A prospective, randomized, double-blind, placebo controlled single centre trial to assess the efficacy and safety of radial extracorporeal shock wave therapy combined with a specific rehabilitation program for acute hamstring muscle complex injury Type 3b in athletes

INVESTIGATORS	ROLE
Javier Crupnik, PT Physiotherapist. KinEf Kinesiología Deportiva Av. Cabildo 808 5°M. 1426. CABA, Argentina Phone: +54-911-51483899 E-mail: jcrupnik@ondasdechoque.com.ar	Principal Investigator
Santiago Silveti, PT KinEf Kinesiología Deportiva Av. Cabildo 808 5°M. 1426. CABA, Argentina Phone: +54-9-341-3998899 E-mail: santiagosilveti@gmail.com	Co-Author
Natalia Wajnstein, MD Especialist in Sports Medicine and Ultrasonography Av. Cabildo 808 5°M. 1426. CABA, Argentina Phone: +54-911-63544478 E-mail: dranataliaw@gmail.com	Co-Author
Peter Stiller, MD Specialist in General Medicine and Emergency Medicine Team doctor for FC Augsburg 1907 (German “Bundesliga” (First League) professional soccer club) Allgemeinmedizin Lechhausen 22 Brentanostr. Augsburg 86167 Germany Phone: +49-821-6509790 Fax: +49-821-65097922 E-mail: peter.stiller@gmx.net	Co-Author
Alisa Vollhardt Extracorporeal Shock Wave Research Unit Department of Anatomy II Ludwig-Maximilians-University 11 Pettenkoferstr. Munich, 80336 Germany Phone: +49-89-2180-72620 Fax: +49-89-2180-72683 E-mail: alisa_vh@gmx.de	Co-Author
Dr. Christoph Schmitz, MD Extracorporeal Shock Wave Research Unit Department of Anatomy II Ludwig-Maximilians-University 11 Pettenkoferstr. Munich, 80336 Germany Phone: +49-89-2180-72620 Fax: +49-89-2180-72683 E-mail: christoph_schmitz@med.uni-muenchen.de	Co-Author

1. Background

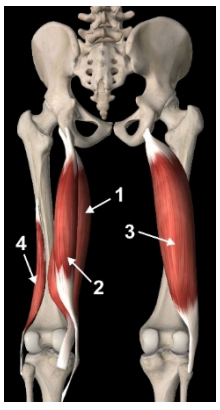
Epidemiology of acute hamstring muscle complex injury in sports

Acute injuries of the hamstring muscle complex (HMC) are frequently observed in various sports disciplines both in elite and recreational sport (Müller-Wohlfahrt et al., 2013; Fiorentino and Blemker, 2014; Kellermann et al., 2017), and are the most common injury in soccer (e.g., Petersen et al., 2014; Lohrer et al., 2016). Despite intensive research into prevention and management of acute HMC injury during the last decade epidemiological data show no decline in injury and re-injury rates (Valle et al., 2015). In this regard Petersen et al. (2010) prospectively observed 374 Danish elite soccer players during a 12-month period and registered 46 first-time and eight recurrent HMC injuries (incidence rates: 12.3% [first-time injuries] and 2% [recurrent injuries]). Statistically significantly more players experienced a first-time acute HMC injury during a match than during training. Moreover, among 32 players who suffered from acute HMC injury in a period of 12 months before the study, eight players incurred an injury that fulfilled the criteria for a recurrent injury (incidence: 25%). Approximately two thirds of the first-time injuries were categorized as moderate, with time to return to play between 8 to 28 days (Petersen et al., 2010).

Anatomy and pathophysiology

Anatomical and functional aspects of the HMC predispose it to injury, including the fact that the muscles cross two joints (Fig. 1) and undergo eccentric contraction during the gait and running cycle (Linklater et al., 2010).

Figure 1. *The hamstring muscle complex (shown from dorsal). 1, semimembranous muscle; 2, semitendinous muscle; 3, long head of the biceps femoris muscle; 4, short head of the biceps femoris muscle (picture generated with Essential Anatomy 3 registered to C.S.).*



Acute HMC injury typically occurs through an eccentric mechanism at the terminal stages of the swing phase of running (Hoskins and Pollard, 2005) (Fig. 2).

Figure 2. *Running cycle.* ***1****, initial contact;* ***2****, take off;* ***3****, initial swing;* ***4*** *and* ***5****, mid-swing;* ***6****, terminal swing. The flash symbol in* ***6*** *indicates the most vulnerable phase of the running cycle for incurring an acute HMC injury (modified from https://www.physio-pedia.com/Running_Biomechanics).*

The long head of the biceps femoris (LHBF) muscle is most commonly affected, and within the LHBF muscle, the proximal myotendinous junction and proximal locations are most commonly affected (Crema et al., 2016).

Clinical presentation and diagnosis

The diagnosis of acute HMC injury is based on the presence of acute-onset pain in the posterior thigh, and presence of the triad of pain on contraction, stretching and palpation (Reurink et al., 2014b). Imaging has a role in confirming the site of injury and characterizing its extent, providing some prognostic information and helping plan treatment (Linklater et al., 2010). In this regard both magnetic resonance imaging (MRI) and ultrasonography (US) have been shown to be effective for identification of hamstring strains and tendinopathy (e.g., Kolouris and Connell, 2005; Petersen et al., 2014; Chu and Rho, 2016). Both MRI and US provide detailed information about the HMC with respect to localization and characterization of injury (Kolouris and Connell, 2005). In a systematic review Fournier-Farley et al. (2016) established several clinical, MRI and US determinants that are associated with a longer recovery time in nonoperative management of acute HMC injury (summarized in Table 1). However, it is important to realize that for an individual HMC injury none of these MRI and US determinants show a direct correlation with the time to return to play (Petersen et al., 2014; Chu and Rho, 2016). Accordingly, the prognosis of HMC injuries should not be guided by imaging findings alone (Petersen et al., 2014).

Table 1. Determinants having an effect on the time to return to play after hamstring muscle complex injury in athletes (according to Fournier-Farley et al., 2016). MRI, magnetic resonance imaging; US, ultrasonography.

Clinical determinants	MRI determinants	US determinants
• Stretching-type injuries • Recreational-level sports • Structural versus functional injuries • Greater range of motion deficit with the hip flexed at 90° • Time to first consultation >1 week • Increased pain on the visual analog scale • >1 day to be able to walk painfree after the injury	• Positive findings • Higher grade of injury • Muscle involvement >75% • Complete transection • Retraction • Central tendon disruption of the biceps femoris • Proximal tendon involvement • Shorter distance to the ischial tuberosity • Length of the hamstring injury • Depth, volume, and large cross-sectional area	• Large cross-sectional area • Injury outside the musculotendinous junction • Hematoma • Structural injury • Injury involving the biceps femoris

Pathological classification

According to Müller-Wohlfahrt et al. (2013) muscle injuries in sports (including acute HMC injuries) should be classified as shown in Figure 3. This classification has important implications for treatment and prognosis (i.e., time to return to play) of acute HMC injury, as outlined in detail below. The anatomical difference between a Type 3a injury (minor partial muscle tear ≤ 5 mm; intrafascicle/bundle-tear) and a Type 3b injury (moderate partial muscle tear > 5 mm; interfascicle/bundle-tear) is shown in Figure 4.

Figure 3. *Classification of muscle injuries in sports (taken from Müller-Wohlfahrt et al., 2013)*

Figure removed because of copyright reasons

Figure 4. *(A) Microscopic anatomy of a skeletal muscle.* ***(B)*** *Schematic illustration of minor/intrafascicle (Type 3a) and moderate/interfascicle (Type 3b) partial muscle tears (taken from Müller-Wohlfahrt et al., 2013).*

Treatment

Acute HMC injuries Type 4 (i.e., subtotal or complete muscle tear or tendinous avulsion according to Müller-Wohlfahrt et al., 2013; Fig. 3) require early surgical repair (e.g., Brucker and Imhoff, 2005; Folsom and Larson, 2008; Barnett et al., 2015). However, acute HMC injuries Type IV are rare (Reurink et al., 2014b).

