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# Efficacy of rehabilitation (lengthening) exercises, platelet-rich plasma injections, and other conservative interventions in acute hamstring injuries: an updated systematic review and meta-analysis

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## ABSTRACT

**Background** Our 2012 review on therapeutic interventions for acute hamstring injuries found a lack of high-quality studies. The publication of new studies warranted an update.

**Objectives** To update and reanalyse the efficacy of conservative treatments for hamstring injury.

**Data sources** PubMed, EMBASE, Web of Science, Cochrane library, CINAHL and SPORTDiscus were searched till mid-February 2015.

**Study eligibility criteria** Randomised controlled trials (RCTs) on the effect of conservative interventions versus a control group or other intervention for hamstring injuries (HI) were included.

**Data analysis** The search results were screened independently by two authors. Risk of bias assessment was performed using a modified Downs and Black scale with a maximum score of 28. Meta-analysis was performed, where possible.

**Main results** 10 RCTs (526 participants), including 6 new RCTs, were identified. Two RCTs were of good/excellent quality, the rest were fair or poor (median Downs and Black score 16 (IQR 9)). Meta-analysis of two studies on rehabilitation (lengthening) exercises showed a significantly reduced time to return to play (HR 3.22 (95% CI 2.17 to 4.77),  $p < 0.0001$ ) but no difference in risk of re-injury. Meta-analysis of three studies investigating platelet-rich plasma (PRP) showed no effect when compared to control (HR 1.03 (95% CI 0.87 to 1.22),  $p = 0.73$ ). Limited evidence was found that progressive agility and trunk stability training may reduce re-injury rates.

**Conclusions** Meta-analysis showed superior efficacy for rehabilitation exercises. PRP injection had no effect on acute hamstring injury. Limited evidence was found that agility and trunk stabilisation may reduce re-injury rates. The limitations identified in the majority of RCTs should improve the design of new hamstring RCTs.

## INTRODUCTION

In 2012, we systematically reviewed the evidence for conservative interventions in the treatment of acute hamstring injuries (HI).<sup>1</sup> We found limited evidence to support the use of agility and trunk stabilisation, (slump) stretching and Actovegin injections.<sup>1</sup> Limited evidence was found that sacroiliac manipulations and non-steroidal anti-inflammatory drugs (NSAIDs)

were not effective.<sup>1</sup> Since the publication of this review, several new randomised controlled trials (RCTs) have been published. After the 2012 Cochrane review of Mason *et al*<sup>2</sup> no new systematic reviews have been published warranting an update.

Given the new evidence, we adjusted the inclusion criteria of our original review<sup>1</sup> to include only RCTs. The purpose of this updated systematic review is to reassess the available literature concerning the conservative management of HI, to review their efficacy and perform meta-analysis, where possible.

## MATERIALS AND METHODS

### Literature search

A literature search was performed in mid-February 2015 in PubMed, EMBASE, Web of Science core collection, Cochrane library, CINAHL and SPORTDiscus. A modified version of the 2012 search was used (see online supplementary appendix 1). Searches were performed by one author (HP) with no limits. The references of the selected articles were manually searched for additional references.

All studies identified by the search were imported in a citation database (EndNote 7.1, Thomson Reuters, New York, USA) and duplicates were removed. Additionally, co-authors of this review, with a specific interest in hamstring injury, were asked about internationally known recently completed and/or submitted RCTs up to February 2015.

### Study selection

All titles were screened by two independent assessors (HP and JLT). Full texts of possibly eligible articles were obtained and assessed independently using the inclusion criteria presented in box 1. Both reviewers compared the articles identified and consensus was reached. If no consensus was reached, a third reviewer (MHM) was consulted.

### Data extraction

Using a standardised data extraction form, study characteristics, patient characteristics and outcome measures were recorded by one author (HP). Point measures and estimations of variance of the selected outcomes were recorded to evaluate therapy efficacy. In the case of multiple measurements, the data of the last measurement were used. If necessary, authors were contacted for additional data.

## Box 1 Inclusion criteria

- ▶ Participants in the study had an acute hamstring injury, diagnosed by physical examination, MRI or ultrasound
- ▶ The studies included were randomised controlled trials
- ▶ There was a well-described conservative therapeutic intervention which was compared to another intervention or a control group
- ▶ Full text of the article was available
- ▶ The article was written in English, German or Dutch
- ▶ In the article at least one of the following outcome measures had to be reported:
  - Time to return to sport or normal function
  - Re-injury rate
  - Pain scores
  - Hamstring force: isometric or isokinetic testing
  - Hamstring flexibility testing
  - Patient satisfaction
  - Adverse effects

## Quality assessment

Two reviewers (MHM and GR) independently assessed the selected studies for risk of bias using a modified version of the Downs and Black scale (D&B)<sup>3</sup> (see online supplementary appendix 2). The original scale consists of 27 questions and allows a maximal score of 32 points. Based on previous literature we modified this scale to a 28-point scale<sup>4–7</sup> by converting it to a binary scale and by adding one additional question evaluating therapist blinding. This was identified as an important form of bias based on the studies we identified in our previous review.<sup>1</sup> Most studies evaluated physical therapy interventions or complementary therapies, adding a possibly biased party if he/she was not blinded. Especially in return to play (RTP) decision-making, lack of therapist blinding is an important source of bias.<sup>8</sup> One point was given if therapist blinding was ensured. Lastly, question 21 was only scored when both time to RTP and re-injury rate were reported in the trial. This was done because we feel that trials reporting both these outcome measures give a more complete and less biased outcome of the therapy success.<sup>1</sup>

A maximum of 28 points could be scored. We adopted the following quality levels based on previous literature<sup>4–7</sup>: excellent (26–28); good (20–25); fair (15–19) and poor ( $\leq 14$ ).

If there was a difference in opinion on a D&B item score, consensus was reached by consulting a third reviewer (JLT). When at least one of the primary D&B assessors was involved as co-author in the RCT, an independent experienced assessor (AS), scored it as the third assessor.

## Data synthesis

One author (HP) calculated weighted means and SDs for demographic information using SPSS V22.0 (IBM statistics, New York, New York, USA). After assessing normality using the Kolmogorov-Smirnov ( $p < 0.05$ ) test mean or median, D&B scores were calculated.

We considered pooling data when studies were sufficiently statistically and clinically homogeneous (ie, intervention and outcome). Data pooling was carried out with RevMan V5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) by two authors (HP and MW). We calculated hazard ratios (HR) with 95% CI for

time-to-event data. HRs were calculated such that  $HR > 1$  indicated faster RTP in the treatment group as compared to the control group. Risk ratios (RR) with 95% CI were calculated for dichotomous outcomes.  $RR < 1$  expressed a smaller risk for re-injury in the treatment group as compared to the control group. A fixed effects model was used to pool data when studies were statistically homogenous. We visually inspected the forest plots for heterogeneity, along with the  $I^2$ -statistic which was considered to represent substantial heterogeneity for  $I^2 > 50\%$ .<sup>9</sup> Heterogeneity was considered present when the  $\chi^2$  was significant ( $p < 0.1$ ).<sup>9</sup> We planned a metaregression analysis or subgroup analysis when statistical heterogeneity was present and  $\geq 10$  studies were available. A random effects model was used when statistical heterogeneity was present. However, when  $< 5$  studies were available for data synthesis we used a fixed effects model.

