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Efficacy of ultrasound-guided versus landmark-guided injections in rheumatology: A systematic review

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ABSTRACT

Background: There is good evidence that ultrasound (US) increases the accuracy of needle placement for joint aspiration and injection. However, considerable uncertainty remains as to whether US-guided injections (USGI) achieve better clinical outcome in rheumatic conditions compared with landmark-guided injections (LGI), and how any effect on outcome relates to accuracy.

Methods: We conducted a literature search using PubMed, yielding 810 references. After applying randomised controlled trials (RCTs), human studies and relevance to rheumatic conditions as eligibility criteria, abstract review produced 26 studies. Study design quality was assessed using the Jadad scale.

Results: The median sample size of the 26 studies was 58.5 (range 20-244) patients. Median Jadad score was low at 2.5 (1-5). Only 6 RCTs had an effective double blinding method, with sham-US/blindfolding of patients and a blinded outcome assessor. Sixteen of 26 (61.5%) trials showed superior outcome of USGI compared to LGI for one or more outcomes measuring pain, function or range of movement. The 3 RCTs with the lowest risk for bias failed to demonstrate clear USGI superiority for the main clinical outcomes. In 2 of the 4 studies that assessed both accuracy and efficacy, USGI did not show greater clinical efficacy overall, although they had superior accuracy and accurate injections were associated with better outcome of at least one clinical criterion.

Conclusion: The majority of trials suggest US guidance associates with superior outcome of injections. However, higher quality RCTs and trials with similar accuracy between the two techniques fail to support this. There is need for further trials with better design and adequate sample power.

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Keywords: Ultrasonography, anatomical landmarks, guided injections, accuracy, efficacy, outcome.

INTRODUCTION

Joint and soft tissue injections are frequent procedures in rheumatological practice, but it is recognised that the success rate with which injections reach their intended target using anatomical landmarks as guidance is limited.[1] High-resolution ultrasound (US) is a valid, "bedside" imaging technique,[2] which is increasingly used in rheumatological practice for diagnostic purpose, but also as image guidance for needle arthrocentesis to perform aspirations, injections or synovial biopsies. US can enhance clinical diagnostic confidence of the structural problem underlying symptoms and facilitates safer and frequently less painful needle guidance where needed.

There is good evidence that US increases the accuracy of needle placement for aspiration and injection of joints.[3–7] However, there remains considerable uncertainty as to whether US guidance translates into increased clinical response in rheumatic conditions and how this response relates to accuracy, the use of an imaging modality per se, or other factors. A previous Cochrane systematic review in 2012 comparing US-versus landmark- guided injections corticosteroid injections for shoulder pain found no overall benefit in favour of US-guidance.[8] Since then, further reviews have been published.[9–12] We therefore aimed to review the current evidence with regards to efficacy and clinical outcome of ultrasound guided intra- and peri- articular injections (USGI) when compared to standard injections using anatomical landmark guidance (LGI) in rheumatological practice.

METHODS

We conducted a literature search using Pubmed, aiming to comprehensively identify randomised controlled trials (RCTs) assessing the efficacy in terms of clinical outcome of USGI versus LGI for rheumatic conditions.

We used filters to include peer-reviewed journal articles describing clinical trials written in English and referring on adult humans for the period up to September 11, 2016. There were no limitations on the anatomical site of injection, the indication or the form of treatment given.

The following search terms were used: *((((ultraso* OR sonogr*)) AND injection*) AND (outcome OR efficacy)) NOT (nerv* OR neur*)*. The eligibility criteria used to identify relevant articles were trials characterized as relating to rheumatological conditions, being randomized-controlled, conducted on humans (no cadaveric studies were included) and assessing clinical efficacy and/or patient outcome of USGI using LGI as a comparison (**Table 1**).

We identified 810 articles using the search terms described. No duplicate articles were found. The titles and abstracts were reviewed for eligibility and articles that did not focus on the purpose of this review were excluded. Twenty-six articles were deemed relevant and their full texts were acquired and examined for eligibility. Three articles were excluded for not fulfilling the inclusion criteria. We also conducted a secondary search through the bibliographies of the remaining 23 articles and were able to identify 3 more relevant articles. A total of 26 articles were finally included in the qualitative synthesis of the review. **Figure 1** shows the PRISMA flow diagram[13] for the different phases of this review.

The quality RCT design of each trial was assessed and graded using the Jadad scale.[14] This quality score ranges from 0 (lowest) to 5 points (highest) and assesses randomization of patients to groups (up to 2 points), double-blind design (up to 2 points) and accountability for all enrolled patients at study end with description of withdrawals and dropouts (up to 1 point). There is an inherent difficulty in ascertaining the double-blind de-

Table 1. Search strategy and inclusion criteria.

