

Review

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Assessment of therapeutic clinical trials for proximal humeral fractures

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Proximal humeral fractures (PHFs) are a common injury among the older population. An ideal therapeutic protocol has yet to be developed, and numerous clinical trials are being conducted to find the best therapeutic approach. The purpose of this study is to evaluate the current body of knowledge available via interventional clinical trials. In December 2022, interventional clinical trials relating to PHFs on Clinicaltrials.gov were screened. Trial characteristics included duration, status, intervention, phase, outcomes, location, and study design. Publications associated with each trial were searched on PubMed/Medline using the ClinicalTrials.gov registry number. The final dataset comprised 64 trials. The most common trial status was completed (36%). The majority did not have a Food and Drug Administration-defined phase (67%), was randomized (81%), involved a single facility (72%), used a parallel assignment intervention model (80%), and used an open-label approach (45%). Eleven trials were associated with a publication, and the publication rate was 17%. Average enrollment was 86 participants, and mean trial duration was 51.4 months. Europe/UK/Russia/Turkey participated in the most trials (70%). Most of the trials were initiated after 2010 (87.5%). Procedure-related interventions (55%) were most common. Disability/function was the most common primary outcome assessed (61%). The low publication rate and the multitude of trials conducted after 2010 highlight the urgency and need for trial results to be published to establish an ideal therapeutic protocol. Since the majority of the trials involved a single institution and an open-label approach, reinforcing blinding and establishing multi-centered trials can improve the validity of the clinical trial results.

Keywords: Proximal humerus fracture; Shoulder; Treatment; Trial; Systematic review

INTRODUCTION

Proximal humeral fractures (PHFs), which make up around 5% of all fractures, are frequent injuries in the older population [1]. PHFs are the third most often observed fragility fracture in the last 20 years, making them a significant cause of morbidity in many osteoporotic patients in our aging population [2]. PHFs are most frequently caused by a low-energy fall in an osteoporotic patient, leading to primarily non-displaced two-part fractures that are frequently treated conservatively with immobilization in a sling with positive clinical outcomes [3].

The type of fracture and the patient characteristics must be taken into account while deciding whether to perform surgery. The majority of PHFs may not require surgery. Recent research does, however, support surgical intervention in displaced three- and four-part fracture patients [4]. The surgeon must choose the device to use for operative intervention, which can be challenging, even for skilled surgeons. LaMartina et al. [5] pointed out the difficulty in choosing a course of treatment, finding that fellowship-trained shoulder surgeons agreed just 63.5% of the time. In the past, hemi-arthroplasty (HA) was used to repair these fractures in older patients and open reduction internal fixation

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(ORIF) was used in younger patients [6,7]. Reverse shoulder arthroplasty (RSA), however, is becoming more common [8,9]. While the use of HA has significantly decreased over time and the use of RSA has dramatically increased, the use of ORIF has remained consistent [10]. According to Acevedo et al. [11], RSA may be especially helpful for patients older than 70 years. A patient's health situation and the type of fracture may also be taken into consideration in addition to age when making decisions [12,13].

Despite this, we have not yet developed an ideal therapeutic protocol for treatment of this condition, and numerous clinical trials are being conducted to find the best therapeutic approach to treat PHF. Clinical trial evaluation and assessment are crucial for identifying successful tactics and treatments, as well as for identifying gaps and prospective areas for improvement. The purpose of this study is to evaluate the current body of knowledge available for PHF via interventional clinical trials.

METHODS

Search Strategy and Selection Criteria

ClinicalTrials.gov—a database registering clinical studies worldwide that are privately and publicly funded on a weekly basis—was screened for information regarding interventional clinical trials targeting PHFs [14]. For the clinical trials to be included in the database, details such as a description of the protocol, inclusion/exclusion criteria, outcome measures, and any relevant history must be provided by the investigator of the respective trial. Previous literature has utilized clinical trial data from this database to reach conclusions [15,16]. Institutional Review Board approval was not required for this study.

In December 2022, the ClinicalTrials.gov registry was queried using the key words “Proximal humeral fracture” without any search restrictions to find all related clinical trials. A total of 131 relevant trials was generated from the search. Similar to studies in previous literature, non-interventional trials were excluded, eliminating 57 trials [15,16]. An additional 10 trials were removed from the study as they did not focus on PHFs. Ultimately, 64 clinical trials remained in the final dataset (Fig. 1).

Data Collection

Information collected from the final set of clinical trials included the status (not yet recruiting, active-not recruiting, enrolling by invitation, recruiting, completed, terminated, withdrawn, and unknown), trial duration, type of experimental intervention, phase, number of testing locations, sample size, primary outcomes, secondary outcomes, study design (intervention model,

allocation, and masking), and publications. If the trial was not completed, the estimated end dates listed on the registry were used to determine the duration. If a clinical trial was conducted on multiple continents, then both were associated with the trial in the data collection. The different interventions were categorized into: physical therapy, drug, device, procedure, and other. Examples and definitions of the different intervention types are presented in Table 1.