We planned a sensitivity analysis to explore the effect of study quality by excluding studies with low D&B scores ( $< 20$ ) from the meta-analysis.

If meta-analysis was not possible, a qualitative analysis of the data was carried out using the five levels of evidence used in 2012.<sup>1–10</sup> Meta-analysis was considered superior to qualitative levels of evidence.

1. Strong evidence: provided by two or more studies with high quality and by generally consistent findings in all studies ( $\geq 75\%$  of the studies reported consistent findings).
2. Moderate evidence: provided by one study with high quality and/or two or more studies with low quality, and by generally consistent findings in all studies ( $\geq 75\%$  of the studies reported consistent findings).
3. Limited evidence: provided by only one study with low quality.
4. Conflicting evidence: inconsistent findings in multiple studies ( $< 75\%$  of the studies reported consistent findings).
5. No evidence: when no studies could be found.

We evaluated the possible presence of publication bias in this review by assessing the symmetry of the funnel plot.

## RESULTS

## Literature search

In total 2190 titles and abstracts were screened; 16 studies were selected for full-text assessment. Reference tracking yielded no additional titles. After full-text assessment, six studies were excluded<sup>11–15</sup> and nine studies met the inclusion criteria.<sup>16–24</sup> Two, at that time unpublished, articles were found through co-authors (JLT and GR).<sup>25–26</sup> The manuscripts were obtained with permission of the authors. One of these trials<sup>26</sup> reported the secondary outcomes of a trial identified in the literature search;<sup>24</sup> we did not consider it as a separate trial, but rather as additional information of the first trial.<sup>24</sup> Figure 1 illustrates the selection process.

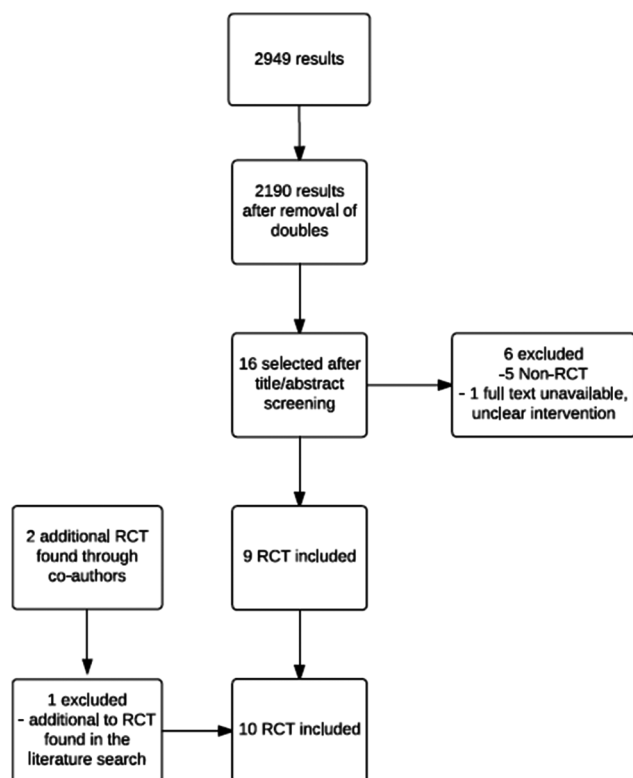
## Description of the included studies

The funnel plot showed no evidence of publication bias when taking the symmetrical distribution of the studies in the funnel plot (figure 2) into account.

Table 1 summarises the characteristics of the included studies. Compared to 2012,<sup>1</sup> two case-control trials were not evaluated<sup>13–27</sup> and six new RCTs were found.<sup>20–26</sup> Five studies<sup>21–26</sup> were rated as homogenous and judged to be suitable for meta-analysis. The data of these trials were pooled per intervention.

## Quality assessment

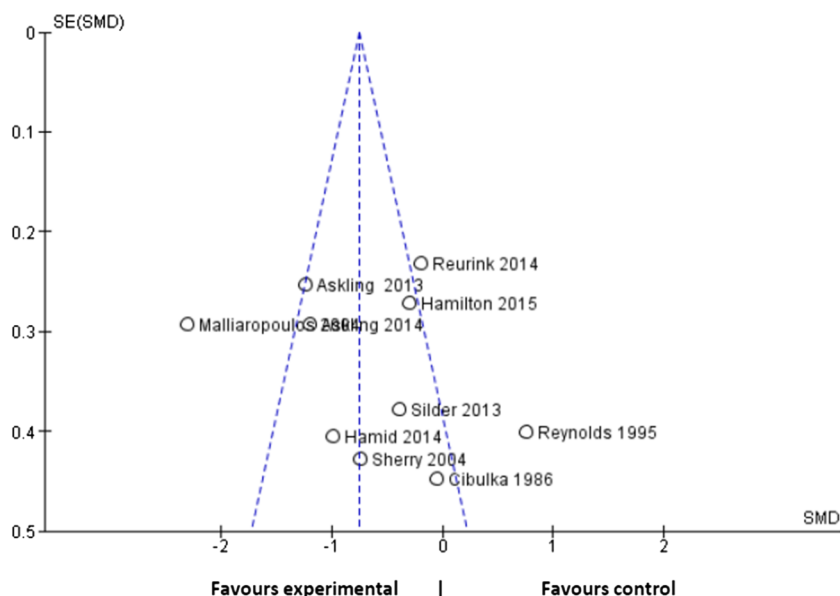
Table 2 shows the overall D&B scores (detailed information in online supplementary appendix 3). Scores ranged from 14 to 27



**Figure 1** Flow chart of article selection (RCT, randomised controlled trial).

with a median of 16 (IQR 9). One three-arm RCT was given two separate D&B scores<sup>25</sup> as it used two different control interventions which were blinded in different ways. The third assessor was asked to assess all trials concerning questions 11–13 which were found to be highly subjective. An independent assessor (AS) was asked to score one trial,<sup>24 26</sup> as the primary D&B assessors were involved as co-authors in the trial. The total score of the independent assessor was identical to our consensus assessment though there was a slight variance between individual items (see online supplementary appendix 3).

**Figure 2** Publication bias funnel plot.



SE= standard error, SMD = Standardized mean difference.

## Participants

A total of 526 participants were included with a mean of 65 (SD 23) per study. The mean and median ages reported across the studies ranged between 20 and 32 years. The majority of participants were males comprising a weighted mean of 86% (SD 13) of the population (range 65–100). Participants from different sports were used in seven studies,<sup>17–20 23–26</sup> two studies used a specific sport population,<sup>21 22</sup> one study did not explicitly mention using a sporting population.<sup>16</sup>

Table 3 summarises the examinations performed on patients to diagnose hamstring injury.

## Interventions and outcomes

Table 4 summarises the interventions used in the studies, the outcomes that were measured and their effect. Two studies evaluated the efficacy of exercises aimed at loading and lengthening the muscle during eccentric actions in addition to a physiotherapy programme.<sup>21 22</sup> Two studies assessed a physical therapy programme focused on agility and trunk stabilisation.<sup>19 20</sup> Three studies compared platelet-rich plasma (PRP) injections and a standardised physiotherapy programme with placebo injections, platelet-poor plasma injections or no injection.<sup>23–26</sup> The remaining studies examined the efficacy of stretching,<sup>18</sup> sacroiliac manipulation<sup>16</sup> and the use of NSAIDs (meclofenamate and diclofenac).<sup>17</sup>

## Data synthesis

We performed a meta-analysis on five studies.<sup>21–25</sup> Two studies evaluated the effect of a partially supervised physiotherapy programme<sup>21 22</sup> with either a lengthening protocol (L-protocol) or a conventional protocol (C-protocol). Of the three RCTs evaluating the efficacy of PRP injections in addition to physiotherapy, we did not pool the platelet-poor plasma data from Hamilton *et al*<sup>25</sup> due to doubts about the validity and the unknown effects of this product.