The treatment of choice of acute HMC injuries Type 3a and 3b (Figs 3 and 4) is a progressive physiotherapeutic exercise programme (e.g., Robinson and Hamilton, 2014; Reurink et al., 2014b; Hamilton et al., 2015). Besides this, there is currently only insufficient scientific evidence to support other treatment methods, including local infiltrations as recommended by Müller-Wohlfahrt et al. (2013) (Reurink et al., 2012; 2014b). In particular, injections of platelet-rich-plasma (PRP) showed no effect when compared to control (e.g., Pas et al., 2015; Zanon et al., 2016; Manduca and Straub, 2017). Results from a very prominent study by Reurink et al. (2014a) on injections of PRP in acute HMC injury Type 3b published in *The New England Journal of Medicine* are shown in Fig. 5.

It is of note that another study that was published very recently in the *The New England Journal of Medicine* demonstrated the negative clinical consequences of protracted immobilization after an acute muscle injury Type 3b in recreational sports. Starting rehabilitation two days after injury rather than waiting for nine days shortened the interval from injury to pain-free recovery and the time to return to play by approximately three weeks without any significant increase in the risk of reinjury (Bayer et al., 2017). The authors of this study concluded that the observed difference supports the importance of early loading of injured musculotendinous tissue.

According to Müller-Wohlfahrt et al. (2013) acute muscle injuries Type 3a and 3b have different time frames for recovery and return to play, with optimal treatment between 10 and 14 days in case of Type 3a and on average approximately six weeks in case of Type 3b (see also Figs 5 and 6). However, particularly in case of acute HMC injury Type 3b there is considerable interindividual variability in the time frame for return to play (Figs 5 and 6).

Most importantly, particularly the high reinjury rate of acute HMC injury suggests

that commonly utilized rehabilitation programs may be inadequate at resolving possible muscular weakness, reduced tissue extensibility, and/or altered movement patterns associated with the injury (Heiderscheit et al., 2010). Accordingly, there is need for developing innovative treatment options particularly for acute HMC injury Type 3b.

Figure removed because of copyright reasons

Figure 5. Kaplan-Meier curves for the cumulative probability of resumptions of sports activity after treating acute HMC injury Type 3b with injections of platelet-rich-plasma or placebo in a study by Reurink et al. (2014a) published in *The New England Journal of Medicine* (modified from Reurink et al., 2014a). Each patient in the PRP+ group received two 3-ml injections of PRP. The first injection was administered within five days after the injury and was followed five to seven days later by the second injection. Patients in the PRP- group received two 3-ml injections of saline (placebo). Besides this, patients in both groups performed an identical, daily, progressively phased, criteria-based rehabilitation program that was based on the best available evidence (Sherry and Best, 2004; Mason et al., 2005; Heiderscheid et al., 2010). The vertical red lines indicate the times to return to play with optimal treatment after acute muscle injury Type 3a (between 10 and 14 days) and Type 3b (approximately 6 weeks) established by Müller-Wohlfahrt et al. (2013). Note the considerable interindividual variability in the time frame to return to play in this study by Reurink et al. (2014a) (range, 14 to 105 days; green line).

Figure removed because of copyright reasons

Figure 6. Kaplan-Meier curves for the cumulative probability of resumptions of sports activity after treating acute HMC injury Type 3b (in approximately 60% of the patients) or acute calf muscle injury Type 3b (in approximately 40%) with a standardized four-stage therapy regimen (daily repeated static stretching (week 1), daily isometric loading with increasing load (weeks 2 to 4), dynamic loading with increasing resistance three times per week (weeks 5 to 8) and functional exercises combined with heavy strength training three times per week (weeks 9 to 12) in a study by Bayer et al. (2017) published in *The New England Journal of Medicine* (modified from Bayer et al., 2017). The therapy started either on day 2 after injury (early-therapy group) or on day 9 after injury (delayed-therapy group), respectively. The vertical red lines indicate the median times to return to play for the two

groups (62.5 days in case of the early-therapy group and 83 days in case of the delayed-therapy group).

Novel treatment options for acute HMC injury Type 3b

Very recently it was demonstrated that extracorporeal shock wave therapy (ESWT) may accelerate regeneration after acute skeletal muscle injury (Zissler et al., 2017; Mattyasovszky et al., 2017). The use of extracorporeal shock waves in medicine was first reported over 30 years ago as a treatment for kidney stones (Chaussy et al., 1980), and is commonly referred to as 'extracorporeal shock wave lithotripsy', or 'ESWL' (Rassweiler et al., 2011). Extracorporeal shock waves are also used as a treatment for musculoskeletal conditions such as plantar heel pain (reviewed in, e.g., Speed, 2014; Schmitz et al., 2015) and boney non-union (Biedermann et al., 2003; Cacchio et al., 2009), and is commonly referred to as 'extracorporeal shock wave therapy' (ESWT) to differentiate from ESWL (Speed, 2014).

With respect to regeneration after acute skeletal muscle injury Zissler et al. (2017) divided adult Sprague-Dawley rats into four experimental groups (2 ESWT+ groups and 2 ESWT- groups) as well as an uninjured control group ($n \geq 6$ in each group). An acute cardiotoxin-induced injury was set into the quadriceps femoris muscle of the rats in the experimental groups. Then, a single session of focused extracorporeal shock wave therapy (fESWT; outlined in detail below) was administered to injured muscles of the rats in the fESWT+ groups one day after injury, whereas the rats in the fESWT- groups received no treatment. At four and seven days after injury, one rat each of the fESWT+ and fESWT- groups was euthanized. Regenerating lesions were excised and analyzed by histomorphometry and immunohistochemistry to assess fiber size, myonuclear content, and recruitment of satellite cells. Zissler et al. (2017) found that the size and myonuclear content of regenerating fibers in fESWT+ muscles were statistically significantly increased compared with fESWT- muscle fibers at both four and seven days after injury. Similarly, at both time points, fESWT+ muscles exhibited statistically significantly higher contents of paired box protein 7 (pax7)-positive satellite cells, mitotically active H3P+ cells, and of cells expressing the myogenic regulatory factors, myoD and myogenin. These data indicate enhanced proliferation and differentiation rates of satellite cells after fESWT. Mitotic activity at four days after injury was doubled in fESWT+ compared with fESWT- muscles. Zissler et al. (2017) concluded that fESWT may stimulate regeneration of skeletal muscle tissue and accelerate repair processes.

Mattyasovszky et al. (2017) (with one of us [C.S.] serving as co-author) isolated cells from muscle specimens taken from adult patients undergoing spine surgery. Muscle cells

were exposed to radial extracorporeal shock wave therapy (rESWT) *in vitro* with different energy flux densities. Cell viability and gene expression of Pax7, neural cell adhesion molecule (NCAM) and myogenic factor 5 (Myf5) as muscle cell markers were compared to non-exposed muscle cells that served as controls. The authors found that isolated muscle cells were positive for the hallmark protein of satellite cells, Pax7, NCAM and Myf5. Exposure to rESWT at low energy densities enhanced cell viability whereas higher energy densities had no significant impact on cell viability. Gene expression of Pax7 was up-regulated after exposure to higher energy densities, whereas Pax7, NCAM and Myf5 gene expression was down-regulated after exposure to even higher energy densities. Mattyasovszky et al. (2017) concluded that rESWT has the potential to modulate the biological function of human skeletal muscle cells.

There are three different types of extracorporeal shock waves that could be used in ESWT for acute HMC injury Type 3b, focused, defocused and radial (Fig. 7), and several modes of operation of focused, defocused and radial extracorporeal shock wave generators (Fig. 8).