Review of Literature

PubMed/Medline was used to search for publications associated with each trial by inputting the ClinicalTrials.gov registry number (NCTID). Each of these publications was reviewed, and the primary results from the trials were analyzed using the available publications.

RESULTS

Trial Characteristics

A total of 64 trials was included in our study. The general characteristics of the clinical trials were presented in Table 2 and organized according to trial phase. Most trials did not have an Food and Drug Administration (FDA)-defined phase (not applicable; $n=43$, 67%). The most common status among the clinical trials was completed ($n=23$, 36%). On the other hand, only one trial was enrolling by invitation. Fifteen trials were recruiting, seven were terminated, seven had an unknown status, five were active but not recruiting, four were not yet recruiting, and two were withdrawn. Trials were terminated or withdrawn for various reasons: slow recruitment (NCT02362100, NCT01532076, NCT03599336,

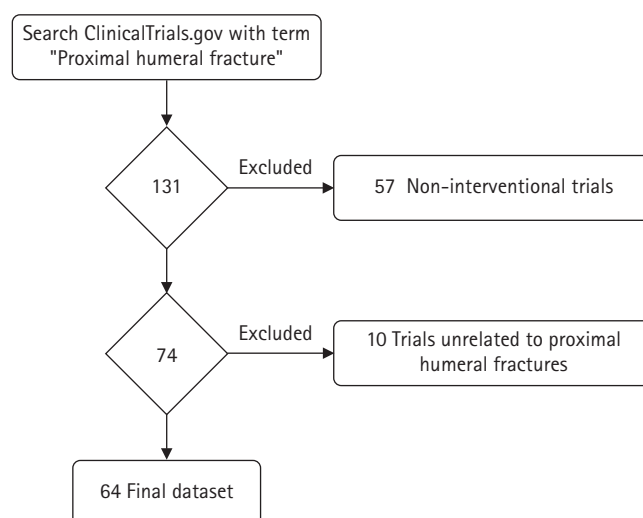


Fig. 1. Clinical trial selection process.

Table 1. Definitions and examples of the different types of interventions used in the proximal humeral fracture clinical trials

Type of intervention	Definition	Example (as stated on the clinical trial entry)
Physical therapy	Interventions that utilize modalities, such as physical exercises, massages, joint mobilization, physical manipulation, instead of drugs or surgery	Non-structured rehabilitation, telerehabilitation, early and intensive exercise program
Drug	Interventions that utilize the administration of drugs	Iloprost, tranexamic acid, liposomal bupivacaine, 1-84 parathyroid hormone, teriparatide, rhPTH(1-34), ropivacaine and tramadol, Kenalog
Device	Interventions that utilize machinery or other medical technology and devices to deliver a treatment	Interferential current, Ultrasling III ER, neutral rotation brace, computed tomography scan
Procedure	Interventions that utilize a surgical or invasive approach with the possible use of anesthesia	Reverse shoulder arthroplasty, Philos plate, MultiLoc nail, other plating systems, cellularized composite graft augmentation
Other	Interventions that do not apply to any other categories	Dry needling, BMC2012 cell therapy, questionnaires and activity tracking

Table 2. Characteristics of clinical trials involving proximal humeral fractures

Variable	Trial phase						Total
	NA	Phase I	Phase I/II	Phase II	Phase III	Phase IV	
Number of trials	43	3	2	6	4	6	64
Number of original publications	13	0	0	1	0	1	15
Number of trials cited in a review	26	2	1	1	1	0	31
Status							
Not yet recruiting	4	0	0	0	0	0	4
Active-not recruiting	5	0	0	0	0	0	5
Enrolling by invitation	1	0	0	0	0	0	1
Recruiting	11	0	1	0	1	2	15
Completed	15	1	0	4	0	3	23
Terminated	4	0	1	1	1	0	7
Withdrawn	0	0	0	1	1	0	2
Unknown status	3	2	0	0	1	1	7
Estimated enrollment							
0–10	4	1	0	1	0	0	6
11–50	10	1	2	2	0	2	17
51–100	21	0	0	3	2	3	29
> 100	8	1	0	0	2	1	12
Start date							
2000–2009	3	0	0	2	2	1	8
2010–2019	30	3	1	3	1	4	42
≥ 2020	10	0	1	1	1	1	14
Trial duration (mo)							
0–12	3	2	0	0	0	1	6
13–24	8	1	0	1	1	2	13
25–60	19	0	2	4	3	3	31
> 60	13	0	0	1	0	0	14
Trial location							
North America (US/Canada)	8	1	0	1	0	1	11
Europe/UK/Russia/Turkey	28	2	2	5	3	4	44
Asia	4	0	0	0	1	1	6
Africa/Egypt	1	0	0	0	0	0	1
South America	2	0	0	0	0	0	2

NA: no Food and Drug Administration-defined phase.

