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Are corticosteroid injections more beneficial than anaesthetic injections alone in the management of rotator cuff related shoulder pain? A systematic review.

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Title Page

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Are corticosteroid injections more beneficial than anaesthetic injections alone in the management of rotator cuff related shoulder pain? A systematic review.

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Key words: Shoulder, rotator cuff, injections, corticosteroids, anaesthetics

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ABSTRACT

Objective: To compare the effectiveness of corticosteroid injections to local anaesthetic injections, in the management of rotator cuff-related shoulder pain (RCRSP).

Design: Systematic review with best evidence synthesis.

Data sources: The Cochrane, PubMed, CINAHL Plus, PEDro and EMBASE electronic databases were searched (inception until 08/06/2017). Reference lists of included articles were also hand searched.

Eligibility criteria: Two reviewers independently evaluated eligibility. Randomised controlled trials were included if they compared subacromial injections of corticosteroid with anaesthetic injections. Two reviewers independently extracted data regarding short-, mid- and long-term outcomes for pain, self-reported function, range of motion and patient-perceived improvement.

Results: Thirteen RCTs (n=1013) were included. Four trials (n=475) were judged as being at low risk of bias. Three studies of low risk of bias favoured the use of corticosteroid over anaesthetic-only injections in the short-term (up to 8 weeks). There was strong evidence of no significant difference between injection types in mid-term outcomes (12-26 weeks). There was limited evidence of no significant difference between injection types in long-term outcomes.

Conclusion: Corticosteroid injections may have a short-term benefit (up to 8 weeks) over local anaesthetic injections alone in the management of RCRSP. Beyond 8 weeks, there was no evidence to suggest a benefit of corticosteroid over local anaesthetic injections.

Trial registration number: PROSPERO CRD42016033161.

What are the new findings?

- Corticosteroid injections may confer superior benefit compared to anaesthetic-only injections in the short term (up to 8 weeks).
- Beyond 8 weeks, corticosteroid and anaesthetic-only injections had the same therapeutic effect for rotator cuff-related shoulder pain
- It is unknown if improvement over time is due to placebo, natural history or a therapeutic effect of the medicines used in the published research

How might these findings inform clinical practice in the future?

- Both corticosteroid and anaesthetic-only injections may have short-term benefit for people considering injection therapy for rotator cuff-related shoulder pain
- Corticosteroid injections may have a superior short-term therapeutic effect compared to anaesthetic-only injections, but not beyond that time point.
- The medium- and long-term effects of corticosteroid and anaesthetic injections are equivocal

BACKGROUND

Shoulder pain is a common musculoskeletal disorder with prevalence estimates ranging from 6.9 to 26.0% for point prevalence, annual prevalence; 4.7 to 46.7%, and lifetime prevalence; 6.7 to 66.7%.(1) Prevalence increases with age(2) and shoulder pain is frequently associated with long term disability.(3-5) Injection therapy is a common intervention for musculoskeletal shoulder pain and is administered in primary and secondary care. In the United Kingdom, general practitioners (GPs) administer corticosteroid (CS) injections to approximately 1 in 10 people presenting with shoulder pain in primary care.(3) Injection therapy for shoulder pain is also performed by physiotherapists, orthopaedic surgeons, rheumatologists, radiologists, sports and exercise medicine doctors and others, in primary and secondary care, as well as in private settings. However, the definitive number of people receiving CS injections for musculoskeletal shoulder conditions remains unknown.

Rotator cuff-related shoulder pain (RCRSP)(6) is an over-arching clinical term and includes a number of other conditions: subacromial impingement syndrome,(7) subacromial pain syndrome (8) and rotator cuff tendinopathy.(9, 10) In addition to local tissue pathology, persistent pain associated with RCRSP may be related to altered processing and output of the central nervous system.(11, 12) Education, advice and exercise are the most common treatments for RCRSP(6) and have comparable results to surgery.(6, 13) Another very common treatment for this condition, is injection therapy, which typically involves injections of corticosteroid in isolation, or more commonly, mixed with anaesthetic(14) into the subacromial space.(15) For patients with RCRSP, corticosteroid, or corticosteroid and anaesthetic preparations are often administered for treatment (3) and anaesthetic injections alone are used for diagnosis, in a procedure known as the Neer impingement test.(7)

Although corticosteroid injections for RCRSP are common, the definitive mechanism of action is uncertain, with suggestions they may have an anti-inflammatory role,(16) reduce tenocyte numbers(17) and inhibit nociceptor activity.(18) There is also uncertainty regarding clinical effectiveness with previous reviews suggesting their benefit maybe unclear,(19, 20) short-lived,(21-23) no greater than non-steroidal anti-inflammatories,(21, 22) or beneficial for up to 9 months.(24) In addition, there is emerging evidence linking the use of corticosteroid injections with negative effects on rotator cuff tissue.(25-27) Due to these risks, anaesthetic-only injections (although not devoid of risk) might, when deemed appropriate, be considered a reasonable alternative to corticosteroid in the management of RCRSP.(6) A recently published meta-analysis assessed short-term outcomes and concluded that corticosteroid injections provide, at best, a minimal transient pain reduction in a small number of patients with rotator cuff tendinosis.(23)

No previous review has directly compared corticosteroid alone, or corticosteroid and anaesthetic injections, with local anaesthetic-alone injections in the treatment of RCRSP. A comparison of this nature is relevant for a number of reasons, including the common use of injection therapy in the

management of RCRSP,(3) as well as: (i) the potential comparable clinical effectiveness of these medicines,(14) and (ii) the potential deleterious effect of corticosteroid on tendon tissue.(26)

To inform the shared-decision making process, those seeking and providing treatment for RCRSP, would be better informed with more knowledge on injection therapy, especially comparing the most commonly performed procedures (corticosteroid alone, or corticosteroid and anaesthetic injections, with local anaesthetic alone injections) in the management of RCRSP. Therefore, the aim of this review was to compare these pharmacological preparations in the management of RCRSP, for clinical effectiveness (symptoms, range of movement and function) in the short-, medium- and long-term.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane collaboration guidelines were followed.(28-30) PROSPERO registration number: CRD42016033161.

Population. Inclusion criteria: Studies with adult participants diagnosed with RCRSP were included.(6) Exclusion criteria: Participants with non-RCRSP shoulder conditions such as shoulder dislocation or instability, fractures, rheumatological conditions or frozen shoulder. Also, people who had undergone previous surgery, as well as those with confirmed full thickness rotator cuff tears.