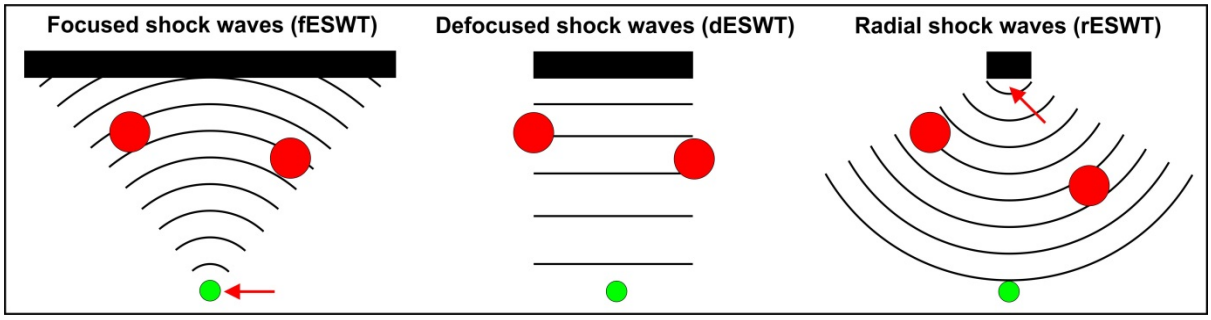


***Figure** 7 (modified from Schmitz et al., 2015). Working principle of focused (on the left), defocused (in the middle) and radial (on the right) extracorporeal shock wave technology. In case of focused shock waves, single acoustic pulses are generated either with a spark-gap (electrohydraulic principle), a technology similar to a loudspeaker (electromagnetic principle), or piezocrystals (piezoelectric principle) (black bars represent shock wave generators; details are provided in Fig. 8 below). By means of reflectors of certain shape and/or the use of acoustic lenses the acoustic pulses are converted into a focused acoustic pressure wave/shock wave with a point of highest pressure (red arrow) at the desired target (green dot) within pathological tissue. By changing the shape of the reflector (and/or the acoustic lens) the acoustic waves emitted from a focused shock wave generator can be converted into a slightly convergent, parallel, or even divergent acoustic pressure wave/shock wave ("defocused shock wave"). In case of radial shock waves a projectile is fired within a guiding tube that strikes a metal applicator placed on the patient's skin. The projectile generates stress waves in the applicator that transmit pressure waves into tissue. The point of highest pressure is found at the*

tip of the applicator. It is of note that any disturbance in the pathway of the acoustic pulses between a focused shock wave source and the target within tissue (such as bone, calcifications, etc.; red dots in the figures) may result in some parts of the acoustic pulse not reaching the target and, thus, weakening the shock wave energy (i.e. the energy density) at the target. The same disturbances would not impact the energy of radial shock waves at the target (for defocused shock waves it is unknown to what extent they are weakened by disturbance in the pathway of the acoustic pulses between the shock wave source and the target within tissue). This is most probably the reason why in muscle tissue, the energy of focused shock waves was found to be decreased by >50% compared to measurements in water, whereas for radial shock waves measurements in muscle tissue and water were consistent (Kearney et al., 2010).

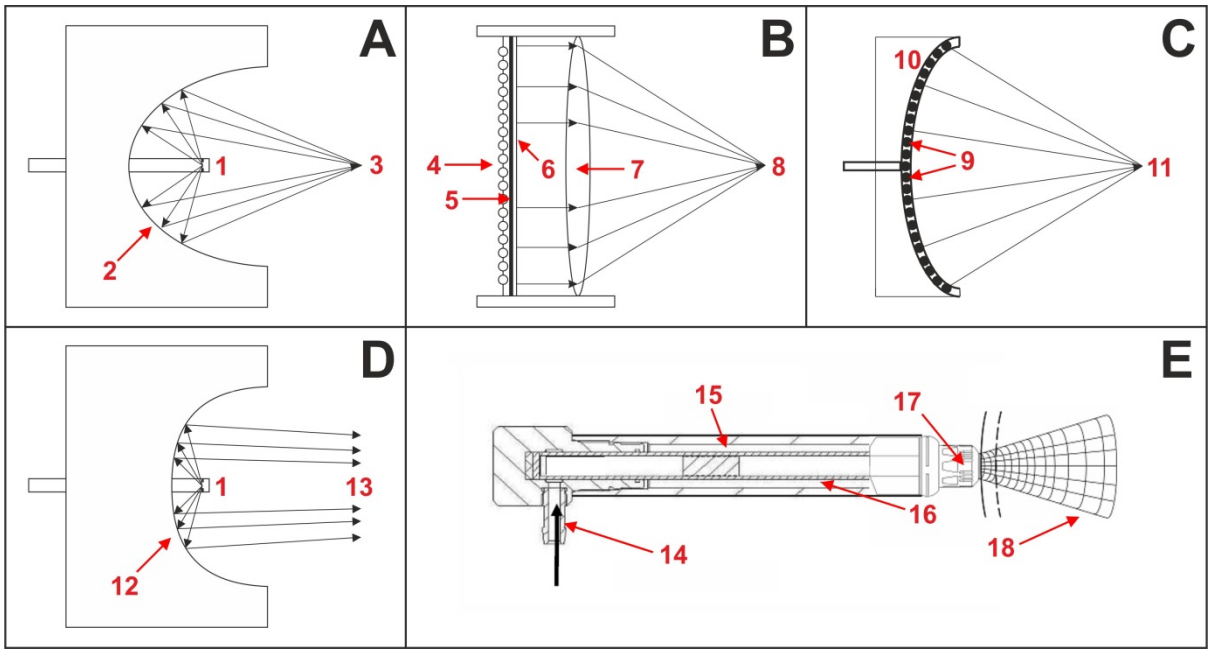


Figure 8 *(modified from Schmitz et al., 2015). Schematic representation of the mode of operation of focused (**A-C**), defocused (**D**) and radial (**E**) extracorporeal shock wave generators. (**A**) Electrohydraulic principle (fESWT): a high voltage discharges rapidly across two electrode tips (spark-gap) (1) that are positioned in water. The spark-gap serves as the first focal point (1). The heat generated by this process vaporizes the surrounding water. This generates a gas bubble centered on the first focal point, with the gas bubble being filled with water vapor and plasma. The result of the very rapid expansion of this bubble is a sonic pulse, and the subsequent implosion of this bubble causes a reverse pulse, manifesting a shock wave. By means of reflectors of certain shape (2), this shock wave can be converted into a convergent/focused acoustic pressure wave/shock wave with a point of highest pressure at the second focal point (3). (**B**) Electromagnetic principle (fESWT): a strong, variable magnetic field is generated by passing a high electric current through a coil (4). This*

*causes a high current in an opposed metal membrane (5), which causes an adjacent membrane (6) with surrounding liquid to be forced rapidly away. Because the adjacent membrane is highly conductive, it is forced away so rapidly that the compression of the surrounding liquid generates a shock wave within the liquid. By means of an acoustic lens (7) of certain shape, this shock wave can be converted into a convergent/focused acoustic pressure wave/shock wave with a point of highest pressure at a focal point (8). (**C**) Piezoelectric principle (fESWT): a large number of piezocrystals (9) are mounted in a bowl-shaped device (10); the number of piezocrystals can vary from a few to several thousands (typically between 1,000 and 2,000). When applying a rapid electrical discharge, the piezocrystals react with a deformation (contraction and expansion), which is known as the piezoelectric effect. This induces an acoustic pressure puls in the surrounding water that can steep into a shock wave. Because of the design of the bowl-shaped device an acoustic pressure wave/shock wave can emerge with a point of highest pressure at a focal point (11). (**D**) Defocused principle (shown here for the electrohydraulic principle). By changing the shape of the reflector (12) the shock wave emitted from the first focal point is converted into a slightly convergent, parallel, or even divergent acoustic pressure wave/shock wave ("defocused shock wave") (13). (**E**) Ballistic principle (rESWT): compressed air (pneumatic principle; 14) or a magnetic field (not shown) is used to fire a projectile (15) within a guiding tube (16) that strikes a metal applicator (17) placed on the patient's skin. The projectile generates stress waves in the applicator that transmit pressure waves into tissue (18).*

To our knowledge randomized controlled trials (RCTs) testing efficacy and safety of rESWT for acute HMC injury Type 3b have not yet been published. In contrast, rESWT has become an established treatment modality for various musculoskeletal conditions such as calcifying tendonitis of the shoulder, tennis elbow and plantar fasciopathy, to mention only a few (details can be found in Schmitz et al., 2015). Among the 44 RCTs on rESWT currently listed in the PEDro database (status of September 09, 2017), 29 (66%) were performed with the rESWT device Swiss DolorClast (Electro Medical Systems, Nyon, Switzerland).