Search strategy	((((ultraso* OR sonogr*)) AND injection*) AND (outcome OR efficacy)) NOT (nerv* OR neur*)
Filters	Clinical trials, Humans, English
Inclusion criteria	• Humans, not cadaveric • Randomized controlled clinical trials • Assessing efficacy or outcome of ultrasound guided injections (USGI) • Comparison with landmark guided injections (LGI)

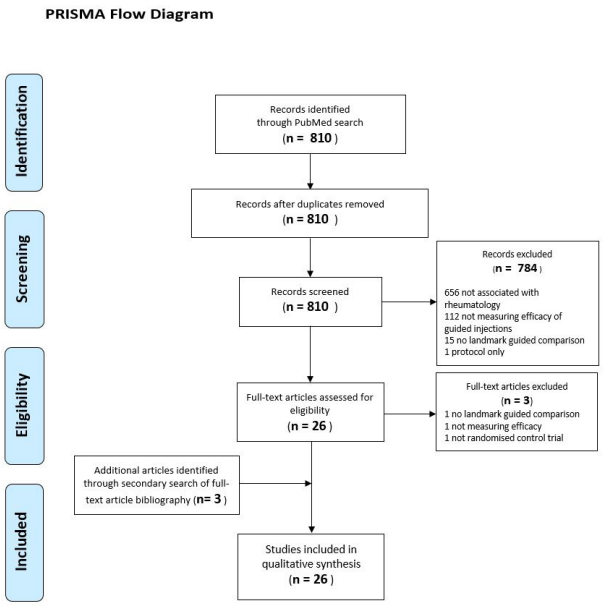

Figure 1. PRISMA Flow Diagram for the review process.

sign in trials involving intra- or peri- articular injections, as it is impossible for the physician performing the injection to be blinded to the treatment arm. It is therefore generally accepted that an outcome assessor who is blinded to the treatment arms is sufficient to guarantee independent assessment of physician-reported outcomes. Similarly, the use of sham-US (i.e., where live US is used at the time of an LGI, but without the injector being able to use any of the US image information) is required to allow effective blinding of patients. This ensures that the patient-reported outcomes are free of bias caused by contextual benefits of US per se rather than its benefit through enhanced injection placement. We therefore graded studies with 2 points for the double-blind design only if the publication included evidence of both sham-US and a blinded outcome assessor being used. In one of the studies,[15] the blindfolding of patients prior to the procedure was also considered as an effective method of maintaining the blindness of patients. Studies with a Jadad score of 4 or higher were considered high quality trials.

RESULTS

We were able to identify 26 RCTs with a median sample size of 58.5 (range: 20-244) patients. There were 3 studies that investigated multiple injections sites, mostly in patients with inflammatory arthritis. In the remaining studies, the most investigated target site was the shoulder (i.e. subacromial bursa, SAB; glenohumeral joint, GHJ; biceps brachii, BB; acromioclavicular joint, ACJ), with 11 trials. Plantar fascia injections were investigated in 3 trials. Knee and wrist joints and carpal tunnel areas were evaluated in 2 trials each. There was 1 trial assessing USGI versus LGI efficacy for each of the volar flexor tendon sheaths (FTS), Morton's neuroma (MN) and the scapulothoracic bursa (STB).

The median Jadad score of the studies was 2.5 (range 1-5), indicating that the majority of the studies were of low quality in design (**Table 2**). Only 4 studies had a score of 4 or more, targeting shoulder,[16] multiple joints[17], plantar fascia[18] and Morton's neuroma.[19] Six of the studies were judged to have an effective double-blinding method; 5 used sham-US and 1 blindfolding of the patients before the injection in conjunction with a blinded assessor. Overall, 18 studies used a blinded outcome assessor. Power calculation for the patient sample was performed in only 9 trials (34.6 %) before the start of the study. There were 4 trials that integrated accuracy assessments in their design, in an effort to correlate accuracy of injections as well as US-guidance to efficacy outcomes (**Table 3**).

The measures and time points of outcome were diverse throughout the studies (**Table 4**). The most commonly assessed outcome was patient-reported pain, being measured at various time points in all but 2 of the 26 trials, either by Visual Analogue Scale (VAS) or by Verbal Numeric Scale (VNS). Other patient-reported outcomes were diverse and included several validated functional questionnaires depending on the site of injection; for example, the Shoulder Disability Questionnaire (SDQ), the Constant and Murley Score (CMS, a composite outcome of pain, functional ability, strength and range of movement), the Disability of Arm, Shoulder and Hand Questionnaire (DASHQ), as well as questionnaires evaluating general health outcomes, such as the Health Assessment Questionnaire (HAQ) and the EuroQol questionnaire (EQ-5D). Assessing the improvement in the range of movement (ROM) of the joint post injection was the most frequent objective outcome measured in eleven of the studies, the majority of these assessing the shoulder joint.