Intervention/control. Inclusion criteria: Randomised clinical trials. Studies were included if they compared groups receiving single or repeated: subacromial injections of corticosteroid with or without local anaesthetic, versus local anaesthetic injection without corticosteroid. Concurrent prescription of exercise therapy, as well as prescription of pain relieving medications, such as analgesics and non-steroidal anti-inflammatory drugs (NSAID's), were permitted inclusions, as this reflects common clinical management of RCRSP.(6, 31)

Exclusion criteria: In the treatment of RCRSP, the subacromial space is the most common target for injections and investigations of injection therapy that did not solely target this region(32, 33) were excluded. Other injection procedures, such as barbotage, were also excluded.

Outcome: Outcome measures included shoulder pain, self-reported function, range of motion (ROM) and patient-perceived improvement. Follow-up time post intervention was defined as short-term (less than 3 months), mid-term (3-12 months), and long-term (a year or longer).(34)

Data Sources: The Cochrane Library, PubMed, EMBASE, PEDro and 'CINAHL plus' databases were searched from inception to June 8th, 2017 by two independent reviewers (TC and MM). No language, date or publication restrictions were applied. Search terms included "shoulder", "impingement", "subacromial", "injections", "corticosteroid", and "local anaesthetic". These terms were linked broadly to the PICO elements for the review question (population, intervention, comparators, and outcome) (Table 1).

The reference lists of retrieved articles, including previous systematic reviews, were assessed for additional study titles and relevant publications; including, articles not identified in the search, personal communications, books and book chapters. None were identified.

Table 1: Search strategy for the review

Sources, searches and search terms	Total yield/hits (number of new/ relevant records)
Pubmed: (subacromial pain syndrome OR shoulder pain OR shoulder impingement syndrome OR subacromial impingement OR subacromial bursitis OR burs* OR rotator cuff tendin* OR impingement OR tendin* OR tendon OR subacromial OR shoulder) AND (Injection therapy OR injectio*) AND (Steroid OR corticosteroid) AND (local anaesthetic OR anaesthetic OR anesthetic) AND (pain OR function)	286 (286)
The Cochrane Library: Browsed by topic – musculoskeletal, search narrowed-shoulder, search narrowed-injection	8 (0)

EMBASE: (subacromial pain syndrome OR shoulder pain OR shoulder impingement syndrome OR subacromial impingement OR subacromial bursitis OR burs* OR rotator cuff tendin* OR impingement OR tendin* OR tendon OR subacromial OR shoulder) AND (Injection therapy OR injectio*) AND (Steroid OR corticosteroid) AND (local anaesthetic OR anaesthetic OR anesthetic) AND (pain OR function)	236 (0)
PEDro: "shoulder pain AND injection", "shoulder AND steroid"	80 (0) 34 (0)
CINAHL plus: (subacromial pain syndrome OR shoulder pain OR shoulder impingement syndrome OR subacromial impingement OR subacromial bursitis OR burs* OR rotator cuff tendin* OR impingement OR tendin* OR tendon OR subacromial OR shoulder) AND (Injection therapy OR injectio*) AND (Steroid OR corticosteroid) AND (local anaesthetic OR anaesthetic OR anesthetic) AND (pain OR function)	58 (0)
Hand searches of relevant reference lists	5 (1)
Total:	287

Study selection: Studies that were not randomised controlled trials (RCTs) were excluded from the review. Selection of studies was independently performed by two reviewers (TC and MM). Where full-text manuscripts were not accessible, the corresponding authors were contacted. If there was no reply or the full text was not available, the study was excluded from this review. Following this process (and after a one month wait) two studies were excluded from the review as only abstracts of these studies have been published.(35, 36) Two eligible studies (37, 38) not published in the English language were professionally translated into English by bi-lingual members of the Cochrane collaboration.

Data extraction: Data were independently extracted by two reviewers (TC and MM) using the Cochrane data extraction form for RCT intervention reviews (http://training.cochrane.org/resource/data-collection-forms-intervention-reviews). Any discrepancies in this process were resolved by discussion between the two reviewers, followed by reassessment of the data. A system to resolve any disagreements was established a priori via discussion with a third reviewer (JL), but no such discrepancies occurred. Data extraction for the two non-English studies were performed by the bi-lingual members of the Cochrane collaboration.

Risk of bias assessment: Two reviewers independently assessed risk of bias using the domain-based Cochrane tool for RCTs (see Table 2 and Figure 2). Trials were evaluated as low risk of bias if all individual criteria were low, and high if at least one was rated as high (and that criterion was deemed by the reviewers to introduce bias).

For further information on this tool please refer to the Cochrane collaboration handbook (39). Exceptions were made if a study was rated as high risk of bias in a particular criterion, but that it was judged by the reviewers not to have affected the overall risk of bias. For example, if a clinician performing the injections in a study was not blind to the treatment but the patient was blinded, and blind outcome assessment was used then the overall risk of bias would be scored as low. Items rated as unclear raised risk of bias.(39) An overall risk of bias rating for each trial was agreed by two reviews (TC and MM). Table 3 details pharmacological information and injection method relating to the studies deemed to be at low risk of bias. A system to resolve any disagreements was established a priori via discussion with a third reviewer (JL). Three such disagreements occurred during the risk of bias assessment and consensus was agreed by discussion following review of the data. Further discussion with the third reviewer was therefore not required.

Data extraction and risk of bias assessment procedures were pilot-tested by TC and MM on three similar articles prior to the formal review process.(40) A Cohen's Kappa coefficient was used to assess inter-rater reliability for judgement of high and low risk of bias for each criterion. The number of agreements was 36/39 (92.31%) with a Kappa score of 0.836 and thus the level of agreement was considered strong.(41)

Data syntheses:

The studies included in our review utilised different medications, doses and outcome measures (see supplementary Table 1). Due to these confounding variables, a decision not to pool data to perform a meta-analysis was reached. Instead, we used best evidence synthesis to synthesise the results following data extraction and assessment of risk of bias. Textual descriptions of studies were written

to aid the synthesis of findings, and tables were used to present study characteristics, data extraction and risk of bias assessments. Studies were grouped in accordance with their level of risk of bias in order to identify those assessed as having the highest level of internal validity.

. The best evidence synthesis was based on the quality of the studies reviewed (43):

- **Strong evidence** – provided by generally consistent findings in multiple high quality RCTs;
- **Moderate evidence** – provided by generally consistent findings in one high quality RCT plus one or more low quality RCTs, or by generally consistent findings in multiple low quality RCTs;
- **Limited or conflicting evidence** – only one RCT (either high or low quality) or inconsistent findings in multiple RCTs
- **No evidence** – no RCTs

To guide clinical recommendations, studies were combined in relation to their outcome timescales(34) and whether their results favoured corticosteroid, local anaesthetic or neither injection type.

RESULTS

The electronic database search, performed on June 8, 2017, identified 287 potentially eligible articles. Ultimately, 13 full-text studies were included in this systematic review and seven studies were excluded.(35, 36, 44-48) Figure 1 details the PRISMA flow chart.