All of us (J.C., P.S. and C.S.) have extensive practical experience with rESWT for various musculoskeletal conditions using the Swiss DolorClast. **Most importantly, all of us have already gained practical experience with rESWT for acute HMC injury Type 3b in athletes.** One of our (P.S. and C.S.) most prominent patients was a professional soccer player at a European top club (regularly playing in the UEFA Champions League) who incurred a HMC injury Type 3b and returned to play (full 90-min match with his national team) 35 days later. In the aforementioned studies by Reurink et al. (2014a) (outlined in detail in Fig. 5 above) and Bayer et al. (2017) (outlined in Fig. 6 above) the cumulative probability of resumptions of sports activity on day 35 after acute HMC injury Type 3b in

professional soccer players (Reurink et al., 2014a) or recreational athletes (Bayer et al., 2017) was only respectively 20% (Reurink et al., 2014a) or 5% (Bayer et al., 2017) after treatment with a rehabilitation program (Fig. 9).

Figure removed because of copyright reasons

Figure 9. *Cumulative probability of resumptions of sports activity after treating acute HMC injury Type 3b in studies by Reurink et al. (2014a) (**A**) and Bayer et al. (2017) (**B**) published in The New England Journal of Medicine. The red lines indicate the cumulative probability of resumptions of sports activity on day 35 after injury after treatment with a rehabilitation program (placebo group in the study of Reurink et al. (2014a) and early-therapy group in the study by Bayer et al. (2017))..*

Considering the limited evidence of efficacy and safety of rESWT for acute HMC injury Type 3b, further research is needed to support the use of rESWT for this condition. Taking into account the proven efficacy and safety of rESWT using the Swiss DolorClast for treating musculoskeletal conditions (Schmitz et al., 2015), the widespread use of the Swiss DolorClast based on its proven efficacy and safety, and our own very promising pilot data of rESWT using the Swiss DolorClast for treating acute HMC injury Type 3b in athletes it is reasonable to hypothesize that (i) the combination of rESWT and a specific rehabilitation program is effective and safe in treatment of acute HMC injury Type 3b, (ii) this combination therapy is statistically significantly more effective than the same specific rehabilitation program alone, and (iii) this combination therapy will gain widespread acceptance as soon as effectiveness and safety will be demonstrated in a randomized controlled trial. This is the main purpose of the proposed study.

2. Hypothesis

- Based on the results of the systematic literature search outlined above it is hypothesized here that the **combination of radial extracorporeal shock wave therapy performed with the Swiss DolorClast device (Electro Medical Systems, Nyon, Switzerland) and a specific rehabilitation program (thereafter, "rESWT + RP")** is effective and safe in treatment of acute HMC injury Type 3b, and is statistically significantly more effective than the combination of sham-rESWT and RP (thereafter, "sham-rESWT + RP").

3. Study Objectives

3.1. General Objective

1) To determine the efficacy and safety of rESWT + RP (compared with sham-rESWT + RP) in treatment of acute HMC injury Type 3b.

3.2. Specific Objectives

1) To determine the individual and mean time to return to play after treating acute HMC injury Type 3b with respectively rESWT + RP or sham-rESWT + RP.
2) To determine the incidence of re-injury during a period of six months after return to play following treatment of acute HMC injury Type 3b with respectively rESWT + RP or sham-rESWT + RP.
3) To evaluate patient's pain score during respectively rESWT or sham-rESWT for acute HMC injury Type 3b using the Visual Analogue Scale (VAS) score.
4) To evaluate patient's satisfaction at six months after the end of treatment.

4. Study protocol

4.1. Introduction

An advanced study design of a clinical trial is ways more than just to decide how many patients will be treated with treatment X and how many patients with treatment Y, and how treatments X and Y should be performed. Actually an advanced study design of a RCT has to consider everything that will be checked later in assessments of the methodological quality of a RCT of health care interventions. There are at least six different assessments available:

1. Jadad et al. (1996) – This is a very basic assessment, attributing to each RCT a quality score out of a maximum of six points: (1) Was the generation of randomization sequence described? (2) Was the method of allocation concealment described? (3) Was an

intention to treat analysis used? (4) What number of patients was lost to follow-up? (5) Was the outcome assessment blind? and (6) Was the patient blind to treatment allocation? The design of the proposed study on rESWT + RP for acute HMC injury Type 3b considers all these aspects.

2. The DELPHI list (Verhagen et al., 1998) – The DELPHI list consists of the following questions: (1) Was a method of randomization performed? (2) Was the treatment allocation concealed? (3) Were the groups similar at baseline regarding the most important prognostic indicators? (4) Were the eligibility criteria specified? (5) Was the outcome assessor blinded? (6) Was the care provider blinded? (7) Was the patient blinded? (8) Were point estimates and measures of variability presented for the primary outcome measures? (9) Did the analysis include an intention-to-treat analysis? The design of the proposed study on rESWT + RP for acute HMC injury Type 3b considers all these aspects, except of the fact that the care providers will not be blinded.
3. The PEDro scale (Physiotherapy Evidence Database; www.pedro.org.au; Blobaum, 2006) - This scale is a development of the DELPHI list and consists of a total of 10 scale items, including random allocation, concealment of allocation, comparability of groups at baseline, blinding of patients, therapists and assessors, analysis by intention to treat and adequacy of follow-up, between-group statistical comparisons, and reports of both point estimates and measures of variability. The design of the proposed study on rESWT + RP for acute HMC injury Type 3b considers all these aspects, except of the fact that the therapists will not be blinded.
4. Chalmers et al. (1981) – This assessment consists of two evaluation forms that include 29 individually scored items, allowing a maximum score of 100.
5. Downs and Black (1998) –This assessment includes 27 individually scored items, allowing a maximum score of 32.
6. The CONSORT statement (Schulz et al., 2010) – The CONSORT statement is intended to improve the reporting of RCTs, enabling readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results.

The assessments of Chalmers et al. (1981), Downs and Black (1998) and Schulz et al. (2000) are very similar. However, Downs and Black (1998) provide the most specific questions. Accordingly, the design of the proposed study on rESWT + RP for acute HMC injury Type 3b was developed according to the criteria set out by Downs and Black (1998). The proposed study on rESWT + RP for acute HMC injury Type 3b will achieve a very high rating on the assessment by Downs and Black (1998).

4.2. Study design

- Main study: randomized controlled trial (RCT) on rESWT + RP vs. sham-rESWT + RP, with blinding of patients and evaluators/assessors, but without blinding of therapists applying the treatments (the rationale for this is provided in Section 4.11. *"Blinding of therapists and assessors"* below).

4.3. Inclusion criteria

- Adults (both male and female) with clinical and ultrasonographic diagnosis of acute HMC injury Type 3b.
- Age range: between 18 and 35 years.
- Physical conditions for rehabilitation (i.e., no surgery required)
- Willingness of the patient to participate in the study, and written informed consent signed and personally dated by the patient.
- No contraindications for rESWT.