TRIALS BY INJECTION SITE

Multiple targets

In a 2011 study, Cunnington et al.[17] reported on the accuracy and clinical outcome of 184 joint injections (shoulder, knee, ankle, elbow, wrist) randomized between landmark- and US- guidance in patients with inflammatory arthritis. This was deemed as a high-quality study, as both assessors and patients (through sham-US) were adequately blinded on treatment allocation (Jadad score 4). There was no significant difference between the 2 groups for any of the major outcome variables, either in subjective outcomes such as pain in VAS, HAQ, EQ-5D or objective outcomes such as inflammatory markers and ROM at 2 and 6

Table 2. Jadad grading of bias risk of identified trials.

Authors	Randomization is mentioned	Randomization method is appropriate	Double-blinding is mentioned	Double-blinding method is appropriate	Account of all patients	Total Jadad score
Multiple targets						
Sibbitt (2011)[21]	1	0	0	0	1	**2**
Cunnington (2010)[17]	1	0	1	1	1	**4**
Sibbitt (2009)[20]	1	0	0	0	1	**2**
Shoulder						
Sabeti-Aschraf (2010)[24]	1	1	0	0	1	**3**
Zhang (2011)[31]	1	0	0	0	1	**2**
Lee (2009)[22]	1	-1	1	1	1	**3**
Dogu (2012)l[16]	1	1	1	1	1	**5**
Hsieh (2013)[23]	1	1	0	0	1	**3**
Zufferey (2012)[26]	1	1	0	0	1	**3**
Chen (2006)[30]	1	0	0	0	0	**1**
Saeed (2014)l[27]	1	1	0	0	1	**3**
Naredo (2004)[28]	1	1	0	0	0	**2**
Ucuncu (2009)[29]	1	0	0	0	0	**1**
Haghigat (2016)	1	0	0	0	1	**2**
Knee						
Sibbitt (2012)[35]	1	0	0	0	0	**1**
Sibbitt (2011)[34]	1	0	0	0	1	**2**
Wrist						
Nam (2013)[36]	1	1	0	0	1	**3**
Luz (2008)[15]	1	0	1	1	0	**3**
Carpal tunnel syndrome						
Makhlouf (2014)l[37]	1	1	0	0	1	**3**
Ustun (2013)[38]	1	1	0	0	0	**2**
Plantar fascia						
Chen (2013)l[33]	1	0	0	0	1	**2**
Kane (2001)[32]	1	0	0	0	1	**2**
Ball (2013)[18]	1	1	1	1	1	**5**
Other						
Mahadevan (2016)[19]	1	1	1	1	1	**5**
Cecen (2015)[39]	1	0	0	0	1	**2**
Chang (2014)[40]	1	1	0	0	1	**3**

Table 3. Characteristics of the identified trials.

Authors	Diagnosis	Sample size	US arm	LG arm	Sham-US	Blinded assessor	Assessed accuracy
Multiple targets							
Sibbitt (2011)[21]	Inflammatory arthritis	244	124	120		Yes	
Cunnington (2010)[17]	Inflammatory arthritis	184	92	92	Yes	Yes	Yes (x-ray)
Sibbitt (2009)[20]	RA/OA	148	74	74			
Shoulder							
Sabeti-Aschraf (2010)[24]	Symptomatic ACJ	20	10	10			
Zhang (2011)[31]	BB tendinitis	98	53	45		Yes	
Lee (2009)[22]	Frozen shoulder	41	21	20	Yes	Yes	
Dogu (2012)l[16]	Subacromial impingement	46	23	23	Yes	Yes	yes (MRI)
Hsieh (2013)[23]	Subacromial bursitis	96	48	48		Yes	
Zufferey (2012)[26]	Acute painful shoulder	70	34	36		Yes	
Chen (2006)[30]	Subacromial bursitis	40	20	20			
Saeed (2014)l[27]	Shoulder pain	125	59	66		Yes	
Naredo (2004)[28]	Shoulder pain	41	21	20		Yes	
Ucuncu (2009)[29]	Shoulder pain	60	30	30			
Haghigat (2016)	Subacromial impingement	40	20	20			
Knee							
Sibbitt (2012)[35]	Knee effusion (RA/OA)	64	22+20	22		Yes	
Sibbitt (2011)[34]	OA	92	46	46		Yes	
Wrist							
Nam (2013)[36]	Ulnar-sided wrist pain	57	28	29		Yes	Yes (x-ray)
Luz (2008)[15]	RA	60	30	30	Blindfold	Yes	Yes (x-ray)
Carpal Tunnel Syndrome							
Makhlouf (2014)l[37]	Symptomatic CTS	77	37	40			
Ustun (2013)[38]	Symptomatic CTS	46	23	23		Yes	
Plantar Fascia							
Chen (2013)l[33]	Plantar Fasciitis	33	16	17			
Kane (2001)[32]	Plantar Fasciitis	28	14	14			
Ball (2013)[18]	Inferior heel pain	43	22	21	Yes	Yes	
Other							
Mahadevan (2016)[19]	MN	45	23	22	Yes	Yes	
Cecen (2015)[39]	Trigger Finger	70	35	35		Yes	
Chang (2014)[40]	Scapulothoracic bursitis	36	18	18		Yes	