Two studies<sup>19 20</sup> evaluating physical therapy programmes based on agility and trunk stabilisation were not pooled because of differences in the content of the intervention and control programmes.

**Table 1** Article characteristics

Author	N	Population	Intervention(s)	Follow-up	Primary outcome	Results
Sherry and Best <sup>19</sup>	24	Athletes with acute hamstring strain, grades 1 and 2 based on physical examination	I1: rehabilitation programme consisting of PATS exercises and icing I2: rehabilitation programme consisting of static stretching, isolated progressive resistance exercise and icing (STST)	1 year	Time to RTP Re-injury	I1: 22.2 days (SD 8.3) I2: 37.4 days (SD 27.6) I1: 0/13 I2: 7/10
Silder <i>et al</i> <sup>20</sup>	29	Athletes with suspected HI within the past 10 days confirmed by physical examination and MRI	I1: rehabilitation programme consisting of PATS programme I2: rehabilitation programme consisting of PETS	1 year	Time to RTP Craniocaudal length of injury	I1: 25.2 days (SD 6.3) I2: 28.8 days (SD 11.4) I1: 7.9 cm (95% CI 2.7 to 13.1) I2: 15.9 cm (95% CI 8.4 to 23.4)
Reynolds <i>et al</i> <sup>17</sup>	44	Patients with sports-related tear of the hamstring, <48 h after injury	I1: two capsules 50 mg meclofenamate and two diclofenac placebo capsules 3 times/day for 7 days I2: two 25 mg diclofenac and two meclofenamate placebo capsules 3 times/day for 7 days C: meclofenamate and diclofenac placebo capsules	7 days	Sum of pain score (VAS) in the last 24 h	I1: 7.9 (SD 6.6) I2: 8.8 (SD 7.7) C: 3.9 (SD 3.3)
Malliaropoulos <i>et al</i> <sup>18</sup>	80	Athletes with a ultrasonographic grade 2 hamstring strain	I1+I2: during first 48 h PRICE followed by rehabilitation programme I1: four stretching sessions daily I2: one stretching session daily	RTP	Time required for full rehabilitation Time to equalisation of knee ROM	I1: 13.27 days (SD 0.71) I2: 15.05 days (SD 0.81) I1: 5.57 days (SD 3.3) I2: 7.23 days (SD 0.525)
Cibulka <i>et al</i> <sup>16</sup>	20	Patients with a clinical diagnosis of hamstring muscle strain and sacroiliac joint dysfunction	I: moist heat, passive stretching and manipulation of sacroiliac joint C: moist heat, passive stretching	None reported	Hamstring peak torque Passive knee extension ROM	I1: 46.4 ft lbs (SD 17.47) I2: 45.7 ft lbs (SD 22.70) I1: 155.0° (SD 14.2) I2: 144.6° (SD 16.7)
Askling <i>et al</i> <sup>21</sup>	75	Elite Swedish football players with MRI (<5 days after injury) confirmed HI	I1: L-protocol aimed at loading the hamstrings during extensive lengthening, mainly during eccentric muscle actions I2: C-protocol consisting of conventional exercises for the hamstrings with less emphasis on lengthening	1 year	Time to RTP Re-injury	I1: 28 days (SD 15) I2: 51 days (SD 21) I1: 0/37 I2: 1/38
Askling <i>et al</i> <sup>22</sup>	56	Swedish elite sprinters and jumpers with MRI (<5 days after injury) confirmed HI	I1: L-protocol aimed at loading the hamstrings during extensive lengthening, mainly during eccentric muscle actions I2: C-protocol consisting of conventional exercises for the hamstrings with less emphasis on lengthening	1 year	Time to RTP Re-injury	I1: 49 days (SD 26) I2: 86 days (SD 34) I1: 0/28 I2: 2/28
Reurink <i>et al</i> <sup>24</sup>	80	Athletes with acute hamstring injuries confirmed by physical examination and MRI	I: two 3 mL platelet-rich plasma injections and a standard rehabilitation programme C: two 3 mL saline placebo injections and a standard rehabilitation programme	1 year	Time to RTP	I: 42 days (IQR 30–58) C: 42 days (IQR 37–56)
Hamid <i>et al</i> <sup>23</sup>	28	Athletes diagnosed with an acute ultrasonographic grade 2 hamstring injury	I: one 3 mL platelet-rich plasma injection and a rehabilitation programme C: rehabilitation programme only	RTS	Time to RTP	I: 26.7 days (SD 7.0) C: 42.5 days (SD 20.6)
Hamilton <i>et al</i> <sup>25</sup>	90	Athletes with acute posterior thigh pain confirmed by MRI as grade 1 or 2 hamstring lesion	I1: one 3 mL platelet-rich plasma injection and a rehabilitation programme I2: one 3 mL platelet-poor plasma injection and a rehabilitation programme C: rehabilitation programme only	6 months	Time to RTP	I1: 21 days (95% CI 17.9 to 24.1) I2: 27 days (95% CI 20.6 to 33.4) C: 25 days (95% CI 21.5 to 28.5)

C, control; C-protocol, conventional rehabilitation protocol; I, intervention; L-protocol, loading and lengthening rehabilitation protocol; PATS, progressive agility and trunk stabilisation; PETS, progressive running and eccentric strengthening; ROM, range of motion; RTP, return to play; RTS, return to sport; STST, stretching and strengthening; VAS, visual analogue scale.



**Table 2** Total D&B scores (maximal 28)\*

Reference	D&B score	Level of evidence
Sherry and Best <sup>19</sup>	16	Fair
Silder <i>et al</i> <sup>20</sup>	18	Fair
Reynolds <i>et al</i> <sup>17</sup>	16	Fair
Malliaropoulos <i>et al</i> <sup>18</sup>	14	Poor
Cibulka <i>et al</i> <sup>16</sup>	15	Fair
Askling <i>et al</i> <sup>21</sup>	15	Fair
Askling <i>et al</i> <sup>22</sup>	15	Fair
Reurink <i>et al</i> <sup>24</sup>	25	Good
Hamid <i>et al</i> <sup>23</sup>	19	Fair
Hamilton <i>et al</i> <sup>25</sup> (PRP vs no injection)	24	Good
Hamilton <i>et al</i> <sup>25</sup> (PRP vs platelet-poor plasma)	27	Excellent

\*Scores for all 28 questions are listed in the online supplementary table S3. Hamilton *et al*<sup>25</sup> was given two separate D&B scores because it used two different controls which were blinded in two different ways.  
D&B, Downs and Black; PRP, platelet-rich plasma.