4.4. Exclusion criteria

- Children and teenagers below the age of 18.
- Adults aged >35 years old.
- Patients with clinical and ultrasonographic diagnosis of acute HMC injury Type 3b who got injured more than seven days before potential enrollment into this study.
- Patients with clinical and ultrasonographic diagnosis of acute HMC injury Type 3A or Type 4.
- Bilateral acute HMC injury (Types 3A, 3B or 4).
- Proven or suspected HMC injury (Types 3A, 3B or 4) of the same lower limb in the time period of six months before potential enrollment into this study.
- Muscle injury caused by external impact on the back of the affected thigh (Category B according to Müller-Wohlfahrt et al., 2013).
- Surgery on the affected lower limb in the time period of one year before potential enrollment into this study.
- Acute or chronic lumbar pathology (because some cases of thigh pain may relate to spinal pathology; c.f. Linklater et al., 2010).
- No willingness of the patient to participate in this study, and/or written informed consent not signed and not personally dated by the patient.
- Contraindications of rESWT:
    - treatment of pregnant patients,
    - treatment of patients with blood-clotting disorders (including local thrombosis),

- treatment of patients treated with oral anticoagulants,
- treatment of patients with local bacterial and/or viral infections/inflammations,
- treatment of patients with local tumors, and
- treatment of patients treated with local corticosteroid applications in the time period of six weeks before the first rESWT session (if applicable).

4.5. Groups and treatments

All subjects will perform a specific rehabilitation program (RP) that will last for eight weeks, independent of the individual time interval to return to play (in line with Bayer et al., 2017). This RP was developed based on recommendations in the literature (Mendiguchia and Brughelli, 2011; Askling et al., 2014; Mendiguchia et al., 2017). The key objective of this RP is that after injury, the subject will develop functional, neuromuscular and biomechanical skills according to the demands of the sport she/he performs, while minimizing the risk of re-injury. Therefore, the proposed RP will take the subject through a combination of low-risk and high-demand movements, based on a systematic process. This process will consist of an orderly sequence of steps or phases – acute phase, subacute/regeneration phase, and functional phase). Each phase will depend on the outcome of the previous phase and will use the individualized response as criterion of progression. The RP will be controlled by the same physiotherapist who will not participate in the inclusion/exclusion process or any subsequent evaluation of the subject.

Acute phase

The goals of the acute phase include:

- prevent re-rupture at the injured site,
- prevent excessive inflammation and formation of scar tissue,
- increase tensile strength, adhesion and elasticity of new granulation tissue,
- reduce build-up of interstitial fluid, and
- detect and treat any lumbo-pelvic dysfunction.

Once a subject will be included in the proposed study she/he will be instructed to avoid the use of medication and apply the RICE principle (rest, ice, compression and elevation) three times per day in order to stop the injury-induced bleeding into the muscle tissue and thereby minimize the extent of the injury (see, e.g., Jarvinen et al., 2007).

With regard to the optimum time interval for starting active rehabilitation after acute HMC injury Type 3b Jarvinen et al. (2007) recommended immobilization for three to five days, followed by active mobilization. Bayer et al. (2017) pointed out that starting rehabilitation two days after injury rather than waiting for nine days shortened the interval from injury to pain-

free recovery and the time to return to play by approximately three weeks without any significant increase in the risk of reinjury. However, it is not known whether starting rehabilitation already two days after injury has any benefit over starting rehabilitation five days after injury. We will therefore follow the recommendation by Jarvinen et al. (2017) and progress to the sub-acute phase after five days.

The criterion for progression to the subacute/regeneration phase will be

- absence of pain five days after injury.

If the symptoms caused by the injured muscle persist for more than five days we will reconsider the existence of more extensive tissue damage and/or intramuscular hematoma that might require special attention and treatment by an orthopedic surgeon.

Subacute/Regeneration Phase

The goals of the subacute/regeneration phase include:

- improve overall core stability,
- improve strength and symmetry,
- reduce pain during prone isometric, isolated hamstring contractions at 15° knee flexion,
- improve hamstring flexibility of both legs,
- improve hip flexor flexibility of both legs, and
- improve neuromuscular control.

During the subacute/regeneration phase the subject will work on both legs daily during a single session. Exercises will be conducted to correct the different risk factors and mechanisms related to the lesion of the hamstring musculature. The exercises will be divided into four groups:

- core stability and lumbopelvic control,
- flexibility and neural mobilization,
- hamstring and gluteal strength, and
- running technique

(see also http://wolterskluwer.http.internapcdn.net/wolterskluwer_vitalstream_com/MP4s/permalink/mss/a/mss_2017_02_28_mendiguchia_msse-d-16-00910r4_sdc1.mp4).

In addition, basic aerobic conditioning will start when the subject will be able to perform at least three sessions of the running technique without any discomfort or pain. Three running sessions per week will be performed at the clinic of the Principal Investigator and will include four sets of five minutes at a low to moderate intensity (individually rated by the subject). Suspension of running sessions will be permitted in the event of discomfort or pain.

The criteria for progression to the functional phase will be:

- no pain in prone position with knee flexed to 15°,
- no pain during slump test,
- < 10% asymmetry when in prone position with knee flexed to 15°,
- < 10% asymmetry during active knee extension test, and
- < 5° asymmetry in the modified Thomas Test.

Functional phase

The goals of the functional phase include:

- increase the optimum length of the hamstrings,
- decrease leg asymmetries in optimum length,
- decrease leg asymmetries in concentric hip extension,
- decrease leg asymmetries in horizontal force production during running, and
- improve torsional capabilities.

The functional phase will comprise daily exercises, with three sessions per week at the clinic of the Principal Investigator (every other day) and the remaining sessions at the club or at home. The exercises will comprise the following:

- core stability and lumbopelvic control,
- flexibility and neural mobilization,
- hamstring and gluteal strength,
- plyometric training, and
- running technique.

During the Functional Phase, the running session will consist of two sets of ten minutes at moderate to high intensity (individually rated by the subject). Suspension of running sessions will be permitted in the event of discomfort or pain.

The criteria for return to play will be (according to van der Horst et al., 2016):

- absence of pain on palpation,
- absence of pain during flexibility testing (active knee extension test and passive straight leg raise test),
- absence of pain during strength testing (isometric force test),
- absence of pain during and after functional testing (repeated sprint ability test and single leg bridge),
- similar hamstring flexibility,
- psychological readiness / athlete confidence, and
- clearance by the medical staff.

The quantity and quality of the supervised rehabilitation sessions at home or the sports club will be documented.

Patients in the rESWT group will receive the below:

- Specific rehabilitation program as outlined above.
- In addition: rESWT as follows:
  - nine rESWT sessions;
  - three sessions per week (interval between sessions: two or three days);
  - rESWT device: Swiss DolorClast (Electro Medical Systems, Nyon Switzerland), EvoBlue handpiece, 15 mm applicator;
  - 2500 rESWs per session, with energy density between 0.12 and 0.16 mJ/mm^2 (achieved by operating the Swiss DolorClast at air pressure between three and four bar), depending on what the patient tolerates;
  - rESWs applied at 15 Hz (i.e., 15 rESWs per second), resulting in treatment time between three and five minutes per session;
  - application of rESWs in prone position, with the patient lying on an examination table;
  - exact location of the application of rESWs determined by clinical and ultrasonographic examinations;
  - treatment of both the side of injury and the entire affected muscle (from distal to proximal in order to relax the affected muscle);
  - application of rESWs in sagittal (dorsal $\rightarrow$ventral) direction; and
  - no use of local anesthesia.

Patients in the sham-rESWT group will receive the below:

- Specific rehabilitation program as outlined above.
- In addition: sham-rESWT as outlined above, with a specially designed placebo EvoBlue handpiece that looks and sounds like the EvoBlue handpiece of the Swiss DolorClast, but does not generate radial shock waves. This is achieved by blocking the projectile ["13" in Fig. 2] shortly before it strikes the metal applicator ["15" in Fig. 2]). The placebo EvoBlue handpiece will not emit any radial shock wave energy.