US: ultrasound, LG: landmark-guided, RA:Rheumatoid arthritis, OA: Osteoarthritis, ACJ: Acromioclavicular joint, BB: Biceps brachii, CTS: carpal tunnel syndrome, MN: Morton's Neuroma

Table 4. Results of the identified trials.

Authors	Assessed outcomes	USGI superiority?
	Multiple targets	
Sibbitt (2011)[21]	Pain VAS at 2 weeks and 6 months, response duration, cost	**Yes**: all outcomes
Cunnington (2010)[17]	Pain VAS, ROM, ESR, CRP, HAQ, EQ-5D, patient-reported effectiveness	**Yes**: better in VAS part of EQ-5D at 2 weeks and in index part of EQ-5D at 6 weeks only
Sibbitt (2009)[20]	Pain VAS (procedural & outcome) at 2 weeks	**Yes**: all outcomes
	Shoulder	
Sabeti-Aschraf (2010)[24]	Pain VAS, AAT and CMS at 1 hour, 1 and 3 weeks	**No**
Zhang (2011)[31]	Pain VAS and CMS at 4 week intervals	**Yes**: all outcomes
Lee (2009)[22]	Pain VAS, ROM, 10-function score weekly for 6 weeks	**Yes**: better at week 1 & 2 in pain VAS and for first 3 weeks in ROM
Dogu (2012)I[16]	ROM, pain VAS (rest, activity, sleep, general), function (ADL, SDQ) at 6 weeks	**No**
Hsieh (2013)[23]	Pain VAS, ROM, SPADI, SDQ, SF36 at 1 week and 1 month	**Yes**: All outcomes
Zufferey (2012)[26]	Pain NRS (rest & activity), ROM, CMS at 2 and 6 weeks	**Yes**: better in night time pain NRS at 2 and 6 weeks
Chen (2006)[30]	ROM at 1 week	**Yes**: all outcomes
Saeed (2014)I[27]	Pain VAS, ROM, shoulder function tests, PGA at 6 and 12 weeks	**Yes**: all outcomes
Naredo (2004)[28]	Pain VAS, ROM, SFA at 6 weeks	**Yes**: all outcomes
Ucuncu (2009)[29]	Pain VAS, ROM, CMS at 6 weeks	**Yes**: all outcomes
Haghigat (2016)[25]	Pain VAS, SPADI, ROM at 6 weeks	**Yes**: better in disability SPADI, abduction and flexion ROM
	Knee	
Sibbitt (2012)[35]	Aspirated fluid volume, successful aspirations, pain VAS (procedural & outcome) at 2 weeks	**Yes**: all outcomes
Sibbitt (2011)[34]	Pain VAS (procedular, injection, outcome) at 2 weeks and 6 months, duration of response, cost	**Yes**: all outcomes
	Wrist	
Nam (2013)[36]	Pain VNS, MMWS, DASHQ, patient satisfaction at 1, 3 and 6 months	**No**
Luz (2008)[15]	Pain VAS, HAQ, DASHQ at 1, 4, 8 and 12 weeks	**No**
	Carpal tunnel syndrome	
Makhlouf (2014)I[37]	Pain VAS (procedural and outcome) at 2 weeks and 6 months, duration of response, total cost & cost per responder	**Yes**: all outcomes

