Osteoarthritis and Cartilage (2009) **17,** 1263–1268

doi:10.1016/j.joca.2009.04.006

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review
Systematic review of non-surgical therapies for osteoarthritis of the hand: an update

D. Mahendira and T. E. Towheed*

Department of Medicine, Queen's University, Kingston, Ontario, Canada, K7L 3N6

Summary

Objective: To update our earlier systematic review which evaluated all published randomized controlled trials (RCTs) evaluating pharmacological and non-pharmacological therapies in patients with hand osteoarthritis (OA). Surgical therapies were not evaluated.

Method: RCTs published between August 2004 and February 2008 were added to the original systematic review.

Results: A total of 44 RCTs evaluating various pharmacological and non-pharmacological therapies in hand OA were analyzed in this update. Generally, these RCTs were of low quality. RCTs were weakened by a lack of consistent case definition and by a lack of standardized outcome assessments. The methods used for randomization, blinding, and allocation concealment were rarely described. The number and location of symptomatic hand joints per treatment group at baseline was usually not stated. The number and location of evaluated hand joints at the end of the study was also usually not stated. A meta-analysis could not be performed since most of the treatments studied did not have more than one identical comparison to allow pooling of the data.

Conclusions: It is apparent that hand OA is a more complex area in which to study the efficacy of therapies when compared to hip and knee OA. The recently published OARSI Consensus Recommendations will improve the design and conduct of future RCTs in hand OA.

Key words: Osteoarthritis, Hand, Digital, Therapy, Systematic review.

Introduction

Therapy for hand osteoarthritis (OA) has received relatively little attention when compared to OA of the hip and knee. The objective of this paper is to update our previous version of the systematic review of therapies for OA of the hand by adding randomized controlled trials (RCTs) published between August 2004 and February 2008[1].

Criteria for inclusion and exclusion

The inclusion and exclusion criteria were identical to those used in the original version of the systematic review. RCTs evaluating surgical therapies were not included. We included RCTs evaluating OA at multiple sites only if efficacy data were presented separately for the hand.

Search strategy and study identification

The following electronic data sources were searched for this updated version of the systematic review: (1) MEDLINE (1966 to February week 4, 2008), (2) PREMEDLINE (February week 4, 2008), (3) EMBASE (1980 to February week 4, 2008), (4) AMED (1985 to February week 4, 2008), (5) CINAHL, Allied Health (1982 to February week 4, 2008), (6) EBM Reviews, including the Cochrane Database of Systematic Review (CDSR), the Database of Abstracts of Reviews of Effectiveness (DARE), ACP Journal Club and the Central Cochrane Database (1980 to February week 4, 2008). Reference lists of all retrieved articles were also manually searched. The flow chart summarizing study identification and retrieval is shown in Fig. 1. The search strategy used in MEDLINE was identical to that used in the earlier version of this review.

Methods

A data abstraction form was used to extract information pertaining to trial demographics, methodology, quality, and outcomes[2,3]. Study quality was evaluated by using Jadad's scoring checklist[4]. The final score ranges from 0 to 5, with a higher score reflecting higher methodological quality. Data abstraction was conducted by the two authors, independently. Results were cross-checked for reliability and differences were resolved by reaching consensus. Allocation concealment was specifically evaluated for each RCT. A formal meta-analysis will be performed, if feasible.

Results

OVERVIEW OF STUDY DEMOGRAPHICS

A total of 44 RCTs were analyzed in this systematic review[5–47] (Tables I–III). Two RCTs were published in the 1970s, five were published in the 1980s, 14 were published in the 1990s and 23 were published in the year 2000 or beyond. Thirty-six RCTs were available as English full paper reports, four were non-English reports with English abstracts, and four were only available as English abstracts.

*Address correspondence and reprint requests to: Tanveer E. Towheed, Department of Medicine, Queen's University, Room 2066, Etherington Hall, Kingston, Ontario, Canada, K7L 3N6. Tel: 1-613-533-6896; Fax: 1-613-533-2189; E-mail: tt5@queensu.ca
Received 17 October 2008; revision accepted 1 April 2009.