Figure 1 near here

Table 2: Quality appraisal and assessment of risk of bias (Furlan et al., 2015) (40)

Study/source of bias	Was the method of randomisation adequate?	Was the treatment allocation concealed?	Was the patient blinded to the intervention?	Was the care provider blinded to the intervention?	Was the outcome assessor blinded to the intervention?	Was the drop-out rate described and acceptable?	Were all randomised participants analysed in the group to which they were allocated?	Are reports of the study free of suggestion of selective outcome reporting?	Were the groups similar at baseline regarding the most important prognostic indicators?	Were co-interventions avoided or similar?	Was the compliance acceptable in all groups?	Was the timing of the outcome assessment similar in all groups?	Other sources: Power analysis?	Other sources: Validated outcome measure?	Other sources: Conflict of interest declared?	Overall risk of bias rating
Petri 1987 (50)	+	?	+	+	+	+	+	+	+	+	+	-	-	?	HIGH
Adebajo 1990 (49)	+	?	+	-	+	+	+	+	+	+	+	-	VAS	?	HIGH
Vecchio 1993 (57)	+	?	?	?	+	+	-	+	+	+	+	-	VAS	?	HIGH
Blair 1996 (58)	?	?	+	+	+	+	?	+	+	+	+	-	-	NO	HIGH
Strobel 1996 (38)	?	?	?	?	?	-	-	?	?	+	+	+	-	?	?	HIGH
Plafki 2000 (51)	+	?	?	?	+	-	-	-	+	+	-	+	-	+	NO	HIGH
McInerney 2003 (56)	+	+	-	-	+	+	+	+	+	+	+	+	+	VAS	?	HIGH
Akgun 2004 (53)	+	?	+	-	+	+	+	+	+	+	+	+	-	+	?	HIGH
Alvarez 2005 (14)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	NO	LOW
Alvarez-Nemegyei 2008 (37)	+	?	+	+	+	-	?	+	?	+	+	+	-	+	NO	HIGH
Watson 2008 (55)	+	+	+	-	+	+	+	+	+	+	+	+	+	+	YES	LOW
Hong 2011 (52)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	NO	LOW
Penning 2012 (54)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	NO	LOW

Legend: + = YES, - = NO, ? = Unclear. VAS = Visual analogue scale (for pain), In relation to conflict of interest - an answer of "YES" would indicate a potential high risk of bias and the opposite for an answer of "NO").

Table 3: Characteristics of low risk of bias studies included in the review (n=4)

Study (reference)	Number of Participants (Male/Female) [Mean age-years] {Mean duration of Symptoms}	Interventions	Outcome measures	Findings
Alvarez 2005 (14) **(Canada)**	58 (31M/27F) [48.0 years] **[Group 1** – 46.0] **[Group 2** – 50.0] {3 years}	**Group 1** – Blind SA injection 5 ml 2% xylocaine **Group 2** – Blind SA injection 4ml 2% xylocaine + 1ml (6mg) betamethasone	**Western Ontario Rotator cuff index** (0-100, 0=best score, 100=worst score).	No statistically significant difference between groups at 3 and 6 months. Mean **WORC** at 12 weeks: **Group 1**: 45.4, **Group 2**: 56.3 (p=0.13) Mean **WORC** at 6 months: **Group 1**: 51, **Group 2**: 59 (p=0.38)
Watson 2008 (55) **(UK)**	179 (83M/96F) [59.0 years} Individual group figures not reported {7 weeks}	**Group 1, 3 and 5** – Blind SA injection 1 ml 1% lidocaine **Group 2, 4, 6** – Blind SA injection 1 ml (40 mg) triamcinolone	**British shoulder disability questionnaire** (0-23, 0=no disability, 23=severe disability). **Short form 36 item** (higher score=better outcome).	Statistically significant improvement at 4 weeks in Group 2, 4 and 6 for BSDQ (p=0.026). Specific data were supplied by the author on written request. There was no statistically significant difference between groups at 3 and 6-12 months. Over course of trial (4 weeks, 12 weeks and 1year) mean: **BSDQ: Group 1, 3 and 5**: 11.7, 8.1, 6.4, **Group 2, 4, 6**: 10.3, 8.7, 7.3 (S.E = 0.48) **SF-36 MCS: Group 1, 3 and 5**: 46.4 47.7, 47.2, **Group 2, 4, 6**: 45.8, 45.9, 47.7(S.E = 0.78) **SF-36 PCS: Group 1, 3 and 5**: 39.6, 41.4, 42.9, **Group 2, 4, 6**: 41.4, 41.0, 42.5 (S.E = 0.63)
Hong 2011 (52) **(Republic of Korea)**	79 (32M/47F) [50.1 years] **[Group 1** – 50.8] **[Group 2** – 48.6] **[Group 3** – 51]	**Group 1** - US guided SAB injection 4 ml (40mg) triamcinolone **Group 2** – US guided SAB injection 2ml (20 mg) triamcinolone + 2 ml 1% lidocaine **Group 3** – US guided SAB injection 4ml 1% lidocaine	**Shoulder disability questionnaire** (0-22, 0=no disability, 22=maximal disability) **Pain VAS** (0-10, 0=no pain, 10=severe pain)	Group 1 and 2 had statistically significant improvement in both outcomes at 8 weeks, compared to Group 3: Mean improvement in outcomes from baseline at 8 weeks (higher number=better improvement): **SDQ: Group 1**: 5.7, **Group 2**: 5.6, **Group 3**: 0.9 (p<0.001). **VAS: Group 1**: 3.5, **Group 2**: 2.8, **Group 3**: 0.6 (p<0.001).