NCT03017105, NCT02091492), lack of funding (NCT02362100), difficulties maintaining follow-up (NCT02362100), release of a publication indicating that the intervention was not always beneficial (NCT02073695), opened under a new principal investigator (NCT02597972), and other unrelated reasons (NCT00326794, NCT00741182).

The most common estimated enrollment size among the trials was between 51 to 100 patients ($n = 29$, 45%). Average enrollment was 86 participants. Only a few trials were initiated before 2010, with 87.5% beginning after 2010. Trial durations ranged from two months to 204 months with a mean of 51.4 months. Europe/UK/Russia/Turkey participated in the largest number of clinical trials ($n = 45$). This was followed by North America with 11 trials, Asia with six trials, South America with two trials, and Africa/Egypt with one trial.

Types of Interventions

Table 3 presents the distribution of the types of interventions used among the trials in the final dataset. The most common type of intervention was procedure-related interventions, which was studied in 35 (55%) trials. This was followed by drug-related interventions ($n = 11$, 17%), physical therapeutic modalities ($n = 9$, 14%), and device-related interventions ($n = 5$, 8%). Four trials (6%) involved an intervention that did not apply to the other categories.

Primary Endpoints

Of the trials, 46 (72%) involved a single facility, while 11 were multi-centered. Seven of the clinical trials did not report the number of institutions involved in the trial (Table 4). In 52 trials (81%), patients were randomized into groups; three trials were non-randomized. The mode of allocation was not reported for nine trials. The majority of the trials utilized a parallel assignment intervention model ($n = 51$, 80%), while 11 trials involved a single group assignment model, and two trials involved a cross-over assignment model. The most common approach was an open-label approach (no masking), in 29 trials (45%). Of all trials, 19 trials single-masked, 12 were double-masked, two were triple-masked, and two were quadruple masked.

Table 3. Types of interventions involved in the included trials

Types of interventions involved	Number of trials
Physical therapy	9
Drug	11
Device	5
Procedure	35
Other	4

The majority of the trials analyzed one primary endpoint; however, four trials explored two primary endpoints. The most common primary endpoint was disability/function, which was used in 39 trials (61%). This was followed by radiographic evaluation with 11 trials, pain with eight trials, adverse events with seven trials, quality of life/patient satisfaction with one trial, and range of motion with one trial. The most common primary outcome assessor was the Constant-Murley Score (21 trials), which was followed by the Disabilities of the Arm, Shoulder, and Hand Score (DASH) or its short version QuickDASH Score (9 trials).

Trial Results and Publications

Results were available for 11 trials, which resulted in a 17% publication rate. Fifteen original publications, excluding publication of a systematic review, were produced from the included trials [17-31]. Three of the trials were linked to multiple original publications. Thirteen of the 15 publications were associated with a trial that was not defined by a phase, one publication was associated with a trial in phase II, and one publication was associated with a trial in phase IV (Table 5). Eight publications were protocols for the respective clinical trial and did not report any results. Three publications compared the outcomes of different surgical interventions. Although two of the three publications found no significant differences between the interventions, one suggested that an RSA was more advantageous than an ORIF at the 2-year follow-up in the treatment of displaced type-B2 and C2 PHFs in elderly patients. Although another publication suggested no significant difference between outcomes in patients who received surgical versus conservative interventions, another publication suggested that surgical intervention resulted in better functional and radiographic outcomes at the 1-year follow-up. Additionally, one publication explored whether a T2-level thoracic paravertebral block was necessary when treating patients undergoing a deltopectoral approach for PHF treatment. Despite the decreased risk of incomplete regional anesthetic, the T2-level thoracic paravertebral block was suboptimal due to the potential risks. Further, one publication explored whether teriparatide could enhance the healing of a PHF and concluded that teriparatide resulted in better healing on radiographic assessment even though there was no significant difference in pain or functional outcomes. Additional details of the publications can be found in Table 5.