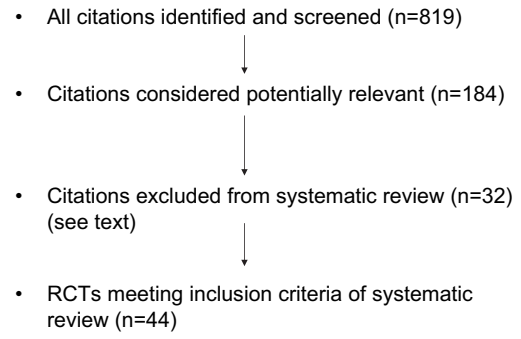

Fig. 1. Flow chart of search strategy.

Thirty-two reports evaluating therapies in hand OA were excluded from this review since they did not meet one or more of the stated inclusion criteria of this systematic review[48–79].

Symptom modifying therapy was evaluated in 39 RCTs, whereas a structural modifying therapy was evaluated in three RCTs[5,19]. Two RCTs evaluated both a symptom modifying as well as a structural modifying therapy[11,18]. A parallel, independent group study design was used in 35 RCTs and a cross-over design was used in nine RCTs. The median number of subjects randomized per study was 41, with a range of 5–910. The median number of subjects completing the trials was 35, with a range of 5–559.

The median duration of the RCTs was 8.6 weeks, with a range of 2 h–260 weeks. Eighty-two percent of the subjects randomized were female. The mean age of randomized subjects in the RCTs was 62.3 years, with a range of 53–82 years. Subjects had a mean duration of OA hand symptoms of 6.1 years, with a range of 2–10.2 years.

Five RCTs had an open follow-up period after study discontinuation. Twenty-seven of the 44 RCTs (61%) had a placebo group/arm. Seven RCTs were multi-centre. The country of origin was heterogeneous with the US having the greatest number of RCTs (14), followed by France (5), Germany (5), Austria (3), Belgium (3), and Italy (3).

Nine RCTs had an oral non-steroidal anti-inflammatory drug (NSAID) treatment group/arm. The individual NSAIDs evaluated were: ibuprofen, naproxen, meclofenamate, rofecoxib, lumiracoxib and indomethacin. Seven RCTs had a topical NSAID treatment group/arm. The individual topical NSAID preparations evaluated were: topical ibuprofen, topical etofenamate, topical diclofenac, and topical niflumic acid. Two RCTs had a topical ASA group/arm. Both studies evaluated topical trolamine salicylate in comparison to a placebo. Four studies evaluated intra-articular steroid use, while four studies examined intra-articular hyaluronan. Seven RCTs evaluated occupational therapy interventions. These included the following: joint protection exercises, splints of various kinds and technical accessories. Other active agents tested included: capsaicin cream (2), glycosaminoglycan polysulfate (GAGPS) (2) and chondroitin sulfate (2). Several RCTs evaluated unconventional OA therapies, such as: laser therapy (2), folate and cobalamin vitamin therapy (1), leeches (1), tiled stove (1), TENs (1), yoga (1), dextrose prolotherapy (1), pressure gradient gloves (1), spa therapy (1), stinging nettle leaf (1), fiorinal of (1) and hydroxychloroquine (1).

FEATURES SPECIFIC TO HAND OA TRIALS

No consistent definition of hand OA was used in these RCTs. Most trials ($N = 32$) did not explicitly distinguish between primary (idiopathic) and secondary OA. Ten RCTs evaluated exclusively subjects with primary hand OA. One RCT enrolled subjects with both primary and secondary hand OA. Erosive hand OA was studied exclusively in two

Table I
Published RCTs in OA of the hand (N = 44)