	{11 months}			
Penning 2012 (54) **(The Netherlands)**	159 (M75/84F) [53 years] **[Group 1** – 53] **[Group 2** – 52] **[Group 3** – 54] **{6 months}**	**Group 1** - Blind SA injection 8 ml 1% lidocaine + 2ml hyaluronic acid **Group 2** – Blind SA injection 8ml 1% lidocaine + 2ml (20 mg) triamcinolone **Group 3** – Blind SA injection 8ml 1% lidocaine + 2ml sodium chloride 0.9%. All injections repeated at 1, 3 and 6 weeks as needed.	**Shoulder disability questionnaire** (0-100, 0=no disability, 100=maximal disability) **Pain VAS** (0-10) **Constant score** (0-100, 0=poor function, 100=full function) **Functional mobility test** (4-28, 4= normal function, 28=poor function) **Shoulder pain score** (7-28, 7=no pain, 28=severe pain) **Patient specific disability score** (0-10, 0=no disability, 10-severe disability)	Group 2 had a statistically significant improvement in all outcomes compared to Group 1 at 3 ($p=0.004$), 6 ($p<0.001$) and 12 ($p<0.001$) weeks and compared to Group 2 at 6 weeks ($p=0.006$). There was no significant difference in outcome between Group 2 and 3 at 3, 6 and 12 weeks. There was no statistically significant difference between all 3 groups 26 weeks. Mean improvement in outcomes from baseline at 3, 6, 12 and 26 weeks (higher number=better improvement): **SDQ: Group 1:** 0.1, 9.8, 11, 12.4, **Group 2**: 16.1, 22.6, 27.3, 23.2 **Group 3**: 6.3, 13.2, 15, 17 **VAS**: **Group 1:** 0.3, 0.7, 0.7, 1.8**, Group 2**: 1.6, 2.6, 2.7, 2.1, **Group 3**: 0.8, 1.6, 2.3, 2.4 **Constant: Group 1:** 0.1, 2.6, 3.4, 4.9, **Group 2** – 3.6, 7, 6.4, 4.6, **Group 3**: 2.5, 4.7, 5.1, 9.2 **FMT: Group 1:** 0.3, 1.0, 1.2, 1.3, **Group 2**: 1.2, 1.9, 2.4, 1.6, **Group 3**: 0.6, 1.1, 1.8, 2.4 **SPS: Group 1:** 1.2, 3.1, 2.9, 3.7, **Group 2:** 3.8, 5.8, 5.4, 5.1, **Group 3**: 2.3, 3.9, 4.2, 4.6 **PSD: Group 1:** 0.5, 1.4, 1.3, 1.7, **Group 2:** 1.4, 2.4, 2.3, 1.9, **Group 3**: 1.6, 2.2, 2.1, 2

Key: ROM = range of motion, M = Male, F = Female, SA = Subacromial, SAB = Subacromial bursal, Blind = landmark-guided, US = Ultrasound, VAS = Visual analogue scale, ABD = abduction, ER = External rotation, Flex = flexion, TR = Total resisted movement score, S-SDQ = Spanish shoulder disability questionnaire, BSDQ = British shoulder disability questionnaire, SF-36 MCS = Short form 36 item mental component score, SF-36 PCS = Short form 36 item physical component score, SDQ = Shoulder disability questionnaire, EQ-5D = EuroQol, FMT = Functional mobility test, SPS = Shoulder pain score, PSD = Patient specific disability score, WORC = Western Ontario rotator cuff index, SE = Standard Error.

Figure 2 near here

Short-term comparisons (0-12 weeks):
Twelve studies assessed short-term (0-12 weeks) outcomes of injection therapy for RCRSP. Five of the twelve studies, four of high risk of bias(38, 49-51) and one of low risk of bias(52) reported in favour of corticosteroid injections for a range of different outcome measures (Table 3).
Three further studies, one of high risk of bias (53) and two of low risk of bias (54, 55) reported improvements in the first 4-6 weeks in favour of corticosteroid, but reported no significant difference between groups at 12 weeks. The remaining four studies; three of high risk of bias(37, 56, 57) and one of low risk of bias(14) reported no significant difference in short-term outcomes between the two types of injection therapy at any time-point.
In summary, three trials(52, 54, 55) (n=417) of low risk of bias favoured corticosteroid injections for the first 4-8 weeks post injection and one trial(14) of low risk of bias (n=48) found no difference between the two types of injection.

Mid-term comparisons (13-26 weeks):
In the mid-term two studies (51, 58) (both of high risk of bias) reported a significant difference in outcome favouring corticosteroid injection. One study(37) (of high risk of bias) reported a significant difference in favour of local anaesthetic injection for pain relief. The remaining two studies,(14, 54) both of low risk of bias and including 217 participants, reported that there was no significant difference in mid-term outcomes between the two types of injection therapy. Penning et al(54) mixed anaesthetic (lidocaine 1%) with sodium chloride (0.9%) and the effect of sodium chloride may have been a confounding influence. Of note, Penning et al(54) reported that this preparation (lidocaine and sodium chloride), designated as the placebo group in this trial, had the best results at 26 weeks with respect to reduction in pain and improvement in functional mobility.

Long-term comparisons (≥ 1 year):
This review identified only two studies with long-term outcome measures of at least one year. In summary, in the long-term there is evidence from only one study (38) (high risk of bias) favouring corticosteroid injections, and one study (55) (low risk of bias, n=179) suggesting no significant difference between injection groups.

Best evidence synthesis:
Using the rating system described in our methods section (43) and taking into account the results from all 13 studies (both of low and high risk of bias) to provide a best evidence synthesis, we summarise the following results:

- There is strong evidence (from 8 trials, 3 of low risk of bias) to suggest a significant benefit of corticosteroid injections over anaesthetic-only injections for the first 4-8 weeks.
- There is strong evidence (from 7 trials, 3 of low risk of bias) to suggest that at 12 weeks there is no significant difference in outcome between injection types.
- There is strong evidence (from 2 trials of low risk of bias) to suggest that there is no significant difference in outcome between injection types in the mid-term (26 weeks).
- There is limited evidence (from one trial of low risk of bias) to suggest that there is no significant difference between injection types in the long-term (1 year or longer).

In summary, corticosteroid injections may have better short-term results than anaesthetic only injections in the first 8 weeks. There does not appear to be any convincing evidence from the studies of low or high risk of bias that corticosteroid injections confer additional benefit over anaesthetic-only injections after this time point.

DISCUSSION
The studies evaluated as being at low risk of bias in this review have indicated that there may be a temporary initial benefit (4-8 weeks) of administering corticosteroid in comparison to anaesthetic injections for the treatment of RCRSP. There does not appear to be any evidence that corticosteroid injections confer any additional benefit after this time point. We are unable therefore to establish whether corticosteroid medications only afford a therapeutic advantage for 4-8 weeks and no added benefit thereafter, or whether they provide an initial benefit after which time both medications are of equal value.

The certainty of any conclusions reached is challenged by the choice, appropriateness and lack of consistency of outcome measures used for the patient populations within the individual studies. Due to variation in study design and inconsistent use of primary outcome measures, we did not pool data. Although our study differs in its primary objectives and methodology, our findings are similar to those reported in a recent review.(23) The authors of this recent review did not identify any additional evidence that was not included in our review that may have influenced our findings. The continued use of corticosteroids is suggested by the authors to be attributable to "habit, to the underappreciation of the placebo effect, to satisfy patient desire for a physical intervention, or for simple remuneration".

The majority of the included studies did not perform injection therapy in isolation. Although use of concurrent therapy (exercise, analgesics and NSAID's) was varied, it was balanced within each individual trial. There is no definitive way of determining the impact of concurrent therapy in addition to the administered injections on the reported outcomes. Because of this uncertainty the influence of an independent injection or an injection in conjunction with other therapy requires further investigation.

