humerus fractures managed in a trauma center. Orthop Traumatol Surge Res 2012; 98: 715-719.

[5] Neer CS 2nd. Displaced proximal humeral fractures. I. Classification and evaluation. J Bone Joint Surg Am 1970; 52: 1077-89.

[6] Yuksel HY, Yilmaz S, Aksahin E, Celebi L, Muratli HH and Bicimoglu A. The Results of Nonoperative Treatment for Three- and Four-Part Fractures of the Proximal Humerus in Low-Demand Patients. J Orthop Trauma 2011; 25: 588-595.

[7] Neer CS 2nd. Displaced proximal humeral fractures. II. Treatment of three-part and four-part displacement. J Bone Joint Surg Am 1970; 52: 1090-103.

[8] Vachtsevanos L, Hayden L, Desai AS and Dramis A. Management of proximal humerus fractures in adults. World J Orthop 2014; 5: 685-693.

[9] Stableforth PG. Four-part fractures of the neck of the humerus. J Bone Joint Surg Br 1984; 66: 104-108.

[10] Kristiansen B and Kofoed H. Transcutaneous reduction and external fixation of displaced fractures of the proximal humerus. A controlled clinical trial. J Bone Joint Surg Br 1988; 70: 821-824.

[11] Zyto K, Ahrengart L, Sperber A and Tornkvist H. Treatment of displaced proximal humeral fractures in elderly patients. J Bone Joint Surg Br 1997; 79: 412-417.

[12] Fjalestad T, Hole MO, Jorgensen JJ, Stromsoe K and Kristiansen IS. Health and cost consequences of surgical versus conservative treatment for a comminuted proximal humeral fracture in elderly patients. Injury 2010; 41: 599-605.

[13] Olerud P, Ahrengart L, Ponzer S, Saving J and Tidermark J. Internal fixation versus nonoperative treatment of displaced 3-part proximal humeral fractures in elderly patients: a randomized controlled trial. J Shoulder Elbow Surg 2011; 20: 747-755.

[14] Olerud P, Ahrengart L, Ponzer S, Saving J and Tidermark J. Hemiarthroplasty versus nonoperative treatment of displaced 4-part proximal humeral fractures in elderly patients: a randomized controlled trial. J Shoulder Elbow Surg 2011; 20: 1025-1033.

[15] Boons HW, Goosen JH, van Grinsven S, van Susante JL and van Loon CJ. Hemiarthroplasty for humeral four-part fractures for patients 65 years and older: a randomized controlled trial. Clin Orthop Relat Res 2012; 470: 3483-3491.

[16] Fjalestad T, Hole MO, Hovden IA, Blucher J and Stromsoe K. Surgical treatment with an angular stable plate for complex displaced proximal humeral fractures in elderly patients: a randomized controlled trial. J Orthop Trauma 2012; 26: 98-106.

[17] Fjalestad T and Hole MO. Displaced proximal humeral fractures: operative versus non-operative treatment--a 2-year extension of a randomized controlled trial. Eur J Orthop Surg Traumatol 2014; 24: 1067-1073.

[18] Rangan A, Handoll H, Brealey S, Jefferson L, Keding A, Martin BC, Goodchild L, Chuang LH, Hewitt C, Torgerson D and Collaborators PT. Surgical vs nonsurgical treatment of adults with displaced fractures of the proximal humerus: the PROFHER randomized clinical trial. JAMA 2015; 313: 1037-1047.

[19] Xie L, Ding F, Zhao Z, Chen Y and Xing D. Operative versus non-operative treatment in complex proximal humeral fractures: a meta-analysis of randomized controlled trials. Springerplus 2015; 4: 728.

[20] Li Y, Zhao L, Zhu L, Li J and Chen A. Internal fixation versus nonoperative treatment for displaced 3-part or 4-part proximal humeral fractures in elderly patients: a meta-analysis of

randomized controlled trials. PLoS One 2013; 8: e75464.
[21] Fu T, Xia C, Li Z and Wu H. Surgical versus conservative treatment for displaced proximal humeral fractures in elderly patients: a meta-analysis. Int J Clin Exp Med 2014; 7: 4607-4615.
[22] Jia Z, Li W, Qin Y, Li H, Wang D, Zhang C, He Q and Ruan D. Operative versus nonoperative treatment for complex proximal humeral fractures: a meta-analysis of randomized controlled trials. Orthopedics 2014; 37: e543-551.
[23] Mao Z, Zhang L, Zhang L, Zeng X, Chen S, Liu D, Zhou Z and Tang P. Operative versus nonoperative treatment in complex proximal humeral fractures. Orthopedics 2014; 37: e410-419.
[24] Handoll HH, Brorson S. Interventions for treating proximal humeral fractures in adults. Cochrane Database Syst Rev 2015; CD000434.
[25] Mao F, Zhang DH, Peng XC and Liao Y. Comparison of Surgical versus Non-Surgical Treatment of Displaced 3- and 4-Part Fractures of the Proximal Humerus: A Meta-Analysis. J Invest Surg 2015; 28: 215-224.
[26] Rabi S, Evaniew N, Sprague SA, Bhandari M and Slobogean GP. Operative non-operative management of displaced proximal humeral fractures in the elderly: A systematic review and meta-analysis of randomized controlled trials. World J Orthop 2015; 6: 838-846.
[27] Song JQ, Deng XF, Wang YM, Wang XB, Li X and Yu B. Operative vs. nonoperative treatment for comminuted proximal humeral fractures in elderly patients: a current meta-analysis. Acta Orthop Traumatol Turc 2015; 49: 345-353.
[28] Sun Y, Li L, Dai J and Wang T. Treatment of complex proximal humeral fracture: plate and tension band fixation versus conservative therapy. Int J Clin Exp Med 2015; 8: 7143-7151.
[29] Xu J, Zhang C and Wang T. Avascular necrosis in proximal humeral fractures in patients treated with operative fixation: a meta-analysis. J Orthop Surg Res 2014; 9: 31.
[30] Panic N, Leoncini E, de Belvis G, Ricciardi W and Boccia S. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. PLoS One 2013; 8: e83138.
[31] Wright JG, Swiontkowski MF and Heckman JD. Introducing levels of evidence to the journal. J Bone Joint Surg Am 2003; 85-A: 1-3.
[32] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D and Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. Bmc Med Res Methodol 2007; 7: 10.
[33] Jadad AR, Cook DJ and Browman GP. A guide to interpreting discordant systematic reviews. Cmaj 1997; 156: 1411-1416.
[34] Young D. Policymakers, experts review evidence-based medicine. Am J Health Syst Pharm 2005; 62: 342-343.