A systematic review assessing the benefits and harms of non-pharmaceutical treatments for PHFs in adults was performed by searching the Cochrane Central Register of Controlled Trials, Medline, Embase, trial registries, and bibliographies of trial reports. Systematic reviews to September 2020 included 31 of

Table 4. Number of facilities involved

Variable	Trial phase						Total
	NA	Phase I	Phase I/II	Phase II	Phase III	Phase IV	
Facilities							
Single	29	2	1	6	4	4	46
Multiple	9	0	0	0	0	2	11
Unreported	5	1	1	0	0	0	7
Allocation							
Randomized	33	2	2	6	4	5	52
Non-randomized	2	0	0	0	0	1	3
NA	8	1	0	0	0	0	9
Intervention model							
Parallel assignment	33	1	2	6	4	5	51
Single group assignment	9	1	0	0	0	1	11
Crossover assignment	1	1	0	0	0	0	2
Masking							
None	21	2	2	2	0	2	29
Single	13	1	0	2	2	1	19
Double	8	0	0	1	1	2	12
Triple	1	0	0	0	1	0	2
Quadruple	0	0	0	1	0	1	2
Primary endpoints							
		Some trials have more than 1 primary endpoint					
Disability/function	30	2	1	2	2	2	39
Pain	4	0	0	1	1	2	8
Range of motion	1	0	0	0	0	0	1
Quality of life/patient satisfaction	1	0	0	0	0	0	1
Radiographic evaluation	7	0	0	1	1	2	11
Adverse events	2	1	1	2	0	1	7

NA: no Food and Drug Administration-defined phase.

the 64 trials from this final dataset [3]. The review analyzed mostly women older than 60 years, and most of the trials were at high risk of bias due to a lack of blinding. There was insufficient evidence to draw a conclusion regarding the difference between surgical, non-surgical, or rehabilitation interventions for PHFs.

DISCUSSION

As of December 2022, only 64 therapeutic clinical trials were identified that explored the management of PHFs. The trials spanned 23 countries and five continents, with Europe sponsoring the largest number of trials at 45. North America followed with 11 trials, while South America and Africa had only two and one trials, respectively. Research on shoulder pathologies has been increasing in Europe in recent decades [32,33]. European PHF research, in specific, has produced numerous publications on the epidemiology of the injury in several European countries, as well as management protocols and treatment trends [34-37]. Europe had the highest number of trials in our study, likely due to its impressive research infrastructure and high investment in the management of shoulder

pathologies [32-37]. Moreover, the majority of the trials was started after 2010, indicating the novelty of this topic. Management of PHF was originally mostly conservative [38]. However, as years passed, integrating operative management for patients with displaced fractures showed good clinical and functional outcomes [39]. As such, research on PHF treatment increased in prominence as innovative technological advancements led to the development and popularization of new surgical options. Despite that, the publication rate found in our study was relatively low, at 17%. This low rate is problematic as it downplays the efforts put into these clinical trials and reduces the reliability of the collectively reported trial results. Low publication rates constitute a major problem in that regard and are often explained by hesitancy to report negative results, absence of academic expectations or incentives, lack of funds, or language difficulties [15,40].

The majority of trials had appropriate models and designs. Most were randomized and had parallel assignment models, allowing appropriate comparison between treatment modalities. Since the trials mainly involved variations of verified treatments, the majority did not have an FDA-defined phase. In specific, the

Table 5. Clinical findings of publications linked to the included proximal humeral fracture clinical trials

Study	Title and NCTID	Number of participants	Intervention	Primary outcome	Result
Johansson (2016) [17]	PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures. A randomized, controlled study of 40 patients (NCT01105832)	40	Standard after-treatment (analgesics and physiotherapy) with daily 20 µg teriparatide injections vs. standard after-treatment only	Radiographic evaluation	39 Patients completed the follow-up and found that the teriparatide group had a better correlation than the control group on radiographic assessments. However, there were no significant differences between the groups in terms of pain, use of strong analgesics, or function during the follow-up examinations. There are no results yet (protocol).
Liaghat et al. (2022) [18]	Effect of structured rehabilitation versus non-structured rehabilitation following non-surgical management of displaced proximal humerus fractures: a protocol for a randomized clinical trial (NCT05302089)	60	Structured rehabilitation vs. non-structured rehabilitation	Disability/function	There are no results yet (protocol).
Cabana et al. (2016) [19]	Is an in-home telerehabilitation program for people with proximal humerus fracture as effective as a conventional face-to face rehabilitation program? A study protocol for a noninferiority randomized clinical trial (NCT02425267)	31	Telerehabilitation vs. face-to-face rehabilitation	Disability/function	There are no results yet (protocol).
Wang et al. (2022) [20]	Is it useful and necessary to add a T2 paravertebral block to the regional anesthesia during proximal humeral fracture surgery in elderly patients? A prospective and randomized controlled trial (NCT03919422)	80	T2 Paravertebral Block With Interscalene Brachial Plexus Block And Superficial Cervical Plexus Block (ICTP) vs. Interscalene Plexus Block And Superficial Cervical Plexus Block (IC)	Pain	The success rate of regional anesthesia was higher in the ICTP group compared to the IC group. In the IC group, more patients required intravenous remifentanyl. Conversion to general anesthesia was performed more often in the IC group. Furthermore, sensory block at the medial proximal upper arm was more frequently achieved in patients in the ICTP group. There was no difference in adverse events or block-related complications. There are no results yet (protocol).
Wang et al. (2020) [21]	The effectiveness of additional thoracic paravertebral block in improving the anesthetic effects of regional anesthesia for proximal humeral fracture surgery in elderly patients: study protocol for a randomized controlled trial (NCT03919422)	80	T2 paravertebral block with interscalene brachial plexus block and superficial cervical plexus block and superficial cervical plexus block	Pain	There are no results yet (protocol).
Launonen et al. (2019) [22]	Nordic Innovative Trials to Evaluate Osteoporotic Fractures (NITEP) Collaboration: The Nordic DeltaCon Trial protocol-non-operative treatment versus reversed total shoulder arthroplasty in patients 65 years of age and older with a displaced proximal humerus fracture: a prospective, randomized controlled trial (NCT03531463)	150	RSA vs. nonoperative treatment	Disability/function	There are no results yet (protocol).