Study (authors and year)	Groups	*N* randomized	*N* completed	Design	Duration (weeks)	Overall efficacy
Thorpe, 1970[8]	Fiorinal vs FIPA vs placebo	10	9	Cross-over	6	(Fiorinal = FIPA) > placebo
Swezey *et al.*, 1979[28]	Pressure glove vs control glove vs no glove	5	5	Cross-over	6	Equal
Seiler, 1983[13]	Meclomen vs placebo	41	22	Parallel	4	Meclomen > placebo
Talke *et al.*, 1985[32]	Topical etofenamate vs oral indomethacin	NA*	NA*	Parallel	3	Equal
Basford *et al.*, 1987[23]	Helium neon laser vs placebo	81	81	Parallel	3	Equal
Caruso *et al.*, 1987[33]	SAMe† vs naproxen vs placebo	51	NA*	Parallel	4	Equal
Pastinen *et al.*, 1988[7]	Glycosaminoglycan polysulfate (GAGPS) IA‡ vs placebo	30	29	Parallel	52	GAGPS > placebo
McCarthy and McCarty, 1992[26]	Capsaicin vs placebo	14	14	Parallel	4	Capsaicin > placebo
Dreiser *et al.*, 1993[15]	Ibuprofen vs placebo	60	54	Parallel	2	Ibuprofen > placebo
Verbruggen and Veys, 1993[19]	GAGPS (IM)§ vs placebo	92	68	Parallel	260	GAGPS > placebo
Flynn *et al.*, 1994[22]	Folate vs folate + B12 vs placebo	30	26	Cross-over	24	Folate + B12 > (placebo = folate)
Garfinkel *et al.*, 1994[25]	Yoga vs no therapy	26	25	Parallel	10	Yoga > no therapy
Rothacker *et al.*, 1994[6]	Trolamine salicylate vs placebo	50	49	Cross-over	NA*	Trolamine > placebo
Schnitzer *et al.*, 1994[17]	Capsaicin vs placebo	59	48	Parallel	9	Capsaicin > placebo
Dougados and Nguyen, 1995[21]	Topical niflumic acid vs placebo	186	186	Parallel	1	Equal
Thiesce and Dougados, 1995[20]	Topical diclofenac vs placebo	20	20	Cross-over	1.5	Equal

*NA = not available.
†SAMe = S-adenosylmethionine.
‡IA = intra-articular.
§IM = intra-muscular.

Table II
*Published RCTs in OA of the hand (*N = *44)*

Study (authors and year)	Groups	*N* randomized	*N* completed	Design	Duration (weeks)	Overall efficacy
Renklitepe *et al*., 1995[31]	Tens electrode glove vs carbon electrode	36	NA*	Parallel	0.7	Glove electrode > carbon electrode
Punzi *et al*., 1996[34]	Hydroxychloroquine (HQ) vs NSAID/analgesics	15	15	Parallel	52	HQ > NSAID + analgesic
Graber-Duvernay *et al*., 1997[29]	Berthollet spa vs topical ibuprofen	116	107	Parallel	24	Spa > ibuprofen
Rothacker *et al*., 1998[14]	Trolamine salicylate vs placebo	86	81	Parallel	0.01	Trolamine > placebo
Buurke *et al*., 1999[12]	Uriel splint vs sporlastic splint vs gibortho splint	10	10	Cross-over	12	Uriel splint > others
Reeves and Hassanein, 2000[11]	Dextrose prolotherapy (DP) vs placebo	27	25	Parallel	24	DP > placebo
Weiss *et al*., 2000[9]	Short splint vs long splint vs no splint	26	26	Cross-over	2	Short splint > long splint > no splint
Randall *et al*., 2000[16]	Stinging nettle leaf vs placebo	27	24	Cross-over	12	Stinging nettle leaf > placebo
Berggren *et al*., 2001[10]	OT vs OT + textile splint vs OT + leather splint	33	33	Parallel	28	All groups had less hand surgery
Zacher *et al*., 2001[30]	Topical diclofenac vs oral ibuprofen	321	NA*	Parallel	3	Equal
Stamm *et al*., 2002[27]	Joint protection and exercise (JPE) vs info only	40	40	Parallel	12	JPE > info only
Verbruggen *et al*., 2002[5]	Chondroitin polysulfate (CPS) vs placebo	130	92	Parallel	156	CPS > placebo
Verbruggen *et al*., 2002[5]	Chondroitin sulfate (CS) vs placebo	92	73	Parallel	156	CS > placebo
Lisse *et al*., 2003[24]	Rofecoxib vs naproxen	910	NA*	Parallel	12	Equal
Rovetta *et al*., 2004[18]	CS and naproxen vs naproxen alone	24	24	Parallel	104	CS + naproxen > naproxen alone

*NA = not available.

RCTs[18,34]. Only 11 RCTs used a validated hand OA classification scheme for study entry. These 11 studies used the ACR classification criteria[80]. Most often, hand OA was defined by the authors themselves with descriptions that lacked sufficient detail and precision ($N = 23$ RCTs). Radiographs were taken at baseline in 24 RCTs. However, detailed X-ray criteria were explicitly stated in only 16 of these 24 RCTs.