The majority of the investigations included in this review described the administration of local anaesthetic-injections as a placebo procedure, assuming that local anaesthetic injections in the subacromial space are inert and do not provide any therapeutic benefit. However, recent evidence suggests that local anaesthetics such as lidocaine and bupivacaine may have an effect of reducing tenocyte numbers(17, 59) and altering collagen organisation in tendons.(60) Increased cellularity has been associated with tendinopathy(61, 62) and if elevated, reducing tenocyte numbers may be a possible mechanism by which injection therapy may contribute to the restoration of tendon homeostasis.(6) The manner by which injections may improve symptoms remains elusive and in addition to; reducing inflammation, restoring tissue homeostasis, reducing the threat of pain, placebo,(6) it has also been suggested that the therapeutic effect of subacromial injections may be the effect of distension of the subacromial space.(14) Due to these possible chemical, biological and physical effects the assumption that local anaesthetic injections are a true placebo is challenged, and suggests their use may provide a therapeutic effect. However, this needs to be balanced by a potential deleterious effect.(60). Further research is required to determine the benefits of the medicines used in these studies compared with; other medicines, other interventions, natural history and a validated placebo. The physiological effects of these interventions on the local tissues needs also to be further investigated.

Implications for practice. There are a paucity of data quantifying the number of corticosteroid injections performed annually in the United Kingdom. Limited evidence from one out-patient survey (n=2000) suggested the shoulder was the most common anatomical site of musculoskeletal injection, accounting for over a third of all injections. Seventy two percent of injections for the shoulder (n=1440) were for the stated treatment of subacromial bursitis (RCRSP). Recent United Kingdom National Health Service figures reveal that almost 800,000 prescriptions of injectable corticosteroids are dispensed nationally within primary care per year.(63) The average cost of each prescription of corticosteroid is estimated at £5.16p, totalling a yearly national cost of over £4,000,000 (Health and Social Care Information Centre, 2015). The average cost of a standard dose of local anaesthetic (5ml of 1% Lidocaine) is £0.24p.(64) We believe it is safe to assume that, whilst exact figures for patients with RCRSP are unknown, the cost of corticosteroid injections for this patient group is sizable and, if local anaesthetics prove safe and effective in future research, significant cost savings could be achieved. Lidocaine only injections would be over twenty times less expensive than the average cost of corticosteroid medication.

Clinically, in addition to cost, is the growing concern regarding the negative effects of corticosteroids upon tendon tissue.(26, 27, 65) It has also been suggested that the use of corticosteroid injections may detrimentally impact the course of lateral epicondyalgia.(66) This review has highlighted a lack of evidence to support the use of corticosteroid injections over local anaesthetic injections for the treatment of RCRSP after an 8-week period, which raises important issues for clinicians. Should clinicians avoid injections entirely? Should clinicians consider local anaesthetic injections for patients with RCRSP as the first choice of management, and only provide corticosteroid injections to those who do not respond to local anaesthetic? Additionally, potentially the risks of both corticosteroid and anaesthetic-only injection outweighs the benefits, as both pharmaceutical products may damage tendon tissue. Future research is needed that compares injections of corticosteroids, local anaesthetic, saline injections, needle only (for the mechanical effect), other products (e.g. hyaluronate

sodium) an advice-only group, true placebo and a control group (to map natural history). In addition, uncertainty persists over the benefit of image-guided versus landmark-guided injection therapy for the treatment of RCRSP,(32, 67) and whether the procedure should be performed locally or systemically.(33)

In an investigation of local (corticosteroid to the subacromial bursa, local anaesthetic to the gluteal region) versus systemic (corticosteroid to the gluteal region, local anaesthetic to the subacromial bursa) for RCRSP, Ekberg et al(33) concluded that as both groups improved, both local and systemic injections of corticosteroid were equally effective. Although this may support a systemic effect of corticosteroid, these findings may be confounded for a number of reasons. This review suggests that corticosteroid injections may confer clinical benefit in the first 8 weeks but beyond this time point both types of injections and anaesthetic injections appear to be equally effective. Therefore, the conclusion that local and systemic corticosteroid injections are equally effective(33) needs to be considered cautiously as the benefit reported in this study may have been due to the administration of corticosteroid and local anaesthetic injections to the subacromial bursa. In addition, as there was no control group, the reported findings(33) may have mapped natural improvement, or possibly an equivalent placebo response in both groups.

The findings of this review suggest that, in the treatment of RCRSP, corticosteroid injections may have a more beneficial effect than anaesthetic injections alone in the short-term (up to 8 weeks). However, the size of this effect is uncertain and beyond this time point, the two medicines appear to have a comparable effect. The combination of anaesthetics and sodium chloride may be associated with better outcome at 26 weeks.(54) Anaesthetic alone may also have a positive effect in the short-term. The uncertainty implies that it is not yet possible to guide clinicians on particular circumstances where (i) there is a definitive role for injection therapy for RCRSP and (ii) when corticosteroid or anaesthetics may be equally responsive or one may be more beneficial than the other. Equally important is that both medicines may have detrimental effect on rotator cuff tissue. Shared decision making empowers people seeking healthcare to voice their opinions and thoughts. The findings of this review may be used to help inform people of the risks and benefits of their choices.

LIMITATIONS:
There is debate regarding how to assess risk of bias and methodological quality in clinical trials.(68) The variety of tools available, covering differing items/domains, suggest a lack of agreement regarding their relevance.(69) The Cochrane risk of bias tool was used in this review. Although widely used, this tool does have some acknowledged challenges; these include modest inter-rater agreement and how to deal with the risk of bias associated with funding/conflicts of interest.(70) In this review inter-rater agreement was strong with both reviewers making similar judgments regarding the importance of potential sources of bias (92.31%, Kappa score of 0.836) and conflict of interest data are presented (Table 2). The assessment of risk of bias in this review was influenced by the amount of incomplete or missing information in included studies(70) (Table 2). This contributed to studies being rated as being at high risk of bias and, as the majority of studies were assessed as being at potentially high risk of bias, this limited the extent to which the objective of this review could be achieved.
Although we performed a thorough search of commercially published literature we did not perform a search of sources grey literature such as conference papers or government reports. As such we acknowledge this as a potential source of publication bias within our literature search.

CONCLUSIONS:
Corticosteroid injections may have a short-term benefit (up to 8 weeks) over local anaesthetic injections alone in the management of RCRSP. However, the certainty of this conclusion is challenged due to variations in outcome measures and study design. Beyond 8-weeks, there was no evidence to suggest a benefit of corticosteroid over local anaesthetics.

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Competing Interests
To the authors knowledge there are no conflicts of interest to declare in conducting this literature review.

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FIGURE LEGEND:

Figure 1 – PRISMA flow chart of study selection process

Figure 2: Risk of bias graph (frequency (%) of scores per item).