Meta-analysis: lengthening exercises (also referred to as 'rehabilitative' for the general reader)

Askling *et al*<sup>21, 22</sup> evaluated the effect of adding exercises aimed at progressively loading the injured muscle (L-protocol) to a conventional physiotherapy programme. The hamstrings were lengthened extensively during eccentric muscle actions. This was compared to exercises which had less emphasis on muscle lengthening (C-protocol). Both protocols contained three types of exercises aimed at increasing flexibility, strengthening the muscle, and a combination of strengthening and trunk/pelvic stabilisation, but the exact exercises differed between groups. Both groups received a standard general rehabilitation programme in addition to their exercises (checked with the author). Patients were cleared for return to sport when there were no signs of injury during physical examination and when they could perform the Askling H-test (a rapid straight leg raise in a special knee brace) without hesitation.<sup>28</sup> Additional data from the author was requested for meta-analysis.

Fixed effects models were used to estimate the effect of the L-protocol versus the C-protocol for RTP (number of days) and

risk of re-injury (figure 3A, B). The pooled effect showed that the L-protocol significantly reduced RTP compared to the C-protocol with an HR of 3.22 (95% CI 2.17 to 4.77),  $Z=5.83$ ,  $p<0.0001$  (figure 2). No difference was found between the two protocols for the risk of re-injury ( $RR=0.25$ , 95% CI 0.03 to 2.20,  $Z=1.25$ ,  $p=0.21$ ) (figure 3). No statistical heterogeneity was present ( $I^2=0\%$ ).

#### Meta-analysis: PRP

Three studies evaluated the effect of PRP injections<sup>23–25</sup> with standardised rehabilitation. Hamid *et al*<sup>23</sup> performed an assessor-blinded study comparing patients receiving a single 3 mL PRP injection (Biomet, mean  $1297 \times 10^3$  platelets/ $\mu$ L, mean  $38.3 \times 10^3$  leucocytes/ $\mu$ L) within 7 days after injury, to patients who received no injection. Both groups followed a standardised rehabilitation programme. Hamilton *et al*<sup>25</sup> performed a double-blinded trial comparing one 3 mL injection of PRP (Biomet, mean  $765.8 \pm 423.6 \times 10^3$  platelets/ $\mu$ L, mean  $26.1 \pm 13.7 \times 10^3$  leucocytes/ $\mu$ L) and platelet-poor plasma (mean  $30.3 \pm 23.0 \times 10^3$  platelets/ $\mu$ L, mean  $0.03 \pm 0.03 \times 10^3$  leucocytes/ $\mu$ L) within 5 days after injury and a single-blinded comparison study arm with no injection. All three groups underwent a six-stage criteria-based standardised rehabilitation. All treating physiotherapists were blinded for group allocation and MRI findings. Patients were randomised to receive either 3 mL of PRP or platelet-poor plasma or no injection. Reurink *et al*<sup>24, 26</sup> undertook a double-blind RCT in which patients were randomised to receive either two injections with 3 mL of PRP, respectively, within 5 days after injury onset and 5–7 days after the first injection (Arthrex mean  $433 \pm 128 \times 10^3$  platelets/ $\mu$ L, mean  $1.9 \pm 2.1 \times 10^3$  leucocytes/ $\mu$ L), or saline placebo injections in addition to a standardised rehabilitation programme.

The D&B scores of the trials differed. Two<sup>24–26</sup> were rated as good or excellent (D&B scores 25 and 24/27, respectively) and one<sup>23</sup> as fair (D&B 19). We, therefore, performed a sensitivity analysis.

A fixed effects model was used to estimate the HR of RTP in the PRP group compared to the non-injected control group. The pooled effect showed no significant effect of PRP compared to control with an HR of 1.03 (95% CI 0.87 to 1.22),  $Z=0.35$ ,  $p=0.73$  (figure 4A). There was substantial heterogeneity ( $I^2=75\%$ ), which was significant ( $p=0.02$ ). Sensitivity analysis revealed that the decision of including high risk of bias studies in the meta-analysis did not affect the effect of PRP when compared to including low risk of bias studies only. When analysing low risk of bias studies only, the HR was 1.00 (95% CI 0.85 to 1.19),  $Z=0.04$ ,  $p=0.97$  (figure 4B). The risk of re-injury at 6 months was pooled for two trials<sup>24–26</sup> as one trial<sup>23</sup> did not report re-injury. This showed no difference between PRP and control ( $RR=0.88$ , 95% CI 0.45 to 1.71),  $Z=0.39$ ,  $p=0.70$  (figure 4C). No heterogeneity was present for re-injury. Owing to the small number of studies investigating the interventions, no meta-regression or subgroup analysis was possible.

#### Descriptive synthesis

##### Progressive agility and trunk stabilisation

Two studies<sup>19, 20</sup> evaluated a rehabilitation programme, which focused on progressive agility and trunk stabilisation (PATS).

Sherry and Best<sup>19</sup> compared PATS to a rehabilitation programme focusing on stretching and strengthening (STST). Both programmes consisted of two discrete phases. Compliance was monitored through self-recorded exercise logs. A mean of 22.2 days (SD 8.3) for the PATS group and 37.4 days (SD 27.6)

**Table 3** Clinical examinations used to diagnose hamstring injury

Reference	Physical examination	Ultrasound	MRI*	Grading system
Sherry and Best <sup>19</sup>	Yes	No	No	Based on physical exam findings
Silder <i>et al</i> <sup>20</sup>	Yes	No	Yes	None
Reynolds <i>et al</i> <sup>17</sup>	Yes	No	No	None
Malliaropoulos <i>et al</i> <sup>18</sup>	Yes	Yes	No	Based on ultrasound findings
Cibulka <i>et al</i> <sup>16</sup>	Yes†	No	No	None
Askling <i>et al</i> <sup>21</sup>	Yes	No	Yes	None
Askling <i>et al</i> <sup>22</sup>	Yes	No	Yes	None
Reurink <i>et al</i> <sup>24</sup>	Yes	No	Yes	Based on MRI findings
Hamid <i>et al</i> <sup>23</sup>	Yes	Yes	No	Based on ultrasound findings
Hamilton <i>et al</i> <sup>25</sup>	Not reported	No	Yes	Based on MRI findings

\*Abnormally high intensity on T2-weighted and/or STIR-weighted images.

†Also evaluated sacroiliac dysfunction defined as pelvic asymmetry, positive standing flexion test and prone knee flexion test.

STIR, short tau inversion recovery.

**Table 4** Interventions and outcomes of RCTs

Intervention	Outcome	Effect	Best evidence synthesis	Quality ratings of studies
Progressive loading during eccentric lengthening PATS exercises	Time to RTP <sup>21 22</sup>	+	Meta-analysis	Fair <sup>21 22</sup>
	Re-injury <sup>21 22</sup>	=	Meta-analysis	
	Time to RTS <sup>19 20</sup>	=	Moderate	Fair <sup>19 20</sup>
	Re-injury <sup>19</sup>	+	Limited	
	Craniocaudal length of injury at RTS <sup>20</sup>	+	Limited	
	Physical examination at RTS <sup>20</sup>	=	Limited	
Stretching exercises	MRI characteristics at RTS <sup>20</sup>	=	Limited	
	Time to RTP <sup>18</sup>	+	Limited	Poor <sup>18</sup>
Platelet-rich plasma	Time to equalisation of knee ROM <sup>18</sup>	+	Limited	
	Time to RTP <sup>23-25</sup>	=	Meta-analysis	Good <sup>24 26</sup>
	Re-injury <sup>24 25</sup>	=	Meta-analysis	Fair <sup>23</sup>
	Adverse events <sup>23-25</sup>	=	Strong	Good/excellent <sup>25</sup>
	Change in pain score <sup>23</sup>	=	Limited	
	Isokinetic testing <sup>25</sup>	=	Limited	
	Changes in T2-weighted MRI after 3 weeks <sup>25</sup>	=	Limited	
	Adherence to rehabilitation programme <sup>25 26</sup>	=	Strong	
	Physical examination <sup>26</sup>	=	Limited	
	Hamstring outcome score <sup>26</sup>	=	Limited	
	Patient satisfaction <sup>26</sup>	=	Limited	
	oedema on MRI <sup>26</sup>	=	Limited	
NSAIDs	Pain score <sup>17</sup>	=	Limited	Fair <sup>17</sup>
	Isokinetic testing <sup>17</sup>	=	Limited	
	Swelling <sup>17</sup>	=	Limited	
	Adverse events <sup>17</sup>	-	Limited	
Sacroiliac manipulation	Hamstring flexibility <sup>16</sup>	=	Limited	Fair <sup>16</sup>
	Isokinetic testing <sup>16</sup>	=	Limited	