Table 4. Results of the identified trials. *(Continued)*

Authors	Assessed outcomes	USGI superiority?
Ustun (2013)[38]	Boston carpal tunnel questionnaire (symptoms & functional score) at 6 and 12 weeks, procedural pain, time to relief	**Yes**: better in time to symptom relief and symptom severity, but not in functional scores of BCTQ
Plantar fascia		
Chen (2013)l[33]	Pain VAS, TT, SF36 at 3 weeks and 3 months	**Yes**: Pain VAS, TT, plantar fascia thickness and echogenicity
Kane (2001)[32]	Pain VAS, HTI	**No**
Ball (2013)[18]	Pain VAS, HTI, plantar fascia thickness at 6 and 12 weeks	**No**
Other		
Mahadevan (2016)[19]	Pain VAS, MOxFQ-Index, patient satisfaction at 3, 6, 12 months	**No**
Cecen (2015)[39]	Pain VAS and Quinell grading at 6 weeks and 6 months	**No**
Chang (2014)[40]	Pain VAS and Rubin scale at 1, 2, 3 weeks and 3 months	**No**

US: ultrasound, USGI: ultrasound guided injection, VAS: Visual Analogue Scale, CRP: C Reactive Protein, HAQ: Health Assessment Questionnaire, EQ-5D: EuroQoL 5 Dimensions, AAT: Arm Adduction Test, CMS: Constant & Murley Score, ADL: Activities of Daily Living, SDQ: Shoulder Disability Questionnaire, SPADI: Shoulder Pain And Disability Index, SF36: Short Form 36, NRS: Numerical Rating Scale, PGA: Physician Global Activity, SFA: Shoulder Function Assessment, DASHQ: Disability of Arm, Shoulder and Hand Questionnaire, VNS: Verbal Numerical Scale, MMWS: Modified Mayo Wrist Score, BCTQ: Boston Carpal Tunnel Questionnaire, TT: Tenderness Threshold, HTI: Heel Tenderness Index, MOxFQ-Index: Manchester Oxford Foot Questionnaire-Index

weeks post-injection. However, there was statistically significant difference in 2 separate components of self-reported quality of life (VAS score at 2 weeks and index score at 6 weeks of the EQ-5D) favoring the USGI group. Furthermore, USGI were more accurate compared to LGI (83 vs 66%, p=0.01). When comparing the outcomes of accurate versus inaccurate injections, the former were superior at improving function at 6 weeks and showed a statistical trend towards better outcome of function at 2 weeks and pain at 2 and 6 weeks.

Two studies by Sibbit et al. demonstrated significantly better clinical outcomes of USGI versus LGI in large cohorts of patients with rheumatoid/osteoarthritis[20] and inflammatory arthritis,[21] injecting a variety of joints. Despite their relatively large sample size (148 and 244 injections, respectively), both studies lack in design quality scoring 2 on the Jadad scale. Both trials showed better outcomes for USGI vs LGI for post-injection pain as measured by VAS at 2 weeks and 6 months in a hospital outpatient setting. As a side aspect, the authors also suggest greater cost effectiveness of USGI by showing that USGI resulted in longer time to repeat injections or referral for surgery compared to LGI. Procedural pain was also found to be less with USGI compared with LGI.

Shoulder

The shoulder is the most investigated target area in the USGI versus LGI comparison in the identified trials. In 8 studies, the injection was aimed to the SAB, while the GHJ, the BB and the ACJ were the targets in 1 trial each.

In a high-quality study (Jadad score 5), Dogu et al.[16] used sham-US to blindly randomise 46 patients to two treatment groups, a pre-injection MRI scan to ensure the diagnosis of subacromial impingement and a post-injection MRI to assess for accuracy. A blinded outcome assessor was also used. The authors con-

cluded that there was no significant difference between USGI and LGI in both subjective (pain VAS, functional score) and objective (ROM) outcomes at 6 weeks. Of note, when the two groups were compared for accuracy of the injections assessed by MRI, they did not differ significantly (USGI: 65.2% vs LGI: 69.5% accurate). Furthermore, the comparison between accurate and inaccurate injections also showed no efficacy differences in pain, function or ROM.

In another study[22] that also used sham-US in patients with adhesive capsulitis injected with a combination of steroids and hyaluronate in the GHJ, the improvement in pain and ROM was greater in the USGI group for the first 2 weeks for pain VAS and 3 weeks for ROM. After the third week, the outcomes did not differ between the 2 groups for the rest of the 6-week follow up; indicating an earlier treatment advantage for USGI. In their 2013 study of 96 patients with subacromial bursitis, Hsieh et al.[23] found that USGI were better than LGI only in passive abduction ROM and the physical functioning and vitality components of the SF-36 at 1 week and 1 month post-injection, but not in pain VAS, shoulder disability or active abduction ROM. A small study[24] comparing the 2 techniques in injecting symptomatic ACJs investigated differences in pain VAS, ROM (Arm Adduction Test) and function (Constant Murley score). Both sonographic and landmark guidance of steroid injections improved the aforementioned measurements at 1 hour, 1 week and 3 weeks after the procedure, but no significant differences between the 2 groups were noted.