The distribution of affected hand OA joints was quite variable and was also inconsistently presented in the trial reports. For example, 11 RCTs did not specify which joints were being evaluated in the hand. Twelve RCTs evaluated exclusively subjects with first carpal metacarpal joint (CMC) OA. Eleven RCTs evaluated subjects with interphalangeal (proximal interphalangeal joint (PIP) and/or distal interphalangeal joint (DIP)) OA, but not first CMC OA. Nine RCTs evaluated all three joint areas (PIP, DIP and first CMC).

Only 15 RCTs presented detailed information pertaining to the number and location of symptomatic hand joints per treatment group at baseline. This information is important to include as a clinical descriptive feature of how much patients are affected by hand OA. Only 19 RCTs specified the number and location of evaluated hand joints at the end of the study. Only 15 RCTs specified a priori a hand joint site for efficacy analysis.

Table III
*Published RCTs in OA of the hand (*N = *44)*

Study (authors and year)	Groups	*N* randomized	*N* completed	Design	Duration (weeks)	Overall efficacy
Grifka *et al*., 2004[35]	Lumiracoxib vs placebo	594	559	Parallel	4	Lumiracoxib > placebo
Lefler *et al*., 2004[36]	Strength training exercises vs control	19	18	Parallel	6	Strength training > control
Meenagh *et al*., 2004[37]	IA corticosteroid vs placebo	40	35	Parallel	24	Equal
Weiss *et al*., 2004[41]	Neoprene splint (PFN) vs custom-made splint (CMS)	25	25	Cross-over	2	PFN > CMS
Brosseau *et al*., 2005[38]	Low level laser therapy vs placebo	88	86	Parallel	6	Equal
Stahl *et al*., 2005[39]	IA corticosteroid vs IA hyaluronate	52	52	Parallel	24	Equal
Wajon *et al*., 2005[40]	TSS* + exercise vs SOS† + exercise	40	34	Parallel	6	Equal
Fuchs *et al*., 2006[42]	IA hyaluronate vs IA steroid	56	51	Parallel	26	Equal
Michalsen *et al*., 2006[43]	Leeches vs topical diclofenac	32	32	Parallel	8.6	Leeches > diclofenac
Stange-Rezende *et al*., 2006[44]	Infrared radiation (IRR) vs control	45	35	Cross-over	8	IRR > control
Roux *et al*., 2007[45]	IA hyaluronate (once vs twice vs thrice)	42	37	Parallel	12	Equal
Widrig *et al*., 2007[46]	Topical ibuprofen gel vs arnica gel	204	174	Parallel	3	Equal
Heyworth *et al*., 2008[47]	IA hylan vs IA corticosteroid vs placebo	60	60	Parallel	26	Equal

*TSS = thumb strap splint.
†SOS = short opponens splint.

Eight RCTs did not specify whether one hand or both hands were evaluated. Seventeen RCTs evaluated one hand only, whereas 18 RCTs evaluated both hands. Fifteen RCTs specified a minimum entry criterion for symptoms and/or objective findings, including specific X-ray criteria at baseline.

There was a lack of standardization of outcomes across the 44 RCTs. Moreover, some outcome variables used in these RCTs have not been validated in OA trials. Pain, function, and patient global assessments were evaluated in 38, 35 and 19 RCTs, respectively. Physician global assessments and health-related quality of life were evaluated in nine and three RCTs, respectively. Examples of outcome variables used in these trials that have not been validated in OA trials include joint swelling, joint tenderness, need for OA related surgery, analgesic usage, sleep quality and range of motion. A standardized, validated questionnaire (generic and/or disease specific) was used for outcome assessment in 18 RCTs. This included the disease specific AUSCAN questionnaire[81] and Dreiser's Functional Index[82].