=, No effect of intervention compared to control or no differences between intervention and control; +, favours intervention; -, favours control; NSAID, non-steroidal anti-inflammatory drug; PATS, progressive agility and trunk stabilisation; RCT, randomised controlled trial; ROM, range of motion; RTP, return to play; RTS, return to sport.

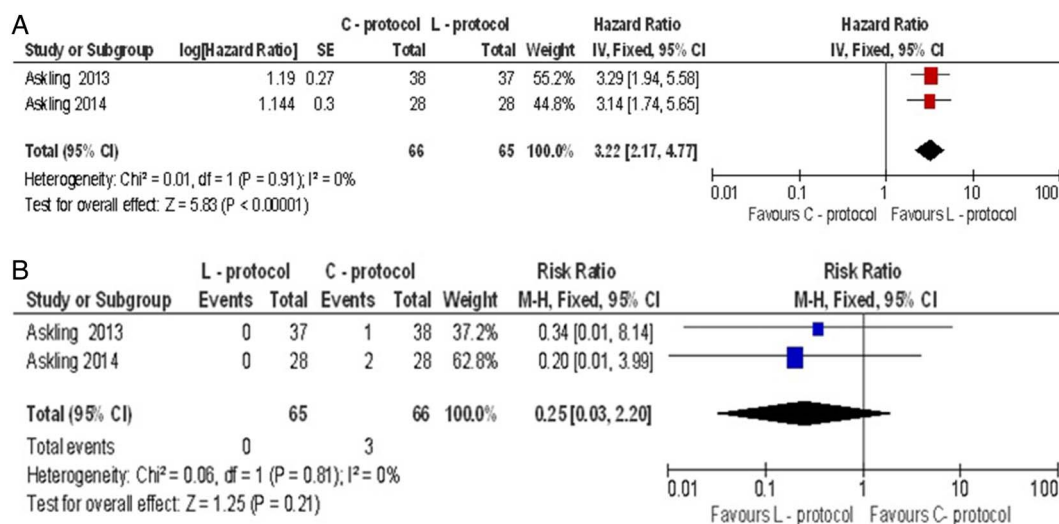
for the STST group was reported, which was not statistically significant ( $p=0.2455$ ). Re-injury rates between groups were statistically significant in favour of PATS (0/13 re-injuries within 16 days after RTP and 1/13 within 1 year, vs 6/10 and 7/10, respectively in the STST group ( $p<0.001$  in both cases)).

Silder *et al*<sup>20</sup> compared PATS with a progressive running and eccentric strengthening (PRES) programme. Both programmes consisted of three phases. No statistically significant difference in RTP was found (PATS: mean of 25.2 days (SD 6.3), PRES: 28.8 days (SD 11.4),  $p=0.346$ ). Re-injury rates were 1/16 in the

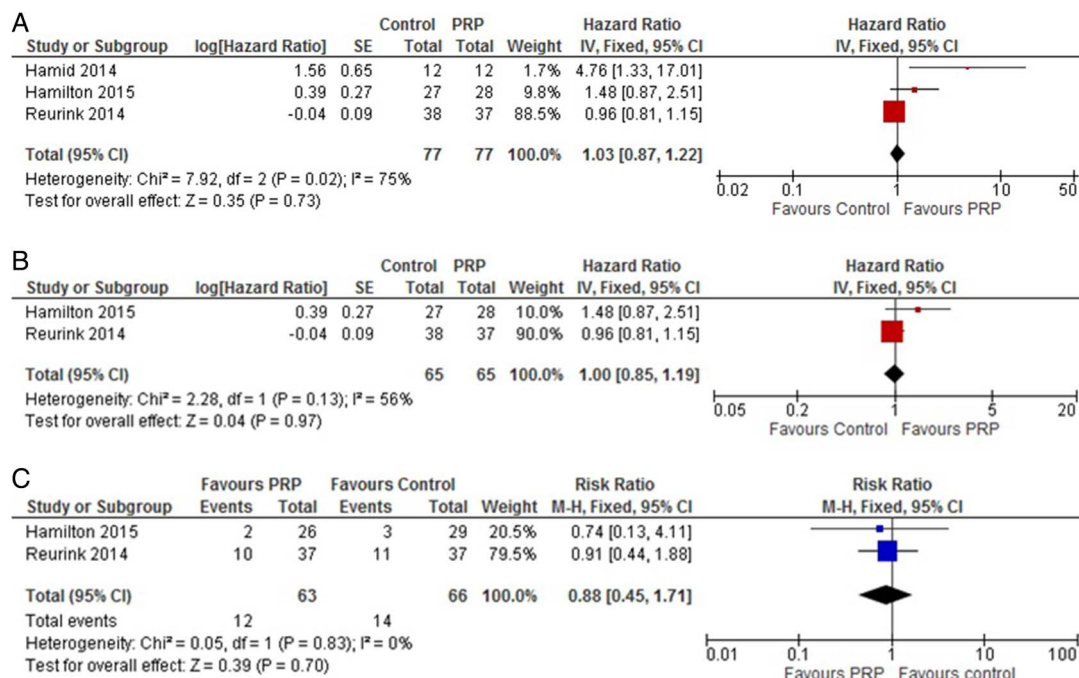
PATS and 3/13 for the PRES group. Significance was not reported. Several other outcome measures based on MRI finding and physical examination were reported in the study. Of these, only the craniocaudal length of injury at RTP on MRI was significantly shorter for the PATS group at RTP ( $p=0.037$ ).

### Stretching

Malliaropoulos *et al*<sup>18</sup> compared two different intensities of static stretching (four times vs once daily) in 80 patient with grade 2 hamstring injury. Full active knee extension was reached



**Figure 3** (A) Pooled HRs of return to play for adding lengthening exercises (L-protocol) and conventional exercises (C-protocol) Log natural logarithm; IV, inverse variance; square size indicates the size of the population investigated in each study; diamond estimated pooled effect: width indicates the 95% CI. (B) Pooled risk ratio for re-injury (<1 year) for adding lengthening exercises (L-protocol) and conventional exercises (C-protocol). square size indicates the size of the population investigated in each study; diamond estimated pooled effect: width indicates the 95% CI.