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Figure 1 – PRISMA flow chart of study selection process

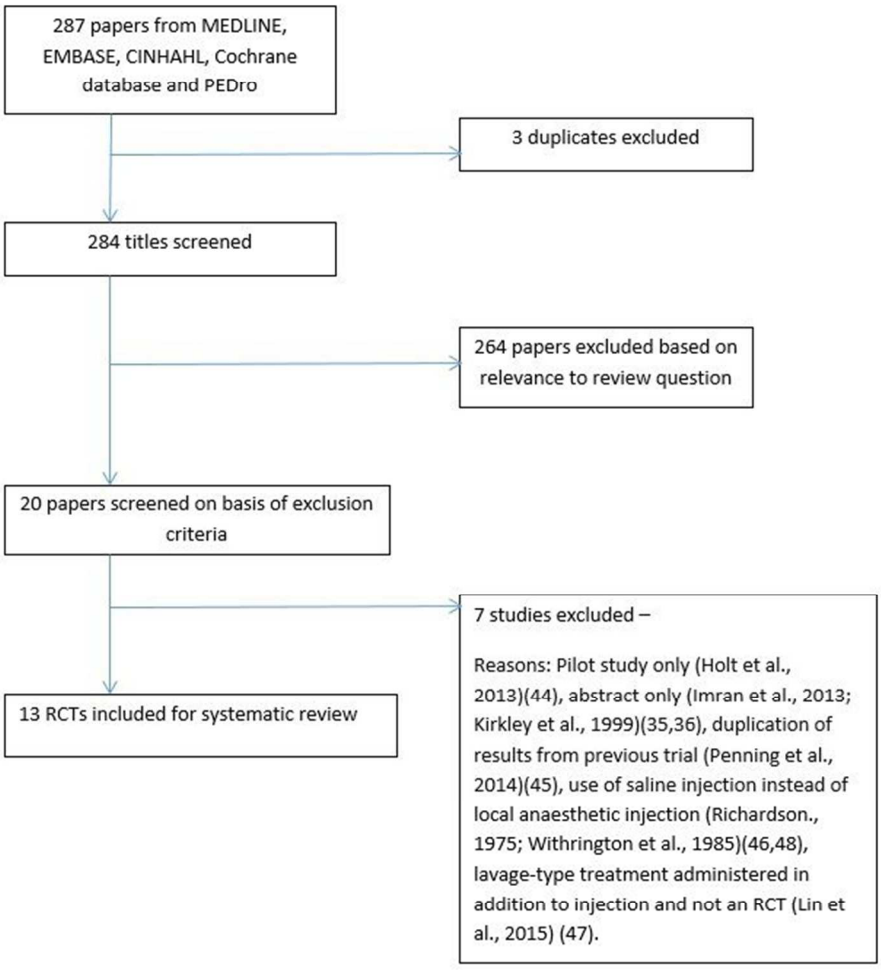

Figure 1 – PRISMA flow chart of study selection process

58x65mm (300 x 300 DPI)

Figure 2: Risk of bias graph (frequency (%) of scores per item).

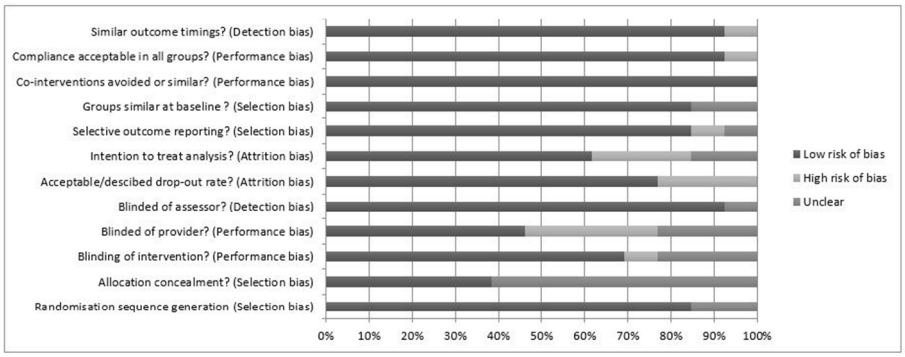

Figure 2: Risk of bias graph (frequency (%) of scores per item)

86x41mm (300 x 300 DPI)

Supplementary Table 1: Characteristics of all studies (high and low risk of bias) included in the review (n=13)

Study (reference)	Number of Participants (Male/Female) [Mean age-years] {Mean Duration of Symptoms}	Interventions	Outcome measures	Findings
Petri 1987 (50) **(USA)**	100 (69M/21F) [Not reported] {4 months}	**Group 1** –Blind SAB injection Lidocaine 4ml 1% + naproxen 500mg 2/day 30 days **Group 2** – SAB injection Lidocaine 3ml 1% + Triamcinolone 1ml of 40mg/ml + Naproxen 500mg 2/day 30 days **Group 3** - SAB injection Lidocaine 3ml 1% + Triamcinolone 1ml of 40mg/ml + Placebo pill 2/day 30 days **Group 4** - Blind SAB injection Lidocaine 4ml 1% + placebo pill 2/day 30 days	**Combined clinical index**. (Combined score including Active abduction ROM, Pain VAS and the Limitation of function scale as equally weighted measures. A higher score indicates a good outcome).	At 4 weeks Group 1 had a statistically significant benefit over Group 4 (p=0.02). Groups 2 and 3 also had a statistically significant benefit over group 4 at 4 weeks (p=0.00005). Mean clinical index at 2 and 4 weeks (higher score indicates better outcome): **Group 1**: 3.68, 4.86 **Group 2**: 4.75, 5.51 **Group 3**: 4.35, 5.24 **Group 4**: 1.76, 2.80
Adebajo 1990 (49) (UK)	60 (32M/28F) [53.3 years] **[Group 1** – 53.8] **[Group 2** – 51.3] **[Group 3** – 54.8] {8 weeks}	**Group 1** - Blind SAB injection lidocaine 3ml 0.5% + diclofenac 50mg 3/day 28 days **Group 2** - Blind SAB injection lidocaine 2ml 0.5% + triamcinolone 1ml of 80mg/ml + placebo pill 3/day 28 days **Group 3** – Blind SAB injection lidocaine 3ml 0.5% + placebo pill 3/day 28 days	**Pain VAS** (0-10, 0=no pain, 10=severe pain). **Active abduction range of motion** (measured in degrees) **Limitation of function scale** (0-3, 0=no limitation of function, 3=severe limitation of function).	Group 1 and 2 had a statistically significant benefit in all outcome measures compared to Group 3 at 4 weeks. Mean improvement in score from baseline (higher number=better improvement): **VAS**: **Group 1**: 3.60 (p≤0.05), **Group 2**: 4.95 (p≤0.001), **Group 3**: 1.35(no p value) **ROM**: **Group 1**: 46.8° (p≤0.05), **Group 2**: 50.4° (p≤0.01), **Group 3**: 5.4° (no p value) **Limitation of Function scale**: **Group 1**: 0.85 (p≤0.05), **Group 2**: 0.85 (p≤0.01), **Group 3**: 0.3 (no p value)
Vecchio 1993 (57) **(UK)**	55 (23M/32F) [56.3 years] **[Group 1 –** 56.5] **[Group 2 –** 56] {4.5 weeks}	**Group 1** - Blind SAB injection lidocaine 6ml 1% **Group 2** - SAB injection lidocaine 1ml 1% plus triamcinolone 1ml of 40mg/ml	**Pain VAS** (0-30, 0=no pain, 30=severe pain). **Active abduction** and **external rotation ROM** (measured in degrees) **Total resisted movement score** (0-9, 0=worst score, 9=best score).	No statistically significant difference between groups at 12 weeks (p>0.05). Mean improvement in score from baseline (higher number=better improvement): **VAS**: **Group 1**: 8, **Group 2**: 8 (p=0.96) **ABD ROM**: **Group 1**: 0° **Group 2**: 0° (p=0.82) **ER ROM**: **Group 1**: 20° **Group 2**: 0° (p=0.33) **TR**: **Group 1**: 1, **Group 2**: 3 (p=0.68)
Blair 1996 (58) **(USA)**	40 (8M/32F)	**Group 1** - Blind SA injection lignocaine 6ml 1% **Group 2** - Injection lignocaine 4ml 1% plus triamcinolone 2ml of 40mg/ml	**Pain VAS** (0-4, 0 = no pain, 4 = severe pain).	Statistically significant improvement favouring Group 2 compared to Group 1 for pain and ROM, no difference in function at mean follow up duration of 33 weeks.