FEATURES OF TRIAL QUALITY

Pre-randomization inclusion criteria were clearly specified in 36 RCTs. Pre-randomization exclusion criteria were clearly specified in 30 RCTs. Subjects were blinded in 25 RCTs and investigators were blinded in 29 RCTs. Fifteen of the 44 RCTs were associated with a pharmaceutical company or manufacturer. Six RCTs excluded subjects for protocol violation. Eleven RCTs excluded subjects for adverse effects. Thirty-three RCTs did not specify as to whether subjects had prior exposure to the test agents. Fifteen RCTs controlled for supplementary analgesic usage or co-intervention during the trial duration. Ten RCTs presented sample size calculations. Nine RCTs provided a clearly stated rationale for the chosen dosage of at least one active agent. Eleven RCTs described the method of randomization. Fourteen RCTs described the method of blinding. Seventeen RCTs defined a priori a main outcome variable. The success of the blinding was only evaluated at the end of the study in one of the included RCTs. Eighteen RCTs presented sufficiently detailed baseline data allowing the reader to ensure that the groups were comparable at baseline. Twenty-four RCTs used appropriate statistical analyses. Examples of inappropriate statistical analyses included: (1) using a parametric statistical test for non-parametric data, (2) stating that a marginally insignificant statistical test was still statistically "significant", (3) using a paired statistical test for independent groups, (4) using multiple comparisons without employing any statistical correction. For example, one RCT evaluated several outcome variables, at separate time points, for the right hand, left hand, both hands, and the dominant hand. Twenty-one RCTs either had no withdrawals or used an intention-to-treat analysis. Only four RCTs adequately described the method used to ensure allocation concealment[83].

METHODOLOGICAL QUALITY BASED ON JADAD'S SCORES

The median Jadad score for the entire group of RCTs was 3, with a range of 0–5. Twenty-five RCTs received a score of 1 for being double-blinded. Twenty-nine RCTs received a score of 1 for providing an adequate description of withdrawals and drop-outs. All RCTs were randomized as per the inclusion criteria of the systematic review and therefore all received a score of 1 for this criterion. The median Jadad score for the 13 RCTs that were added to this version of the systematic review was only 2. Thus, it does not appear that the quality of the more recent hand OA trials has improved.

META-ANALYSIS

A formal meta-analysis could not be performed as most of the therapies studied did not have more than one identical comparison to allow pooling of the data. Also, the studies were too clinically diverse making a meta-analysis inappropriate.

SUMMARY OF RESULTS OF THERAPIES

Due to the inherent methodological limitations in these studies, it is difficult to offer any reliable practical recommendations for the choice of appropriate therapy in subjects with clinically significant hand OA (Tables I–III). However, based on these 44 analyzed RCTs, one can conclude that there is at least *some* evidence from a published RCT for the efficacy for the following therapies: trolamine salicylate, GAGPS, fiornal and FIPA, splints for first CMC OA, occupational therapy, dextrose prolotherapy, oral NSAIDs, stinging nettle leaf, topical capsaicin, vitamin B12 with folate, yoga, leeches, strength training exercise and spa therapy. At least *some* evidence also exists from a published RCT for structural efficacy in hand OA for the following therapies: chondroitin sulfate, chondroitin polysulfate, and GAGPS.

Discussion

Results of this systematic review allow for a number of general conclusions. First, there are few published RCTs evaluating the wide range of therapies available for hand OA. However, 13 RCTs were published from August 2004 to February 2008, which is a relative increase from previous years. Second, RCTs in hand OA are weak methodologically. The most important issues relate to deficiencies in allocation concealment, inadequate description of the methods of randomization and blinding, failure to use intention-to-treat analyses, inappropriate statistical analyses, and failure to provide sample size calculations. Third, a number of more specific methodological limitations related to hand OA are also apparent. The number and location of symptomatic joints per treatment group at baseline was usually not stated. In addition, the number and location of evaluated joints per treatment group at the end of study was also usually not stated. RCTs were often lacking important details regarding whether one or both hands were evaluated, whether the first CMC joint and/or IP joints were evaluated, and the selection a priori of both a target joint site (first CMC vs IP joints) and a principal outcome measure for efficacy evaluation. These are some of the issues that were addressed by the OARSI task force in the recently published Consensus Guidelines for the Design and Conduct of trials in subjects with hand OA[83].

Conflict of interest

There are no known conflicts of interests pertaining to the work of this systematic review.

Acknowledgment

The authors are grateful to Jessie McGowan, MLIS, AHIP, Senior Information Scientist, Institute of Population Health/

Ottawa Health Research Institute, Trials Search Coordinator, EPOC (The Cochrane Collaboration) for the design and execution of the electronic searches.

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