**Figure 4** (A) Pooled HRs for return to play for platelet-rich protein (PRP) and control interventions. Log natural logarithm; IV, inverse variance; square size indicates the size of the population investigated in each study; diamond estimated pooled effect: width indicates the 95% CI. Data using platelet-poor plasma (PPP) as control were excluded from analysis. (B) Sensitivity analysis, the HR for return to play for PRP and control based on high-quality randomised controlled trials (RCTs) only. Log natural logarithm; IV, inverse variance; square size indicates the size of the population investigated in each study; diamond estimated pooled effect: width indicates the 95% CI. Data using platelet-poor plasma (PPP) as control were excluded from analysis. (C) Pooled risk ratio for re-injury for platelet-rich plasma (PRP) and control. IV, inverse variance; square size indicates the size of the population investigated in each study; diamond estimated pooled effect: width indicates the 95% CI. Data using platelet-poor plasma as control were excluded.

earlier in the high-intensity group with a mean of 5.57 (SD 0.71) days vs 7.32 (SD 0.53) days ( $p < 0.001$ ). Time to RTP was shorter in the high-intensity group (mean of 13.27 days (SD 0.71) days compared to 15.05 (SD 0.81) days ( $p < 0.001$ )).

#### Sacroiliac manipulation

Cibulka *et al*<sup>16</sup> found no effect of sacroiliac manipulation on peak quadriceps torque and passive knee extension after manipulation compared to non-manipulated controls. A significant difference in peak torque change was reported in favour of manipulation (8.1 (sacroiliac mobilisation group) vs 0.4 ft lbs (control)). It should be noted that significantly lower pre-test peak torques of the experimental group were reported (8.4 ft lbs lower,  $p < 0.005$ ).

#### Non-steroidal anti-inflammatory drugs

Reynold *et al*<sup>17</sup> evaluated the effect of 50 mg meclofenamate and placebo (group 1) versus 25 mg diclofenac twice daily, and placebo (Group 2) versus placebo only (group 3) for a period of 7 days. No significant effects on pain scores (measured with a visual analogue scale), swelling and isokinetic hamstring tests (peak torque, total work and average power) were found. Adverse events were reported in 5/13 patients in group 1, 6/17 in group 2 and 2/14 in group 3. None of these required alteration or reduction of the medication. Statistical analysis was not performed for adverse events.

#### PRP injections

Hamid *et al*<sup>23</sup> found that although the PRP group showed significantly lower pain severity scores during the rehabilitation, it

had no effect on change in pain scores or pain intensity scores. No adverse events were reported. Re-injury rates were not reported.

Both Hamilton *et al*<sup>25</sup> and Reurink *et al*<sup>24–26</sup> found no significant differences between other secondary outcomes. Both reported no significant adverse events.

Hamilton *et al*<sup>25</sup> found that RTP in the platelet-poor plasma group was significantly longer when compared to PRP (−5.7 days (95% CI −10.1 to −1.4),  $p = 0.01$ ). No difference was found between platelet-poor plasma and no injection (2.8 days (95% CI −1.6 to 7.2),  $p = 0.210$ ).

## DISCUSSION

### Main findings

We systematically reviewed 10 RCTs that evaluated the effects of different interventions for acute hamstring injuries. These studies were generally of fair quality with one poor quality<sup>18</sup> and two good/excellent quality studies.<sup>24–26</sup> The poor-quality and fair-quality studies mostly lacked adequate blinding, were underpowered and did not properly adjust for loss to follow-up. Based on the meta-analysis of two studies of fair quality,<sup>21–22</sup> we found that adding lengthening exercises reduce the time to RTP when compared to conventional exercises. Meta-analysis of the PRP trials<sup>23–26</sup> showed no additional effect for PRP injections on RTP or in reducing re-injury. For re-injury reduction, limited evidence from one trial<sup>19</sup> was found for agility and trunk stabilisation exercises; however, moderate evidence from two fair quality trials<sup>19–20</sup> showed no reduction in time to RTP for these exercises.

Limited evidence, through one poor-quality study,<sup>18</sup> is available to support high-frequency compared with low-frequency stretching in grade 2 HI. Based on fair-quality studies, limited evidence is available that NSAIDs<sup>17</sup> and sacroiliac mobilisation<sup>16</sup> have no therapeutic effect in acute hamstring injury rehabilitation.

### Physical therapeutic interventions

Meta-analysis showed that adding lengthening exercises to a standard physical therapy programme was more effective than using conventional exercises in reducing time to RTP, but had no effect on re-injury rate. These results should be interpreted with care and require reproduction by other research groups and different athlete populations. It should also be noted that both trials were unblinded and the D&B scores indicate that both trials were of fair quality (D&B scores of 15) making them prone to detection and performance bias. Several differences were found between trials (unequal male/female distributions, age, proportion of stretch type injury, length of injury and sports type) but these did not influence statistical heterogeneity of the data.

We found moderate evidence that PATS does not reduce the time to RTP. Both studies<sup>19, 20</sup> used different control (STST and PRES) interventions and the content of the PATS programmes differed (two vs three phases). It should also be noted that both trials used small sample sizes ( $n=24$ <sup>19</sup> and  $n=29$ <sup>20</sup>). Sherry and Best<sup>19</sup> did prove its superiority over STST with regard to re-injury rate. However, as previously observed,<sup>1</sup> the re-injury rate in the STST group was remarkably high (70%), suggesting a possible adverse effect of this programme.

We found limited evidence that static stretching four times a day was superior to once daily stretching.<sup>18</sup> No other studies evaluated static stretching or used it as a control making it impossible to state whether stretching itself is efficacious.

### Platelet-rich plasma

Our meta-analysis and descriptive synthesis show that there is no superior efficacy for PRP injections. The results from the meta-analysis should be considered carefully as there is substantial heterogeneity in the data. First, two trials<sup>23, 25</sup> used a non-blinded, no injection group as control whereas Reurink *et al* used a blinded placebo group (saline) as control group,<sup>24, 26</sup> allowing for performance bias in the results. This actually strengthens the results presented because no effect could be found despite the presence of bias. Second, all trials differed slightly in injection techniques and PRP content. Third, we did not pool the platelet-poor plasma data from Hamilton *et al*<sup>25</sup> because there were concerns about its validity as placebo. There is little experience with platelet-poor plasma and due to its content (pH, osmolality, remaining leucocytes and platelets), myotoxic effects cannot be excluded and its enhancing effect remains unclear. Saline was considered a more valid placebo as ample evidence is available that it has no myotoxic effect on muscle tissue.<sup>29</sup> Lastly, there were differences in patient characteristics. Thus, no meta-regression or subgroup analysis was possible to investigate the effect of patient characteristics.

The RCTs by Reurink *et al*<sup>24, 26</sup> and Hamilton *et al*,<sup>25</sup> were of high quality. Please note that members of this review group are co-authors of these studies. The D&B score of the independent assessor (AS) was comparable and did not affect the quality category of Reurink *et al*<sup>24, 26</sup> (good) and the co-author involved with the Hamilton *et al*<sup>25</sup> trial (JLT) was not involved in the D&B scoring.

Hamid *et al*<sup>23</sup> reported that PRP shortened the time to RTP. The PRP preparation in this study had the highest platelet count

( $1297 \times 10^3/\mu\text{L}$ ). However, this study risked bias due to a lack of a placebo or any attempt to mask the lack of injection allowing for a placebo effect among patients. Re-injury rates were not reported, making the assessment of a possible premature RTP and the long-term efficacy impossible.