(Continued to the next page)

Table 5. Continued

Study	Title and NCTID	Number of participants	Intervention	Primary outcome	Result
Fjalestad et al. (2014) [23]	Clinical investigation for displaced proximal humeral fractures in the elderly: a randomized study of two surgical treatments: reverse total prosthetic replacement versus angular stable plate Philos (The DELPHI-trial) (NCT01737060)	124	RSA vs. ORIF with/Philos plate and Ticon cerclages	Disability/function	There are no results yet (protocol).
Fraser et al. (2020) [24]	Reverse shoulder arthroplasty is superior to plate fixation at 2 years for displaced proximal humeral fractures in the elderly: a multicenter randomized controlled trial (NCT01737060)	124	RSA vs. ORIF with/Philos plate and Ticon cerclages	Disability/function	At 2 years, the RSA group had a better functional outcome than the ORIF group.
Bones et al. (2022) [25]	Pegs not superior to screws for fixation of fractures of the proximal humerus (NCT01737060)	110	Anatomical locking plate system-proximal humeral plating with pegs (ALPS-PHP) vs. Philos plate with screws	Disability/function	Both groups had an equal number of peg and screw penetrations, and there was no significant difference in the development of avascular head necrosis. However, patients in both groups who did not have joint penetrations had better functional outcomes at 12 months.
Fjalestad et al. (2012) [26]	Surgical treatment with an angular stable plate for complex displaced proximal humeral fractures in elderly patients: a randomized controlled trial (NCT00863473)	50	ORIF using angular stable plate and cerclages vs. nonoperative treatment	Disability/function	After 12 months, there was no statistically significant difference in Constant scores. There was also no significant difference in mean patient self-assessment. However, surgically treated patients had significantly better radiographic outcomes.
Launonen et al. (2019) [27]	Operative versus non-operative treatment for 2-part proximal humerus fracture: a multicenter randomized controlled trial (NCT01246167)	250	Philos locking plate vs. Epoca Prosthesis vs. conservative treatment (Sling)	Disability/function	At the 2-year follow-up, there was no statistically significant difference in any of the studies outcomes. Furthermore, 3 complications that required another surgery were seen in the operative group compared to none in the conservative group.
Launonen et al. (2012) [28]	Conservative treatment, plate fixation, or prosthesis for proximal humeral fracture. A prospective randomized study (NCT01246167)	250	Philos locking plate vs. Epoca Prosthesis vs. conservative treatment (Sling)	Disability/function	There are no results yet (protocol).
Helfen et al. (2016) [29]	Operative treatment of 2-part surgical neck fractures of the proximal humerus (AO 11-A3) in the elderly: cement augmented locking plate Philos™ vs. proximal humerus nail MultiLoc® (NCT02609906)	40	Proximal humerus internal locking system screws with cement augmentation vs. MultiLoc-Nail	Disability/function	There are no results yet (protocol).
Hengg et al. (2019) [30]	Cement augmentation of the proximal humerus internal locking system in elderly patients: a multicenter randomized controlled trial (NCT01847508)	67	Cement augmentation of the proximal humerus internal locking system screws (Philos) vs. Philos without cement augmentation	Radiographic evaluation	Due to premature termination, 67 patients (56 eligible) were enrolled, resulting in an underpowered study. The follow-ups were performed as planned, and the augmented group had a slightly higher mechanical failure rate than the control group.
Howard et al. (2018) [31]	Open reduction internal fixation vs non-operative management in proximal humerus fractures: a prospective, randomized controlled trial protocol (NCT02362100)	30	Locking plate surgical fixation vs. non-operative treatment	Disability/function	There are no results yet (protocol).