Function and abduction-flexion ROM improvements, but not pain VAS and rotation ROM, were significantly higher in the USGI group of a trial in patients with shoulder impingement syndrome.[25] In the remaining studies, USGI proved to be more efficacious than LGI in all outcomes. Notably, none of these trials assessed the accuracy of injections and/or used sham-US for effective patient blinding. Zufferey et al.[26] reported on the USGI improving clinical outcomes, both in terms of pain at rest and in functional outcomes, when used in the setting of the acutely painful shoulder and aimed at the identified site of pathology in comparison to LGI performed with the SAB as a blind target. In chronic shoulder pain, USGI was associated with significantly greater improvement in pain, function and ROM outcomes in studies from Ireland,[27] Spain,[28] and Turkey.[29] Shoulder abduction ROM improvement was also shown to be greater with USGI in a 2006 trial.[30] Finally, US guidance increased both pain and function outcomes in isolated BB tendinitis, reducing the need for repeated steroid injections.[31]

Plantar Fascia

A high quality trial[18] evaluated injection outcomes in patients with inferior heel pain. While steroid injections were superior compared to placebo, the authors identified no significant differences in pain VAS, heel tenderness index (HTI; a qualitative assessment of tenderness on palpation by the physician) and plantar fascia thickness at 6 and 12 weeks post-injection, in the arms that compared USGI (22 patients) to LGI (21 patients). In a small 2001 study, Kane et al.[32] were also not able to show better clinical outcomes of USGI for scintigraphy proven plantar fasciitis compared to LGI. In 24 studied plantar fascia injections, no significant differences were observed in pain VAS and HTI in the two groups 6 weeks after the injections, as both groups improved with overall response rates (50% reduction in VAS and/or HTI) of 93% and 80% respectively. In contrast, a trial investigating the effectiveness of device-assisted USGI in plantar fasciitis[33] reported better outcomes in the USGI group. There was a greater increase in tenderness threshold at 3 weeks (8.63 vs 7.28 kg/cm^2) and 3 months (9.02 vs 7.18 kg/cm^2) and a greater reduction in pain VAS at 3 months (1.88 vs 3.63 cm) post injection. Furthermore, the authors noted that the incidence of hypoechoic plantar fascia and atrophic heel pad was significantly less in the USGI group at the 3-month follow-up, indicating less disruption in the mechanical properties of the plantar fascia with sonographic guidance.

Knee joint

The efficacy of the 2 injection techniques in improving clinical outcomes in the knee joint was compared in 2 high-risk for bias trials by Sibbit et al. In the first,[34] 94 patients with non-effusive knee osteoarthritis were randomized between LGI and USGI. Ultrasound-guided injection performed better in pain reduction measured with VAS during needle insertion, during the injection and at 2 weeks post-injection; offering absolute differences of 48%, 52% and 42% respectively. The duration of therapeutic effect was also determined to be significantly increased by a mean of 1.1 month (36%). Furthermore, USGI reduced the cost by patient per year and by responder per year in a hospital outpatient setting. In 2012, the same authors[35] investigated the effect of sonographic guidance in injecting effusive knee joints in patients with rheumatoid arthritis and osteoarthritis. Ultrasound-guided injections significantly reduced procedural pain by 48%, increased aspirated fluid volume by 183% and improved pain outcome at 2 weeks with greater VAS reduction.

Wrist joint

Neither of the 2 studies comparing injections in the wrist joint under sonographic and landmark guidance

showed significant differences in outcome between the 2 techniques. Luz et al.[15] injected 60 wrist joints in patients with rheumatoid arthritis after randomizing them between USGI and LGI and blindfolding them prior to injection. The measured subjective outcomes, including pain VAS, HAQ and Disability of Arm, Shoulder and Hand Questionnaire (DASHQ) scores did not differ significantly between the 2 groups at 1, 4, 8 and 12 weeks. Interestingly, there was no difference in the accuracy of injections between the 2 groups (90% accuracy). In a more recent trial[36] of 57 patients with distal radio-ulnar joint pathology, sonographic guidance was not significantly better than LGI at 1, 3 and 6 months post injection in a primary composite outcome of VNS pain, DASHQ and patient satisfaction (Likert scale) or a secondary outcome of wrist function, even though USGI were more accurate than LGI (100% vs. 75.8%) and accurate injections were superior in clinical outcomes as described above.