Several previous reviews<sup>30–33</sup> have found a dearth of evidence to support PRP as a treatment for muscle injury. Considering our quantitative and qualitative findings, higher levels of evidence are now available to discourage the use of PRP injections in the rehabilitation of hamstring injuries.

### Other interventions

Limited evidence was found that NSAIDs<sup>17</sup> and sacroiliac manipulation<sup>16</sup> have no effect on outcome. Furthermore, the study by Cibulka *et al*<sup>16</sup> contains several methodical shortcomings (unclear definitions, differences in baseline characteristics) making it prone to bias. Also, its findings with regard to hamstring peak torque can be explained by the difference in pre-test peak torques between groups.

NSAIDs are often proposed as an analgesic in the early phase of muscle injury.<sup>34–37</sup> Although the evidence is limited,<sup>17</sup> we found no evidence to support the use of NSAIDs for pain management. Furthermore, there is increasing evidence that NSAIDs may be counterproductive for muscle healing.<sup>29</sup> Considering the lack of support for their efficacy and the possible detrimental effect on muscle healing, NSAIDs are not recommended in HI.

### Limitations

Our review has several limitations. First, we did not perform a grey literature search. We did find one on-going trial through the co-authors. It is possible that other pending trials are available.

Second, we used a modified D&B scale to assess the quality in trials. In 2012, the PEDro scale was used<sup>1</sup> making comparison of the trial quality more difficult. However, the association between both scales was previously found to be moderately high ( $r\ 0.71$ ,  $p<0.01$ )<sup>38</sup> and after the modifications to our D&B scale, all questions from the PEDro scale were assessed as part of the D&B. We, therefore, feel that the use of our modified D&B scale was valid. We compared the effect on quality assessment between both scales and found no difference in 50%. In the remaining 50%, the PEDro scale always showed higher quality ratings, suggesting our current review was more critical in assessing the available evidence.

We altered a few keyword combinations because we found that the original search included too many irrelevant articles and that the number of hits using this search had in some cases quadrupled. Each alteration was checked for potentially missed articles. We are confident that no relevant articles were missed.

Lastly, we excluded all clinical controlled trials since enough RCTs were now available to focus specifically on randomised studies, adding to the level of evidence of this review. Owing to this exclusion criterion, two treatment options were not reviewed compared to 2012.<sup>1</sup>

### Updated clinical relevance: what should be implemented in clinical practice

New evidence is available to assist in clinical decision-making for the treatment of hamstring injuries. Askling's *et al*<sup>21, 22</sup> lengthening protocol enhances RTP compared to conventional therapy (meta-analysis), and PATS might be implemented for reducing the re-injury rate (limited evidence). Statistical evidence suggests that PRP injections have no added effect on RTP or re-injury rate (meta-analysis).



## Future directions

The quality of the RCTs included was generally relatively low. The main areas that the studies failed to address in their designs were lack of blinding, sample size and adjustment for loss to follow-up.

Most RCTs had a risk of bias due to lack of blinding of patients and/or therapist. Although it is difficult to blind therapists in physiotherapy studies, every attempt should be made to make this possible. If this is not possible, the use of strict criteria for progression during a rehabilitation programme should be used to minimise performance bias. Blinding of assessors and patients should also be ensured. When evaluating adjuvant treatment, such as PRP, we believe the use of placebo is imperative.

The comparability between trials was poor. Although most trials evaluated a physical therapy intervention, standard control therapies varied between studies making comparison and data pooling difficult. For future research we recommend that 'standard therapy' is clearly described and based on a previously described intervention or control therapy.

Lastly, we noticed that the preferred outcome measure, RTP, varied greatly between studies, indicating that RTP criteria lack a universal definition. As it is a highly relevant clinical outcome, we feel authors should report predefined specified criteria (eg, no residual symptoms on physical examination and the unrestricted completion of sport-specific exercises), which need to be met before RTP clearance. Re-injuries should always be reported as this reflects on interventions long-term success and possible pre-mature RTP.<sup>1</sup>

## Conclusion

Of 10 included studies, only two good or excellent quality RCTs with low risk of bias were identified. For enhanced time to RTP, meta-analysis showed superior efficacy for adding lengthening exercises, but not for PRP injections. For reducing re-injury rate, there is limited evidence to include agility and trunk stabilisation exercises. The identified limitations of most RCTs should guide the design of new hamstring RCTs.

For daily practice, adding lengthening exercises and PATS should be considered to reduce the RTP duration and re-injury risk following acute hamstring injuries.

### What are the new findings?

- Meta-analysis of lengthening and loading rehabilitative exercises in acute hamstring injuries show a positive effect on return to play.
- Meta-analysis of platelet-rich plasma injections in acute hamstring injuries shows no effect.
- Progressive agility and trunk stabilisation may reduce re-injury rates.

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## Appendix 1

**Table S1** Search strategy

Search strategy	Records2011/2015
<u>Pubmed</u>	139/240
(hamstring injur*[tw] OR hamstring muscle injur*[tw] OR hamstring muscle strain*[tw] OR hamstring rupt*[tw] OR hamstring strain*[tw] OR hamstring tear*[tw]) AND ("therapeutics"[mesh] OR "therapy"[subheading] OR therapy[tw] OR therapist*[tw] OR rehabil*[tw] OR treat[tw] OR treated[tw] OR treatment*[tw] OR manag*[tw] OR intervent*[tw])	
<u>EMBASE</u>	336/1138
((hamstring* OR thigh OR semitendin* OR semimembran* OR "femoral biceps" OR "biceps femoris") ADJ3 (injur* OR tear* OR rupt* OR strain*)).ti,ab,de AND (exp therapy/ OR therapy.fs OR therap*.ti,ab,de OR rehabil*.ti,ab,de OR treat*.ti,ab,de OR manag*.ti,ab,de OR intervent*.ti,ab,de)	
<u>Web of Science core collection</u>	352/433
(TI=((hamstring* OR semitendin* OR semimembran* OR "biceps femoris" OR "femoral biceps") SAME (injur* OR tear* OR rupt* OR strain*)) AND TS=(therap* OR rehabil* OR treat* OR manag* OR intervent* OR physiother*)) OR (TS=((hamstring* OR semitendin* OR semimembran* OR "biceps femoris" OR "femoral biceps") SAME (injur* OR tear* OR rupt* OR strain*)) AND TI=(therap* OR rehabil* OR treat* OR manag* OR intervent* OR physiother*))	
<u>Cochrane library</u>	22/40
((hamstring* OR thigh* OR semitendin* OR semimembran* OR 'femoral biceps' OR 'biceps femoris') NEAR/3 (injur* OR tear* OR rupt* OR strain*)) AND (therap* OR rehabil* OR treat* OR manage* OR intervent*)	
In all text. Restricted to clinical trials.	
<u>CINAHL</u>	377/548
TX (((hamstring* N3 injur*) OR (hamstring* N3 tear*) OR (hamstring* N3 rupt*) OR (hamstring* N3 strain*) OR (thigh* N3 injur*) OR (thigh* N3 tear*) OR (thigh* N3	

rupt\*) OR (thigh\* N3 strain\*) OR (semitendin\* N3 injur\*) OR (semitendin\* N3 tear\*) OR (semitendin\* N3 rupt\*) OR (semitendin\* N3 strain\*) OR (semitemembran\* N3 injur\*) OR (semitemembran\* N3 tear\*) OR (semitemembran\* N3 rupt\*) OR (semitemembran\* N3 strain\*) OR (femoral biceps N3 injur\*) OR (femoral biceps N3 tear\*) OR (femoral biceps N3 rupt\*) OR (femoral biceps N3 strain\*) OR (biceps femoris N3 injur\*) OR (biceps femoris N3 tear\*) OR (biceps femoris N3 rupt\*) OR (biceps femoris N3 strain\*)) AND (therap\* OR rehabil\* OR treat\* OR manage\* OR intervent\*)))