NCTID: ClinicalTrials.gov registry number, RSA: reverse shoulder arthroplasty, ORIF: open reduction internal fixation.

majority of trials explored procedure-related interventions [14]. Such analysis is valid in these circumstances since the treatment of PHFs mainly relies on fracture characteristics. While conservative treatment can be pursued for minimally displaced fractures, more critical cases require surgical intervention for optimizing function [39,41,42]. Hence, it is important to explore the different surgical options available for this pathology to help further develop treatment guidelines and strategies.

The published results explored anesthesia-related, conservative, and surgical treatment options in the setting of PHFs. In a study by Wang et al. [20], adding a T2-level thoracic paravertebral block was helpful to decrease the occurrence of incomplete anesthesia in elderly patients undergoing a PHF surgery using a deltopectoral approach; however, it does not eliminate all such cases and does involve potential risks. Understanding the benefits and risks of administering regional anesthesia is important to reduce the risk of increased postoperative pain. In a study by Johansson [17], even though conservative treatment with teriparatide injections was correlated with better radiographic outcomes, there was no significant improvement in pain or function.

Regarding surgical options, in a study by Fraser et al. [24], RSA had better clinical results than an ORIF using an angular stable plate at 2-year follow-up for type-C2 PHFs in elderly patients, while there was no significant difference for type-B2 PHFs in elderly patients. In a study by Bønes et al. [25], using pegs instead of screws for fixation of PHFs showed no significant difference in the development of avascular head necrosis. However, the use of pegs and screws both showed better functional outcomes at 12 months when the patient did not have a joint penetration. In a study by Hengg et al. [30], cement augmentation of the proximal humerus internal locking system screws had a slightly higher mechanical failure rate compared to the group without cement augmentation.

The controversy between conservative and surgical treatment was also addressed. In a study by Fjalestad et al. [26], at the 12-month follow-up, even though an ORIF using an angular stable plate and cerclages had significantly better radiographic outcomes compared to nonoperative treatment, there was no significant difference in clinical outcomes. Launonen et al. [27] observed no significant difference between outcomes at 2-year follow-up for patients who received a Philos locking plate, Epoca prosthesis, or conservative treatment (sling) in the setting of a two-part PHF. However, the operative group experienced three cases of complications that required a subsequent surgery. In both studies, no interventional modality was superior.

All but four trials explored one primary endpoint, while the rest explored two endpoints. The most commonly explored endpoint was function/disability, and the most commonly utilized

outcome score was the Constant-Murley score. This outcome scoring tool is appropriate in this setting since it helps explore pain, function, range of motion, and strength of the affected shoulder [43,44]. That being said, several study design limitations existed. The majority of trials involved only a single institution, and around 45% adopted an open label approach. This increased the risk of bias and decreased the generalizability and reliability of trial results [45].

CONCLUSIONS

Assessing the interventional clinical trials targeting PHFs can help to establish an ideal therapeutic protocol. The urgency and need to establish an ideal therapeutic protocol can be seen by the multitude of trials conducted after 2010, most of which were procedure related. Although there were numerous trials, the publication rate was low. The common use of a single institution and the common use of an open-label approach need to be addressed in future studies.

Interventions targeting PHFs are mainly categorized into physical therapeutic modalities, drug-related interventions, device-related interventions, procedure-related interventions, and other interventions that do not apply to the other categories. The majority of the trials evaluated procedure-related interventions, which emphasizes the interest in establishing an ideal treatment protocol, as well as advantages and disadvantages of different options. Primary endpoints mainly involved disability/function, radiographic evaluation, pain, and adverse events. Further study is needed to determine the effectiveness and advantages of different treatment options to determine the best protocol.