4.6. Recruitment of patients

- Patients in the rESWT group and the sham-rESWT group will be recruited from the Club Deportivo UAI Urquiza (Villa Lynch, Province Buenos Aires, Argentina) and will be recruited over the same period of time (approximately 12 months).
- Recruitment of patients will start immediately after approval of the study by the Ethics Committee of the Universidad Abierta Interamericana (Buenos Aires, Argentina).

- Officials of the Club Deportivo UAI Urquiza will be instructed that athletes who experience sudden, sharp pain in the posterior aspect of the thigh during training or competition shall immediately stop activity. These athletes will then be evaluated regarding the presence of the inclusion criteria of this study on the day of injury.
- All potential patients that fulfill the inclusion criteria and do not fulfill any of the exclusion criteria outlined above will be offered to participate in this study until the total number of patients (rESWT group: n=20; sham-rESWT group: n=20) will be recruited. Accordingly, the patients that will be prepared to participate in this study will be representative of the entire population from which they were recruited. We will report the proportion of those asked who agreed.
- The intervention will be undertaken in a specialist centre that is representative of the clinics most of the source population would attend if seeking treatment of acute HMCinjury Type 3b.

4.7. Informed Consent Process

Should patients agree to be part of this study, they will be guided through the informed consent process first, as described here. The Informed Consent Process will be done at the clinic of the Principal Investigator of this study (Javier Crupnik, Av. Cabildo 808, 5º M, Buenos Aires, Argentina). A copy of the Participant Information Sheet will be given to them. The patient will be given sufficient time to read and understand everything written on the document. The Principal Investigator will be there to explain and answer any queries that may arise. The patient will sign the Informed Consent Form if agreeable thereafter.

4.8. Randomization and blinding of patients

- Patients that fulfill the inclusion criteria and do not fulfill any of the exclusion criteria will be randomly allocated to either rESWT + RP (n=20) or sham-rESWT + RP (n=20).
- Randomization will be performed as described by Rompe et al. (2008) in a randomized, controlled study on rESWT for Achilles tendinopathy. Specifically, a computerized random-number generator will be used to formulate an allocation schedule. Patients will be randomized to either treatment (rESWT + RP or sham-rESWT + RP), with use of the method of randomly permuted blocks. The randomization scheme will be generated with the use of the website, www.randomization.com. Fifty patients will be randomized into five blocks. A medical assistant at the clinic of the Principal Investigator will allocate interventions by means of opaque sealed envelopes that will be marked according to the allocation schedule. The medical assistant will be unaware of the size of the blocks.

- The randomized intervention assignment as outlined above will be concealed from both patients and health care staff until recruitment will be complete and irrevocable.
- Patients will be blinded in this study.
- The assessor will be blinded in this study. The assessor is the person who will assess the outcome of treatment during follow up. In this study, the assessor will be a medical assistant at the clinic of the Principal Investigator.
- The therapist will not be blinded in this study. The therapist is the person who will administer either rESWT or sham-rESWT to the patient. In this study, the therapist will be the Principal Investigator (J.C.).

4.9. Study treatment and visits

As outlined in Section 4.5 “Groups and treatments” above all subjects will perform RP that will last for eight weeks, independent of the individual time interval to return to play.

- The RP will start with a first visit to the clinic of the Principal Investigator during which clinical and ultrasonographic diagnosis will be performed. This first visit may take place on the day of injury (D0) or the first day (D1) or second day (D2) after injury (the sooner the better).
- After the first visit an individual number of days will follow until the fifth day after injury (D5) will be reached (acute phase). During this time the subject will apply the RICE principle (rest, ice, compression and elevation). Visits to the clinic of the Principal Investigator may be scheduled during this time but are not mandatory.
- On D5 the subacute/regeneration phase of the RP will start, with three visits per week to the clinic of the Principal Investigator (outlined in detail in Section 4.5 “Groups and treatments” above). The exact time for progression from the subacute/regeneration phase to the functional phase of the RP will be individually determined, depending on whether the criteria for progression will be fulfilled. During the functional phase there will also be three visits per week to the clinic of the Principal Investigator.
- Study treatments (rESWT or sham-rESWT) will start on D5. Each subject will be treated with nine sessions of rESWT or sham-rESWT, with three sessions per week. Accordingly, study treatments may take place at D5, D7, D9, D12, D14, D16, D19, D21 and D23.
- Six months after inclusion into the study there will be a separate visit for evaluating patient’s satisfaction with the treatment outcome.

The time interval necessary for reaching return to play will be as follows:

- Based on our experience we expect that approximately 75% of the subjects treated with rESWT + RP will reach return to play within five weeks after D0.
- Furthermore, we expect that only approximately 25% of the patients treated with sham-rESWT + RP will reach return to play within five weeks after D0.

The Principal Investigator will perform the following procedures at the first visit:

- check eligibility
- obtain informed consent
- perform randomization
- collect patient's demographics & medical history

Furthermore, the Principal Investigator will perform the following procedures at all visits:

- record any concomitant medication
- perform clinical examination
- perform physical examination of the injured muscle
- dispense study treatment
- perform efficacy assessment
- report adverse events (AE) and serious adverse events (SAE)
- complete relevant section of case report form (CRF)

4.10. Outcome of Interest

4.10.1. Primary clinical outcome and definition of treatment success

- Primary clinical outcome will be the individual time (days) necessary to return to play.
- Individual treatment success is defined as the possibility to return to play with the following criteria fulfilled (according to van der Horst et al., 2016):
    - absence of pain on palpation,
    - absence of pain during flexibility testing (active knee extension test and passive straight leg raise test),
    - absence of pain during strength testing (isometric force test),
    - absence of pain during and after functional testing (repeated sprint ability test and single leg bridge),
    - similar hamstring flexibility,
    - psychological readiness / athlete confidence, and
    - Medical Staff clearance.

4.10.2. Secondary clinical outcomes

Secondary clinical outcomes will be:

- individual patient's satisfaction at six months after inclusion into the study (using a scale ranging from 0 [maximum dissatisfaction] to 10 [maximum satisfaction]), and
- presence or absence of re-injury during a time period of six months after inclusion into the study (defined as sudden, sharp pain in the posterior aspect of the thigh that was initially injured, accompanied by the same objective criteria initially used for the diagnosis of acute HMC injury Type 3b).

4.10.3. Additional evaluations

In addition to primary and secondary clinical outcomes the following parameters will be evaluated and reported:

- Patient's sex, age, weight, height, and body mass index.
- Interval between injury and the first treatment (in days).
- Patient's individual training load (number of training sessions per week; duration of training sessions).

4.11. Blinding of therapists and assessors

- Therapists applying the treatments will not be blinded. This will be done because even when using coded "active" and "placebo" handpieces in a study on rESWT, blinding of therapists can only be achieved when another person prepares the device before rESWT or sham-rESWT. This, however, is almost impracticable and has not been done in any of the more than 100 studies on radial and focused ESWT listed in the PEDro database (Schmitz et al., 2015). The solution to this issue is a strict, standardized way of interaction between the therapist and the patients, irrespective of treatment allocation (as mentioned in a study by Buchbinder et al., 2002). This approach will also be applied in the present study.
- All assessments before the first treatment (baseline) and during the follow-up period will be performed by assessors blind to the intervention.

5. Follow-up and statistical analysis

- Follow-up will be the same for all study patients (outlined in detail in Section 4.10. above).
- The design of this study guarantees that there will be full compliance with the allocated treatment and, thus, no contamination of one group.