Sportdiscus

388/550

TX (((hamstring\* N3 injur\*) OR (hamstring\* N3 tear\*) OR (hamstring\* N3 rupt\*) OR (hamstring\* N3 strain\*) OR (thigh\* N3 injur\*) OR (thigh\* N3 tear\*) OR (thigh\* N3 rupt\*) OR (thigh\* N3 strain\*) OR (semitendin\* N3 injur\*) OR (semitendin\* N3 tear\*) OR (semitendin\* N3 rupt\*) OR (semitendin\* N3 strain\*) OR (semitemembran\* N3 injur\*) OR (semitemembran\* N3 tear\*) OR (semitemembran\* N3 rupt\*) OR (semitemembran\* N3 strain\*) OR (femoral biceps N3 injur\*) OR (femoral biceps N3 tear\*) OR (femoral biceps N3 rupt\*) OR (femoral biceps N3 strain\*) OR (biceps femoris N3 injur\*) OR (biceps femoris N3 tear\*) OR (biceps femoris N3 rupt\*) OR (biceps femoris N3 strain\*)) AND (therap\* OR rehabil\* OR treat\* OR manage\* OR intervent\*)))

Total: 2949

## Appendix 2: Modified Downs and Blacks list

### Modified Downs and Black checklist

Allocate 1 point per question answered with "Yes"	Points
<b>REPORTING</b>	
<b>1. Is the hypothesis/aim/objective of the study clearly described?</b>	.....
<b>2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?</b> <i>If the main outcomes are first mentioned in the Results section, the question should be answered no.</i>	.....
<b>3. Are the characteristics of the patients included in the study clearly described?</b> <i>In cohort studies and trials, inclusion and/or exclusion criteria should be given</i>	.....
<b>4. Are the interventions of interest clearly described?</b> <i>Treatments and placebo (where relevant) that are to be compared should be clearly described.</i>	.....
<b>5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?</b> <i>A list of principal confounders is provided.</i>	.....
<b>6. Are the main findings of the study clearly described?</b>	.....



Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.

**7. Does the study provide estimates of the random variability in the data for the main outcomes?**

*In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.*

**8. Have all important adverse events that may be a consequence of the intervention been reported?**

*This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided)*

**9. Have the characteristics of patients lost to follow-up been described?**

*This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered "no" where a study does not report the number of patients lost to follow-up*

**10. Have actual probability values been reported (e.g. 0.035 rather than  $<0.05$ ) for the main outcomes except where the probability value is less than 0.001?**

**EXTERNAL VALIDITY**

**11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?**

*The study must identify the source population for patients and describe how the patients were selected. Patients should be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all member of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be marked as no.*

**12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?**

*The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.*

**13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?**

*For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, e.g. the intervention was undertaken in a specialist center unrepresentative of the hospitals most of the source population would attend.*

**14. Was an attempt made to blind study subjects to the intervention they have received?**

*For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.*

**15. Was an attempt made to blind those measuring the main outcomes of the intervention?**

.....

**16. Was an attempt made to blind those treating the patient?**

.....

**17. If any of the results of the study were based on “data dredging”, was this made clear?**

.....

*Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.*

**18. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?**

.....

*Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, e.g., survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.*

**19. Were the statistical tests used to assess the main outcomes appropriate?**

.....

*The statistical techniques used must be appropriate to the data. E.g. non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of data (normal or not) is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.*

**20. Was compliance with the intervention/s reliable?**

.....

*Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the nul, the question should be answered yes.*

**21. Were the main outcome measures used accurate (valid and reliable)?**

.....

*For studies where the outcome measures return to play and re-injury rate are clearly described, the question should be answered yes.*

#### INTERNAL VALIDITY

**22. Were the patients in different intervention groups (trials and cohort studies)?**

.....

*E.g., patients for all comparison groups are selected from the same hospital.*

**23. Were study subjects in different intervention groups (trials and cohort studies) recruited over the same time?**

.....

*For a study which does not specify the time period over which patients were recruited, the question should be answered as no.*

**24. Were study subjects randomised to intervention groups?**

.....

*Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. E.g. alternate allocation would score no because it is predictable.*

<p><b>25. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?</b></p> <p><i>If assignment was concealed from patients but not from staff, it should be answered no.</i></p>	.....
<p><b>26. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?</b></p> <p><i>This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the different treatment groups but was not taken into account in the analyses.</i></p>	.....
<p><b>27. Were losses of patients to follow-up taken into account?</b></p> <p><i>If the numbers of patients lost to follow-up are not reported, the question should be answered as no. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.</i></p>	.....
<p>POWER</p> <p><b>28. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance &lt;5%?</b></p> <p><i>Sample sizes have been calculated to detect a difference of x% and y%.</i></p>	.....
TOTAL	.....

### Appendix 3

**Table S3** D&B scores for the 28 questions of the included RCTs

Author	Question number																												Total
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	<u>11*</u>	<u>12*</u>	<u>13*</u>	<u>14</u>	<u>15</u>	<u>16</u>	<u>17</u>	<u>18</u>	<u>19</u>	<u>20</u>	<u>21</u>	<u>22</u>	<u>23</u>	<u>24</u>	<u>25</u>	<u>26</u>	<u>27</u>	<u>28</u>	
Sherry & Best <sup>20</sup>	1	0	1	1	0	1	1	0	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	0	1	0	16
Silder et al. <sup>21</sup>	1	1	1	1	0	1	1	0	1	1	1	0	1	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	18
Reynolds et al. <sup>18</sup>	1	1	0	1	0	1	1	1	0	0	0	0	0	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	16
Malliaropoulos et al. <sup>19</sup>	1	1	0	1	0	1	1	0	0	1	1	0	0	0	0	0	1	1	1	0	0	1	1	1	0	0	0	1	14
Cibulka et al. <sup>17</sup>	1	1	0	1	0	1	1	0	1	0	0	0	1	0	0	0	1	1	1	1	0	1	1	1	0	0	1	0	15
Askling et al. <sup>22</sup>	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	1	1	1	1	0	1	0	1	15
Askling et al. <sup>23</sup>	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	1	1	1	1	0	1	0	1	15
Reurink et al. <sup>25</sup>	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	25
Reurink et al. <sup>25</sup>																													
scored by independent assesor (AS)	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	25
Hamid et al. <sup>24</sup>	1	1	1	1	1	1	1	1	0	1	0	0	1	0	1	0	1	1	1	0	0	1	1	1	0	1	0	1	19
Hamilton et al. <sup>26</sup>																													
PRP versus no injection	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	24
Hamilton et al. <sup>26</sup>																													
PRP versus PPP	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	27

\*Questions 11-13 were found to be highly subjective by all the assessors and interpretations varied greatly. Consensus was most often reached through the third assessor (JT).