	[56.5 years] **[Group 1** – 57] **[Group 2** – 56] **{8 months}**		**Shoulder flexion** and **external rotation ROM** (measured in degrees). **Functional scale** (0-2, 0=poor function, 2=no loss of function).	**Mean VAS**: **Group 1**: 2.0, **Grp 2**: 1.2 (p<0.005). **Mean Flex ROM improvement**: **Group 1**: 10°, **Group 2**: 24° (p<0.005) **Mean ER ROM improvement**: **Group 1**: 5°, **Group 2**: 11° (p<0.005) **Average functional scale**: **Group 1**: 1.7, **Group 2**: 1.8 (no p value).
Strobel 1996 (38) **(Germany)**	31 (13M/18F) [58.5 years] **[Group 1** – 58] **[Group 2** – 59] **{not reported}**	**Group 1** - Blind SA injection through acromioclavicular joint 5 ml 0.5% mepivacaine hydrochloride **Group 2** - Blind SA injection through acromioclavicular joint 0.5% mepivacaine hydrochloride (amount not specified) + 20mg triamcinolone hexacetonide	**Pain VAS** (0-4, 0=no pain, 4=severe pain). **Shoulder mobility** – active abduction ROM assessment (measured in degrees).	Improvement in both outcomes at 1-year follow-up for Group 2. Differences for VAS have significance level of 1% otherwise level of significance not estimated.
Plafki 2000 (51) **(Germany)**	50 (34M/16 F) [43.5 years] **[Group 1** – 43.4] **[Group 2** – 42.3] **[Group 3** – 44.8] **{17 months}**	**Group 1** – US guided SAB injection 10ml 0.5% bupivacaine **Group 2** – US guided SAB injection 10 mg triamcinolone + 0.5% bupivacaine 10ml **Group 3** – US guided SAB injection 4 mg dexamethasone + 10ml 0.5 % bupivacaine	**Patte score** (>85% score = excellent outcome).	Group 1 stopped after 10 patients as 4 patients complained of an increase in pain. Favourable results were seen in less than half of other 2 groups 19/40 at 26 weeks (no p value available and no specific data published).
McInerney 2003 **(56)** **(Ireland)**	98 (61M 37F) [48 years] **[Group 1** – 47.6] **[Group 2** – 48.5] {not reported}	**Group 1** - Blind SAB injection 40 mg methylprednisolone + 2 ml 0.5% bupivacaine **Group 2** - Blind SAB injection 2ml bupivacaine 0.5%	**Pain VAS** (0-10, 0=no pain, 10 =severe pain). **Active abduction ROM** (measured in degrees)	No statistically significant difference between groups at 3, 6 and 12 weeks with either outcome. **Mean pain scores at 12 weeks:** 1.38 in both groups (p=0.99) **Mean ABD ROM at 12 weeks: Group 1**: 168.9°, **Group 2**: 170.3° (p=0.8)
Akgun 2004 (53) **(Turkey)**	48 (15M/33F) [48.8 years] **[Group 1** – 48.5] **[Group 2** – 50.5] **[Group 3** – 47.5] **{Group 1** – 19 months} **{Group 2** – 13 months} **{Group 3** – 12 months}	**Group 1** – Blind SA injection 10 ml 1% lignocaine + 40mg methylprednisolone x 2 injections over 10 day interval **Group 2** – 1st injection - Blind SA 10 ml 1% lignocaine + 40mg methylprednisolone 2nd injection - 10 ml 1% lignocaine over 10 day interval **Group 3** - Blind SA injection 10 ml 1% lignocaine x 2 injections over 10 day interval	**Pain VAS** (0-10, 0=no pain, 10=severe pain). **Constant score** (0-100, 0=poor function, 100=full function)	No significant difference in overall VAS between groups at any stage. Significant improvements in sleep disturbance (VAS) and daily living activity outcomes in favour of Group 1 at 4 weeks (but no significant difference in outcomes between groups at 12 weeks. **Mean VAS (Rest, Activity and Sleep) at 4 weeks: Group 1**: 0.5, 1.1, 0.8, **Group 2**: 1.0, 1.4, 0.8, **Group 3**: 1.0, 1.7, 2.0 (p>0.05) **Mean VAS at 12 weeks (Rest, Activity and Sleep): Group 1**: 0.8, 0.8, 0.94, **Group 2**: 1.3, 0.81, 0.8, **Group 3**: 0.7, 0.7, 0.9 (p>0.05) **Mean Constant scores at 4 and 12 weeks: Group 1**: 87.8, 91.6, **Group 2**: 84.1, 89.8, **Group 3**: 82.1, 91.6 (p>0.05) **Mean Daily living activities score at 4 and 12 weeks: Group 1**:18.2, 18.5, **Group 2**: 17.1, 17.7, **Group 3**: 15.1, 18.1 (p>0.05)
Alvarez 2005 (14) **(Canada)**	58 (31M/27F) [48.0 years]	**Group 1** – Blind SA injection 5 ml 2% xylocaine **Group 2** – Blind SA injection 4ml 2% xylocaine + 1ml (6mg) betamethasone	**Western Ontario Rotator cuff index** (0-100, 0=best score, 100=worst score).	No statistically significant difference between groups at 3 and 6 months. Mean **WORC** at 12 weeks: **Group 1**: 45.4, **Group 2**: 56.3 (p=0.13) Mean **WORC** at 6 months:

	[Group 1 – 46.0] **[Group 2** – 50.0] {3 years}			**Group 1**: 51, **Group 2**: 59 (p=0.38)
Alvarez-Nemegyei 2008 (Mexico) (37)	56 (13M/43F) [52.5 years] **[Group 1** – 53.0] **[Group 2** – 52.0] **{Group 1** - 8 weeks} **{Group 2** - 3 weeks}	**Group 1** - Blind SA injection 2 ml methylprednisolone (40mg/ml) + 1 ml lidocaine 1% **Group 2** - Blind subacromial injection 3 ml 1 % lidocaine subacromial injection	**Spanish Shoulder Disability Questionnaire** (0-100, 0=no disability, 100=maximal disability) **Pain intensity** (0-10, 0=no pain, 10=severe pain). Shoulder ROM (measured in degrees)	No statistically significant difference between groups for S-SDQ and ROM at any stage of the 5-month follow-up (p=0.96). The data were presented in graphical form and precise figures not reported.
Watson 2008 (55) **(UK)**	179 (83M/96F) [59.0 years} Individual group figures not reported {7 weeks}	**Group 1, 3 and 5** – Blind SA injection 1 ml 1% lidocaine **Group 2, 4, 6** – Blind SA injection 1 ml 40 mg triamcinolone	**British shoulder disability questionnaire** (0-23, 0=no disability, 23=severe disability). **Short form 36 item** (higher score=better outcome).	Statistically significant improvement at 4 weeks in Group 2, 4 and 6 for BSDQ (p=0.026). Specific data were supplied by the author on written request. There was no statistically significant difference between groups at 3 and 6-12 months. Over course of trial (4 weeks, 12 weeks and 1year) mean: **BSDQ: Group 1, 3 and 5**: 11.7, 8.1, 6.4, **Group 2, 4, 6**: 10.3, 8.7, 7.3 (S.E = 0.48) **SF-36 MCS: Group 1, 3 and 5**: 46.4 47.7, 47.2, **Group 2, 4, 6**: 45.8, 45.9, 47.7(S.E = 0.78) **SF-36 PCS: Group 1, 3 and 5**: 39.6, 41.4, 42.9, **Group 2, 4, 6**: 41.4, 41.0, 42.5 (S.E = 0.63)
Hong 2011 (52) **(Republic of Korea)**	79 (32M/47F) [50.1 years] **[Group 1** – 50.8] **[Group 2** – 48.6] **[Group 3** – 51] {11 months}	**Group 1** - US guided SAB injection 4 ml (40mg) triamcinolone **Group 2** – US guided SAB injection 2ml (20 mg) triamcinolone + 2 ml 1% lidocaine **Group 3** – US guided SAB injection 4ml 1% lidocaine	**Shoulder disability questionnaire** (0-22, 0=no disability, 22=maximal disability) **Pain VAS** (0-10, 0=no pain, 10=severe pain)	Group 1 and 2 had statistically significant improvement in both outcomes at 8 weeks, compared to Group 3: Mean improvement in outcomes from baseline at 8 weeks (higher number=better improvement): **SDQ: Group 1**: 5.7, **Group 2**: 5.6, **Group 3**: 0.9 (p<0.001). **VAS: Group 1**: 3.5, **Group 2**: 2.8, **Group 3**: 0.6 (p<0.001).
Penning 2012 (54) **(The Netherlands)**	159 (M75/84F) [53 years] **[Group 1** – 53] **[Group 2** – 52] **[Group 3** – 54] **{6 months}**	**Group 1** - Blind SA injection 8 ml 1% lidocaine + 2ml hyaluronic acid **Group 2** – Blind SA injection 8ml 1% lidocaine + 2ml/20 mg triamcinolone **Group 3** – Blind SA injection 8ml 1% lidocaine + 2ml sodium chloride 0.9%. All injections repeated at 1, 3 and 6 weeks as needed.	**Shoulder disability questionnaire** (0-100, 0=no disability, 100=maximal disability) **Pain VAS** (0-10) **Constant score** (0-100, 0=poor function, 100=full function) **Functional mobility test** (4-28, 4= normal function, 28=poor function) **Shoulder pain score** (7-28,	Group 2 had a statistically significant improvement in all outcomes compared to Group 1 at 3 (p=0.004), 6 (p<0.001) and 12 (p<0.001) weeks and compared to Group 2 at 6 weeks (p=0.006). There was no significant difference in outcome between Group 2 and 3 at 3 and 12 weeks. There was no statistically significant difference between all 3 groups 26 weeks. Mean improvement in outcomes from baseline at 3, 6, 12 and 26 weeks (higher number=better improvement): **SDQ: Group 1:** 0.1, 9.8, 11, 12.4, **Group 2**: 16.1, 22.6, 27.3, 23.2 **Group 3**: 6.3, 13.2, 15, 17 **VAS**: **Group 1:** 0.3, 0.7, 0.7, 1.8**, Group 2**: 1.6, 2.6, 2.7, 2.1, **Group 3**: 0.8, 1.6, 2.3, 2.4 **Constant: Group 1:** 0.1, 2.6, 3.4, 4.9, **Group 2**: 3.6, 7, 6.4, 4.6, **Group 3**: 2.5, 4.7, 5.1, 9.2

			7=no pain, 28=severe pain) **Patient specific disability score** (0-10, 0=no disability, 10-severe disability)	**FMT: Group 1:** 0.3, 1.0, 1.2, 1.3, **Group 2**: 1.2, 1.9, 2.4, 1.6, **Group 3**: 0.6, 1.1, 1.8, 2.4 **SPS: Group 1:** 1.2, 3.1, 2.9, 3.7, **Group 2:** 3.8, 5.8, 5.4, 5.1, **Group 3**: 2.3, 3.9, 4.2, 4.6 **PSD: Group 1:** 0.5, 1.4, 1.3, 1.7, **Group 2:** 1.4, 2.4, 2.3, 1.9, **Group 3**: 1.6, 2.2, 2.1, 2.

Key: ROM = range of motion, M = Male, F = Female, SA = Subacromial, SAB = Subacromial bursal, Blind = landmark-guided, US = Ultrasound, VAS = Visual analogue scale, ABD = abduction, ER = External rotation, Flex = flexion, TR = Total resisted movement score, S-SDQ = Spanish shoulder disability questionnaire, BSDQ = British shoulder disability questionnaire, SF-36 MCS = Short form 36 item mental component score, SF-36 PCS = Short form 36 item physical component score, SDQ = Shoulder disability questionnaire, EQ-5D = EuroQol, FMT = Functional mobility test, SPS = Shoulder pain score, PSD = Patient specific disability score, WORC = Western Ontario rotator cuff index, SE = Standard Error.