- The patient's age, gender, body mass index, sport that practices, position in the field, sporting gesture that caused the injuriy are potential confounding factors when treating acute HMC injury Type 3b with rESWT. Normal distribution of these data will be tested using the D'Agostino-Pearson omnibus test. In case of passing the normality test we will report mean and standard error of the mean of these variables; otherwise we will report inter-quartile ranges of these variables. Comparison between groups will be performed with Student's t test in case of passing the normality test or the nonparametric Mann-Whitney test in case of not passing the normality test.
- As outlined in Section 4.11.1. "Primary clinical outcome and definition of treatment success" above, the primary clinical outcome will be the individual time (days) necessary to return to play. The primary clinical outcome will return a single data point (number of days) for each patient. Time of return to play is not normally distributed data. Accordingly, we will report inter-quartile ranges of this variable. Comparison between groups will be performed using the nonparametric Mann-Whithney test.
- As outlined in Section 4.11.2. "Secondary clinical outcomes" above, one secondary clinical outcome will be assessment of patient's satisfaction at six months after inclusion into this study (using a scale ranging from 0 [maximum dissatisfaction] to 10 [maximum satisfaction]). This secondary clinical outcome will return a single data point (on a scale ranging from 0 zo 10) for each patient, which is not normally distributed data. Accordingly, we will report inter-quartile ranges of this variable. Comparison between groups will be performed using the nonparametric Mann-Whithney test.
- As also outlined in Section 4.11.2. "Secondary clinical outcomes" above, another secondary clinical outcome will be presence or absence of re-injury during a time period of six months after inclusion into the study. This secondary clinical outcome will return a single data point ("yes" or "no") for each patient, which is not normally distributed data. Accordingly, we will report absolute and relative numbers of "yes" and "no" of this variable. Comparison between groups will be performed using Fisher's exact test.
- The probability value of less than 0.05 (p-value < 0.05) will be considered as statistically significant (Lang &Secic, 2006).
- All calculations will be performed using GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego, CA, USA).
- All main conclusions of the study will be based on analyses of intention to treat rather than anaylses of treatment. Note that there are various available methods for handling missing data in clinical trials (European Medicines Agency, 2010). In case of missing data (i.e., in case a patient will withdraw or will be lost during the treatment or the follow-up periods) we will determine together with the statistics experts at the Institute for

Medical Informatics, Biometry and Epidemiology (IBE) at the Ludwig-Maximilians-University of Munich (Munich, Germany) the most appropriate method for performing analyses of intention to treat. After randomization and the first rESWT or placebo treatment, no patient will be replaced.

- All efforts will be made to keep the proportion of patients lost to follow-up too small to affect the main findings of this study.
- Patient-centered care throughout this study will ensure that no patients will be lost to follow-up, or the number of patients lost to follow-up will be so small that findings would be unaffected by their inclusion.
- We will report actual probability values for all outcomes except where probability values less than 0.001 are found.
- We will avoid any retrospective unplanned subgroup analysis and, thus, “data dredging”.

5.1. Power analysis

In the aforementioned studies by Reurink et al. (2014a) (outlined in detail in Fig. 5 above) and Bayer et al. (2017) (outlined in Fig. 6 above) the cumulative probability of resumptions of sports activity on day 35 after acute HMC injury Type 3b in professional soccer players (Reurink et al., 2014a) or recreational athletes (Bayer et al., 2017) was only respectively 20% (Reurink et al., 2014a) or 5% (Bayer et al., 2017) after treatment with a rehabilitation program (Fig. 9).

On this basis we performed a Power analysis for a percentage of 25% as well as (ii) for various other percentages (ranging between 10% and 99.9%) of patients with treatment success when treated with sham-rESWT + RP (n=20), accounting for a two sided-confidence interval of 95% (and, thus, a type-1 error rate of 5%) and a percentage of patients with treatment success when treated with rESWT + RP (n=20) of 75%. Calculations were performed using the software, Open Source Epidemiologic Statistics for Public Health (www.openepi.com). The results are summarized in Table 3 (on the next page).

Furthermore, we calculated the minimum sample size in both groups (rESWT + RP, sham-rESWT + RP) that would be necessary for detecting a difference in treatment success between the patients treated with rESWT + RP and the patients treated with sham-rESWT + RP accounting for a two sided-confidence interval of 95% and a power of 0.8. Calculations were also performed using the software, Open Source Epidemiologic Statistics for Public Health (www.openepi.com). The results are summarized in Table 4 (also on the next page).

Table 3. Power for the proposed RCT on rESWT + RP for acute HMC injury Type 3b, accounting for a two sided-confidence interval of 95% and a percentage of patients with treatment success when treated with rESWT + RP of 75%. *, calculated from data reported by Reurink et al. (2014a) and Bayer et al. (2017).

Percent of patients treated with sham-rESWT + RP with treatment success [%]	**Power based on Normal approximation [%]**	**Power based on Normal approximation with continuity correction [%]**
99.9	67.4	44.8
90	23.4	10.3
80	5.3	5.3
70	5.0	5.0
60	16.9	8.0
50	36.8	23.6
40	61.7	47.1
30	84.1	73.2
25*	**91.8**	**84.2**
20	**96.6**	**92.3**
10	**99.8**	**99.3**
0	**100**	**100**

Table 7. Sample size in the proposed RCT on rESWT + RP for acute HMC injury Type 3b, accounting for a two sided-confidence interval of 95% and a power of 0.8. The percentage of patients with treatment success when treated with rESWT + RP was set at 75 based on own experience (unpublished data). *, calculated from data reported by Reurink et al. (2014a) and Bayer et al. (2017).

	Sample size of both groups (rESWT + RP, sham-rESWT + RP) according to…		
Percent of patients with treatment success when treated with sham-rESWT + RP [%]	**Kelsey et al. (1996)**	**Fleiss et al. (2003)**	**Fleiss et al. (2003) with continuity correction**
99.9	28	27	35
90	99	98	111
80	1095	1094	1134
70	1221	1220	1259
60	154	152	165
50	59	58	66
40	32	31	36
30	**20**	**19**	**23**
25*	**16**	**15**	**19**
20	**13**	**12**	**16**
10	**10**	**8**	**11**

In summary, the proposed study would have a power of less than 0.8 in finding a difference in treatment success (possibility to return to play with criteria defined by van der Horst et al. [2016] fulfilled) between rESWT + RP and sham-rESWT + RP for treating acute HMC injury Type 3b if the percentage of patients with treatment success when treated with

sham-rESWT + RP would be higher than 30%. This, however, is not to be expected considering the aforementioned data by Reurink et al. (2014a) and Bayer et al. (2017) (c.f. Fig. 9). This reinforces the validity of the protocol of this study for testing efficacy and safety of rESWT + RP using the Swiss DolorClast for acute HMC injury Type 3b.

6. Patient protection procedures

6.1. Procedures in the event of Adverse Events

- Potential unwanted side effects of rESWT may be petechial bruises of the skin at the location of application of rESWs and temporary numbness. These unwanted side effects normally vanish within one or two days.
- Should any unwanted side effects persist for longer than usual, the investigators will treat these patients according to usual standard of care of the institution.

6.2. Procedures in the event of Emergency

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study.

6.3. Procedures in the event of Pregnancy

A patient must be instructed to inform the Principal Investigator if she becomes pregnant during the study. As pregnancy is a contraindication for treatment with rEWST, the patient will be terminated from the study. The investigator will follow up the pregnancy until the outcome is known.

6.4. Patient data protection

Patients' anonymity will be maintained and confidentiality of records and documents that could identify patients will be protected. Patients will only be identified by their assigned identification number on all CRFs and other records and documents. The Principal Investigator will keep a Patient Identification List with complete identification information (name, address, contact number) on each patient. Documents not for submission to the Ethics Committee of the Universidad Abierta Interamericana (Buenos Aires, Argentina), such as patient’s written informed consent form, will be maintained by the Principal Investigator in strict confidence.