Carpal tunnel syndrome

The impact of sonographic guidance on clinical outcome of injections for carpal tunnel syndrome (CTS) was investigated in 2 recent trials. Makhlouf et al.[37] compared the efficacy of steroid USGI to LGI in 77 wrists with CTS symptoms. Ultrasound-guided injections were shown to be superior in all measured outcomes, both in intermediate- and long-term follow-up. Ultrasound-guided injections were associated with 63.3% less pain in 2 weeks and 38.6% greater reduction in pain scores from baseline, 93.5% increase in responder rate and 49.1% less pain at 6 months. Ultrasound guidance prolonged the therapeutic effect of injections by 71%, increasing time to next procedure by 30%. In a small Turkish study,[38] a symptom and function questionnaire (Boston Carpal Tunnel Questionnaire, BCTQ) and the time to symptom relief were used to assess the 6- and 12- week efficacy of USGI versus LGI in symptomatic CTS. Ultrasound-guided injections were superior to LGI in time to symptom relief (4.11 vs 6.23 days) and the symptom severity component of the BCTQ, but no differences were observed in the functional score. Interestingly, USGI were also shown to be less painful than LGI in patients with CTS; procedural pain was significantly lower in the first trial (34% less needle introduction pain, 77.1% less injection pain) and the same trend was exhibited in the second, but did not reach statistical significance.

Other targets

The trials assessing injections of other joint targets failed to show superiority of USGI versus LGI. In a recent high quality study[19], USGI was not superior to LGI in patients with **Morton's neuroma**, although there was a trend towards better function and patient satisfaction results in 3 months post-injection. Cecen et al.[39] used pain VAS and Quinell grading (qualitative assessment of finger locking) to compare the efficacy of USGI and LGI in 70 symptomatic **trigger fingers** at 6 weeks and 6 months after a steroid injection. Symptomatic improvement was noted at both time points in the 2 groups, but no significant differences were observed between them. Finally, Chang et al.[40] randomized 36 patients with disabling scapular pain (**scapulothoracic bursitis**) to receive either an US-guided intramuscular subscapularis injection or a blinded scapulothoracic bursa injection. The primary outcome, which was the reduction in the VAS of pain in the scapular area, did not differ significantly between the two techniques at any of the time points (i.e., 1, 2, 3 weeks and 3 months post-injection), suggesting equal efficacy.

Discussion

In general, joint and soft tissue injections are a frequently used clinical tool for rheumatologists, orthopedic surgeons and general practitioners in chronic disease management. Steroid injections, in particular, are thought to provide benefit in symptom relief with various possible mechanisms; i.e. anti-inflammatory effect, increased synovial fluid viscosity, reduced synovial perfusion, reduced joint temperature.[41] Other injectable agents, such as hyaluronic acid viscosupplementation, may have beneficial effects in pain and function in certain diagnoses.[42]

Computerized tomography (CT), magnetic resonance imaging (MRI) and fluoroscopy are some of the imaging techniques that have been used to increase the accuracy of joint injections. However, US is a practical, quick, widely available and radiation-free alternative. The published literature offers support on the increased accuracy of USGI, as several trials have demonstrated their superiority in several joint targets,[17,43] such as the shoulder,[44] the knee,[32,45] the hip,[10,46] the DRU[36] and other targets.[17,28] This is also supported by recent meta-analyses and systematic reviews.[11,47] While the issue of improved accuracy of USGI seems to be widely accepted, the question as to whether sonographic guidance of injections offers better clinical outcomes over palpation-guided injections still remains unanswered.[48,49]The purpose of this article was to try to answer this question by systematically reviewing the current literature.

Overall, 16 of the 26 identified trials (61.5%) showed greater efficacy of the USGI when compared to LGI for one or more outcome measures. When categorizing the results per injection site, the shoulder was the most investigated joint target. Of the identified trials, 82% (9/11) demonstrated superiority of the USGI over the LGI technique, both in terms of patient- and of physician-reported outcomes. In 7 out of 11 of the RCTs, a 6-week time point for assessment among others was

used, indicating good mid-term efficacy overall. Furthermore, the comparison between the two techniques was in favour of sonographic guidance in the majority of the trials assessing multiple joint targets, knee and carpal tunnel area. On the contrary, most of the plantar fascia studies and none of the RCTs examining wrist injections were able to ascertain benefit of the USGI technique, as was the case for MN, FTS and STB injections.