NOTES

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Conflict of interest

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REFERENCES

- Court-Brown CM, Garg A, McQueen MM. The epidemiology of proximal humeral fractures. *Acta Orthop Scand* 2001;72:365–71.
- Barrett JA, Baron JA, Karagas MR, Beach ML. Fracture risk in the U.S. Medicare population. *J Clin Epidemiol* 1999;52:243–9.
- Handoll HH, Olliviere BJ, Rollins KE. Interventions for treating proximal humeral fractures in adults. *Cochrane Database Syst Rev* 2012;12:CD000434.
- Chivot M, Lami D, Bizzozero P, Galland A, Argenson JN. Three- and four-part displaced proximal humeral fractures in patients older than 70 years: reverse shoulder arthroplasty or nonsurgical treatment. *J Shoulder Elbow Surg* 2019;28:252–9.
- LaMartina J, Christmas KN, Simon P, et al. Difficulty in decision making in the treatment of displaced proximal humerus fractures: the effect of uncertainty on surgical outcomes. *J Shoulder Elbow Surg* 2018;27:470–7.
- Schairer WW, Nwachukwu BU, Lyman S, Craig EV, Gulotta LV. Reverse shoulder arthroplasty versus hemiarthroplasty for treatment of proximal humerus fractures. *J Shoulder Elbow Surg* 2015;24:1560–6.
- Solberg BD, Moon CN, Franco DP, Paiement GD. Surgical treatment of three and four-part proximal humeral fractures. *J Bone Joint Surg Am* 2009;91:1689–97.
- Sebastiá-Forcada E, Cebrián-Gómez R, Lizaur-Utrilla A, Gil-Guillén V. Reverse shoulder arthroplasty versus hemiarthroplasty for acute proximal humeral fractures: a blinded, randomized, controlled, prospective study. *J Shoulder Elbow Surg* 2014; 23:1419–26.
- Shukla DR, McAnany S, Kim J, Overley S, Parsons BO. Hemiarthroplasty versus reverse shoulder arthroplasty for treatment of proximal humeral fractures: a meta-analysis. *J Shoulder Elbow Surg* 2016;25:330–40.
- Hasty EK, Jernigan EW, Soo A, Varkey DT, Kamath GV. Trends in surgical management and costs for operative treatment of proximal humerus fractures in the elderly. *Orthopedics* 2017;40:e641–7.
- Acevedo DC, Vanbeek C, Lazarus MD, Williams GR, Abboud JA. Reverse shoulder arthroplasty for proximal humeral fractures: update on indications, technique, and results. *J Shoulder Elbow Surg* 2014;23:279–89.
- Neer CS 2nd. Displaced proximal humeral fractures: I. classification and evaluation. *J Bone Joint Surg Am* 1970;52:1077–89.
- Olsson C, Petersson CJ. Clinical importance of comorbidity in patients with a proximal humerus fracture. *Clin Orthop Relat Res* 2006;442:93–9.
- ClinicalTrials.gov [Internet]. National Library of Medicine; 2022[cited 2023 Dec 1]. Available from: <https://clinicaltrials.gov/>
- Fares J, Kanojia D, Rashidi A, Ahmed AU, Balyasnikova IV, Lesniak MS. Diagnostic clinical trials in breast cancer brain metastases: barriers and innovations. *Clin Breast Cancer* 2019; 19:383–91.
- Vanderbeek AM, Rahman R, Fell G, et al. The clinical trials landscape for glioblastoma: is it adequate to develop new treatments. *Neuro Oncol* 2018;20:1034–43.
- Johansson T. PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures. A randomized, controlled study of 40 patients. *Acta Orthop* 2016;87:79–82.
- Liaghat B, Brorson S. Effect of structured rehabilitation versus non-structured rehabilitation following non-surgical management of displaced proximal humerus fractures: a protocol for a randomised clinical trial. *BMJ Open* 2022;12:e064156.
- Cabana F, Pagé C, Svolteis A, Langlois-Michaud S, Tousignant M. Is an in-home telerehabilitation program for people with proximal humerus fracture as effective as a conventional face-to face rehabilitation program? A study protocol for a noninferiority randomized clinical trial. *BMC Sports Sci Med Rehabil* 2016;8:27.
- Wang X, Zhang H, Chen Y, et al. Is it useful and necessary to add a T2 paravertebral block to the regional anesthesia during proximal humeral fracture surgery in elderly patients? A prospective and randomized controlled trial. *Front Surg* 2022;9:755298.
- Wang X, Zhang H, Xie Z, Zhang Q, Jiang W, Zhang J. The effectiveness of additional thoracic paravertebral block in improving the anesthetic effects of regional anesthesia for proximal humeral fracture surgery in elderly patients: study protocol for a randomized controlled trial. *Trials* 2020;21:204.
- Launonen AP, Fjalestad T, Laitinen MK, et al. Nordic Innovative