Whilst this crude analysis may suggest, at least for some indications, the superiority of USGI over LGI, there remain significant gaps in the published evidence base to allow firm conclusions. For instance, the three trials with the highest methodological quality as assessed by maximum Jadad scores of 5 failed to convincingly demonstrate improved clinical outcomes from USGI compared to LGI in terms of pain in the plantar fascia[18] and multiple target joints,[17] as well as both pain and function in the shoulder.[16] A possible explanation for this observation may lie in the comparison of accuracy between the two techniques. The accuracy of subacromial injection, as determined by MRI, was similar in both groups in the study by Dogu et al.[16] and relatively low for US guidance (15/23 in the USGI and 16/23 in the LGI group), possibly indicating either a relatively competent injector for LGI or inexperienced injector for USGI. This may explain why outcome could perhaps not be expected to be superior in the USGI group. In the trial by Cunnington et al.,[17] USGI were more accurate than LGI (83% vs 66% respectively) and this was mainly true for the shoulder, elbow and ankle targets. In individuals with accurate injections, patient VAS score for function at 6 weeks (but not 2 weeks) was better. Also, a trend towards improvement in VAS for function at 2 weeks and VAS for pain at 2 and 6 weeks was noted. However, the improved accuracy of USGI failed to translate into statistically significant superiority versus LGI in any of the primary outcome parameters; no outcomes other than the EQ- 5D-related VAS score at 2 weeks and index scores at 6 weeks were superior in the USGI group. Possible reasons for this could be the variance in joint targets, as well as the fact that the trial was not powered to detect differences in accuracy within individual joints between the two techniques.

In addition to these two low risk-of-bias studies, two further identified studies verified accuracy of injection by an independent method: a study by Nam et al.[36] found superior accuracy of USGI into the distal radioulnar joint vs LGI, but this did not lead to improved outcome. A study comparing USGI vs LGI to wrist joints in RA patients[15] found similar and high accuracy rates in both groups and no significant difference in outcome. In summary, these studies verifying accuracy of USGI/LGI independently suggest that, while USGI can be expected to improve accuracy in cases where it is lower with LGI, it has yet to be shown in suitably powered studies to lead to improved outcome of pertinent measures such as pain. Where accuracy is already high with LGI, it (and with it, the outcome) is unlikely to be improved further through US-guidance. It is also important to be aware that there is evidence from placebo-controlled randomized trials for certain conditions, such as rotator cuff impingement, that accuracy may matter very little in that an intramuscular gluteal injection of glucocorticoids may produce improvement that is non-inferior to an USGI of the subacromial space.[50]

Although this was not a specific object of this review, we noted that the issue of procedural pain was examined in 6 trials.[20,21,34,35,37] In all but one of these trials, the USGI technique was associated with significantly less pain during the procedure of the injection. In the remaining one,[38] a similar trend was observed, but it did not reach statistical significance. However, none of these trials used sham-US in their design and this affects their bias risk. The authors postulated that better control and direction of the needle, avoidance of pain-sensitive structures and nerve damage, less haemorrhage and patient's distraction while looking at the US image might be possible explanations of this finding.

An effort to perform a meta-analysis of the identified data would meet several obstacles. For instance, the comparison of USGI to LGI is inherently in high risk for bias, on account of factors related to the presence and use of US that may interfere with patient-reported outcomes. Some of them are the reduction in pain by the distraction at a neurocognitive level caused by the US image, the patient's belief that the injection is more accurate on account of image acquisition, the cooling effect of the gel and/or the pressure of the transducer. Sham-US-guided controls and blinding of subjects were absent in most studies, thus increasing the risk for this bias, as reflected in overall low Jadad scores. In addition, the studies varied significantly in the used measures of clinical efficacy, mainly in terms of function of the targeted structures. Furthermore, inconsistencies in the clinical experience and competence of the physician performing the USGI or LGI, as well as the differences in the medication used and the site targeted, even in the same joint (the different structures of the shoulder for example), reduce the ability for comparison between the studies.

Our systematic review has certain limitations. We used only one, albeit the largest available, of the current literature databases and we did not include non-English language, which could have resulted in omitting evidence found in trials of other databases or languages.

In conclusion, we have shown that the quality of available evidence comparing USGI versus LGI for rheuma-

tological conditions remains limited. While the majority of the trials suggest and conclude that the use of US might improve the clinical efficacy and outcome of intra- and peri- articular injections for several anatomic sites (e.g. the shoulder, the knee and the carpal tunnel area), better quality studies and studies that have found similar accuracy rates of LGI vs USI, fail to show clear superiority of the USGI on clinical outcomes. We would postulate that there continues to be a need for high-quality studies to answer the hypothesis that USGI injections are superior to LGI in clinical outcomes. Finally, we would suggest that such studies have the following design: a clear case definition, ideally using imaging as well as clinical criteria; clinically meaningful subjective and objective outcome criteria, ideally with known minimal clinically important differences; adequate study power; the use of sham-US for LGI and an independent outcome assessor for objective outcome measures to ensure adequate blinding; and finally, an independent method to ascertain accuracy in all intervention groups.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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