- Trials to Evaluate osteoporotic Fractures (NITEP) Collaboration: the Nordic DeltaCon Trial protocol-non-operative treatment versus reversed total shoulder arthroplasty in patients 65 years of age and older with a displaced proximal humerus fracture: a prospective, randomised controlled trial. *BMJ Open* 2019;9:e024916.
23. Fjalestad T, Iversen P, Hole MØ, Smedsrud M, Madsen JE. Clinical investigation for displaced proximal humeral fractures in the elderly: a randomized study of two surgical treatments: reverse total prosthetic replacement versus angular stable plate Philos (The DELPHI-trial). *BMC Musculoskelet Disord* 2014;15:323.
 24. Fraser AN, Bjørdal J, Wagle TM, et al. Reverse shoulder arthroplasty is superior to plate fixation at 2 years for displaced proximal humeral fractures in the elderly: a multicenter randomized controlled trial. *J Bone Joint Surg Am* 2020;102:477–85.
 25. Bønes I, Karlberg AC, Liljeholm M, Fraser AN, Madsen JE, Fjalestad T. Pegs not superior to screws for fixation of fractures of the proximal humerus. *J Orthop Surg Res* 2022;17:66.
 26. Fjalestad T, Hole MØ, Hovden IA, Blücher J, Strømsøe 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.
 27. Launonen AP, Sumrein BO, Reito A, et al. Operative versus non-operative treatment for 2-part proximal humerus fracture: a multicenter randomized controlled trial. *PLoS Med* 2019;16:e1002855.
 28. Launonen AP, Lepola V, Flinkkilä T, et al. Conservative treatment, plate fixation, or prosthesis for proximal humeral fracture: a prospective randomized study. *BMC Musculoskelet Disord* 2012;13:167.
 29. Helfen T, Siebenbürger G, Mayer M, Böcker W, Ockert B, Haasters F. Operative treatment of 2-part surgical neck fractures of the proximal humerus (AO 11-A3) in the elderly: cement augmented locking plate Philos™ vs. proximal humerus nail Multi-Loc®. *BMC Musculoskelet Disord* 2016;17:448.
 30. Hengg C, Nijs S, Klopfer T, et al. Cement augmentation of the proximal humerus internal locking system in elderly patients: a multicenter randomized controlled trial. *Arch Orthop Trauma Surg* 2019;139:927–42.
 31. Howard L, Berdusco R, Momoli F, et al. Open reduction internal fixation vs non-operative management in proximal humerus fractures: a prospective, randomized controlled trial protocol. *BMC Musculoskelet Disord* 2018;19:299.
 32. Haislup BD, Rate WR, Civiletti MD, Cohen AS, Bodendorfer BM, Gould HP. The 100 most impactful articles on the rotator cuff: an altmetric analysis of online media. *J Exp Orthop* 2022;9:92.
 33. Freehill MT, Murray IR, Calvo E, Lädermann A, Srikumaran U. Shoulder surgery postoperative immobilization: an international survey of shoulder surgeons. *Biology (Basel)* 2023;12:291.
 34. Vicenti G, Bizzoca D, Zaccari D, et al. Choice of treatments of the coronal shear fractures of the humerus: a national survey of Italian AO members. *Injury* 2023;54 Suppl 1:S78–84.
 35. Karimi D, Houkjær L, Gundtoft P, Brorson S, Viberg B. Positive predictive value of humeral fractures in the Danish National Patient Registry. *Dan Med J* 2023;70:A10220612.
 36. Sumrein BO, Berg HE, Launonen AP, et al. Mortality following proximal humerus fracture—a nationwide register study of 147,692 fracture patients in Sweden. *Osteoporos Int* 2023;34:349–56.
 37. Mattila H, Keskitalo T, Simons T, Ibounig T, Rämö L. Epidemiology of 936 humeral shaft fractures in a large Finnish trauma center. *J Shoulder Elbow Surg* 2023;32:e206–15.
 38. Van Bergen SH, Mahabier KC, Van Lieshout EM, et al. Humeral shaft fracture: systematic review of non-operative and operative treatment. *Arch Orthop Trauma Surg* 2023;143:5035–54.
 39. Cosic F, Kirzner N, Edwards E, Page R, Kimmel L, Gabbe B. The translated proximal humerus fracture: a comparison of operative and nonoperative management. *J Orthop Trauma* 2023;37:e341–8.
 40. Mayir B, Bilecik T, Çakır T, et al. Analysis of the publishing rate and the number of citations of general surgery dissertations. *Turk J Surg* 2017;33:33–6.
 41. Martinez-Catalan N. Conservative treatment of proximal humerus fractures: when, how, and what to expect. *Curr Rev Musculoskelet Med* 2023;16:75–84.
 42. Walter N, Szymiski D, Kurtz SM, et al. Proximal humerus fractures: epidemiology, comparison of mortality rates after surgical versus non-surgical treatment, and analysis of risk factors based on Medicare registry data. *Bone Joint Res* 2023;12:103–12.
 43. Kirkley A, Griffin S, Dainty K. Scoring systems for the functional assessment of the shoulder. *Arthroscopy* 2003;19:1109–20.
 44. Angst F, Schwyzer HK, Aeschlimann A, Simmen BR, Goldhahn J. Measures of adult shoulder function: Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH) and its short version (QuickDASH), Shoulder Pain and Disability Index (SPADI), American Shoulder and Elbow Surgeons (ASES) Society standardized shoulder assessment form, Constant (Murley) Score (CS), Simple Shoulder Test (SST), Oxford Shoulder Score (OSS), Shoulder Disability Questionnaire (SDQ), and Western Ontario Shoulder Instability Index (WOSI). *Arthritis Care Res (Hoboken)* 2011;63 Suppl 11:S174–88.
 45. Day SJ, Altman DG. Statistics notes: blinding in clinical trials and other studies. *BMJ* 2000;321:504.