Monitors and auditors from the Argentinean National Administration of Drugs, Food and Medical Technology (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), Avenida de Mayo 869 (C1084AAD), Ciudad Autónoma de Buenos Aires, Argentina) or other regulatory agencies, will be granted direct access to patients' medical

records and other study documents for verification of study procedures and data without violating the confidentiality of the patient. The patient should be informed that by signing a written informed consent form, the patient is authorizing such access. All electronic data processed at ANMAT will be identified by patient numbers only, thereby ensuring that patients' identity remains unknown to ANMAT.

6.5. Insurance

With respect to any liability directly or indirectly caused by the investigational products in connection with this study, the Principal Investigator assumes liability by law for possible injury to the patients. Every effort will be made to achieve that (i) the Principal Investigator and his staff will follow the instructions of the manufacturers of the Swiss DolorClast device in accordance with this protocol and any amendments thereto, and (ii) the Principal Investigator and his staff will in general performe this study in accordance with scientific practice and currently acceptable techniques and know how.

6.6. Rescue medication/procedure

rESWT and RP themselves do not require specific rescue medication / procedures.

7. Study Termination/Suspension

The Principal Investigator holds the right to suspend or terminate patient’s participation in this study in the event of deterioration of clinical condition at the discretion of the Principal Investigator.

7.1 Patient Withdrawal & Drop-out

Patients are free to withdraw from this study at any time for any reason.
Patients may also be withdrawn from this study at any time at the discretion of
the Principal Investigator. Should a patient withdraw or is withdrawn, every effort will be made to complete and report the observations as thoroughly as possible. Possible reasons for withdrawal will be documented. For e.g.:

- adverse event(s),
- abnormal laboratory values,
- improvement of patient’s condition such that he/she no longer requires study treatment,
- insufficient therapeutic effect,
- protocol violation (eg. incorrectly enrolled or randomised),
- patient requires use of unacceptable concomitant medication,
- patient not compliant with protocol procedures,

- patient develops a condition during the study that violates the inclusion/exclusion criteria,
- lost to follow-up,
- death, and
- any other reason, in the Principal Investigator's opinion, that would impede the patient's participation in the study.

7.2. Procedures for handling withdrawal

Patients who withdraw or are withdrawn from this study will have the below information recorded:

- The reason(s) for their withdrawal
- Presence of any AEs and if so will be followed up by regular scheduled visits, telephone contact and correspondence until satisfactory clinical resolution of AEs is achieved.
- At least one follow-up contact (scheduled visit, telephone contact, correspondence) for safety evaluation during the 30 days following the last session of study treatment.
- In the event of pregnancy, the patient should be monitored until conclusion of the pregnancy and the outcome of pregnancy reported.

7.3. Patient replacement policy

After randomization and either the first rESWT treatment or the first sham-rESWT treatment, respectively, no patient will be replaced.

7.4. Medications permitted or not permitted during this study

No other adjunct specific treatment for acute HMC injury Type 3b is allowed during the duration of the study. Other medications not permitted are as explained in the Exclusion Criteria. Medications permitted are those not mentioned in the Exclusion Criteria.

8. Ethical Consideration

The researchers have conssidered the ethical issues that may arise with the conduct of this study. This trial will only be conducted after seeking approval from the Ethics Committee of the Universidad Abierta Interamericana (Buenos Aires, Argentina).

9. Patient Withdrawal & Compensation

Participation in this study is completely voluntary. The participants will not be paid for joining this study nor will they be expected to pay to join this study. Participants are able to withdraw themselves from this study at any time without any reason and consequences to their follow-up treatments. Standard routine care will still be provided to them. The researchers hold the right to use any data collected until a participant would withdraw from this study.

10. Adverse Events

10.1. Definitions

Adverse event (AE)

Any untoward medical occurrence in a patient administered an investigational product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavourable and unintended sign, symptom, laboratory observation or disease temporarily associated with the use of the investigational products, whether or not related to the investigational products.

The following should be reported as AE:

- Treatment emergent symptoms which include:
  - medical conditions or signs or symptoms that were absent before starting study treatments, and
  - medical conditions or signs or symptoms present before starting study treatments and worsen (increase severity or frequency) after starting study treatments.
- Abnormal laboratory values or tests that induce clinical signs or symptoms or require therapy.
- Any adverse experience even if no rESWs have been administered.

Any doubtful event should be treated as an AE.

Unexpected adverse event

Any adverse event not reported in the safety section of the Investigator's Brochure or if the event is of greater frequency, specificity or severity.

Serious adverse event (SAE)

Any adverse event occurring that:

- results in death, or
- is a life threatening adverse experience defined as any adverse event that places the patient, in the view of the Principal Investigator, at immediate risk of death from the

reaction as it occurred (note that this does not include a reaction that, in case it would have occurred in a more severe form, would have caused death, and/or
- results in patient hospitalisation or prolongation of existing hospitalisation.

The following hospitalisations are not considered to be SAEs:
- those planned before entry into the study,
- elective treatment for a condition unrelated to study indication or study treatment,
- those that occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria in SAE definition), and
- parts of normal treatment or monitoring of this study indication and are not associated with any deterioration in condition.

Furthermore, the following events are not considered to be SAEs:
- those that result in a significant or persistent disability or incapacity defined as any event that results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions,
- those that are a congenital anomaly or birth defect,
- those that are any instance of overdose, either accidental or intentional (suspected or confirmed), and
- any other important medical event, based upon appropriate medical judgement, that may jeopardise the patient or may require medical or surgical intervention to prevent or avert one of the outcomes listed above.

10.2. Detecting and documenting AE

Information about all AEs, whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other means, will be recorded on the Adverse Event Page of the CRF and followed up as appropriate.

Each AE will be described by:

a) Nature of AE

This will be documented in terms of a medical diagnosis(es). When this is not possible, the AE will be documented in terms of signs and/or symptoms observed by the Principal Investigator or reported by the patient.

b) Duration of AE

Start and end dates will be documented.

c) Assessment of causality

The Principal Investigator will attempt to explain each AE and assess its relationship, if any, to the study treatments. Causality should be assessed using the following definitions:

• Very likely

- The AE follows a reasonable temporal sequence from study treatments administration,
- abates upon discontinuation of study treatments, and
- reappears on repeated exposure (re-challenge).

• Probable

- The AE follows a reasonable temporal sequence from study treatments administration,
- abates upon discontinuation of study treatment, and
- cannot reasonably be explained by known characteristics of the patient's clinical state.

• Possible

- The AE follows a reasonable temporal sequence from study treatments administration,
- but could have been produced by the patient's clinical state or other mode of therapy administered to the patient.

• Doubtful

- The temporal association between study treatments and AE is such that the study treatments are not likely to have any reasonable association with the observed event.

• Very unlikely

- The AE is definitely produced by the patient's clinical state or other mode of therapy administered to the patient.

The degree of certainty with which an AE is attributed to study treatments or alternative cause like natural history of disease or concomitant treatment will be guided by the following considerations:

- time relationship between treatment and occurrence of AE,
- de-challenge and re-challenge information, if applicable,
- dose response relationships,
- lack of alternative explanations, i.e. no concomitant drug used and no other inter-current disease,
- reaction of similar nature being previously observed with the study treatments, and
- reaction having often been reported in the literature for the study treatments.

d) Severity of AE

- **Mild:** awareness of signs or symptoms, but they are easily tolerated.
- **Moderate:** enough discomfort to cause interference with usual activity.
- **Severe**: incapacitating, with inability to work or do usual activity.

10.3. Reporting of SAE

Information about all SAE will be recorded on the Serious Adverse Event Section of the CRF. All events documented in the SAE Form must be reported within 24 hours to ANMAT

Any death or congenital abnormality, if brought to the attention of the Principal Investigator within six months after cessation of study treatments, whether considered treatment related or not, should be reported to ANMAT

10.4. Treatment and follow up of AE

Treatment of any AE is at the sole discretion of the Principal Investigator. Patients with AE will be followed up until the event has resolved or until the condition has stabilized. Otherwise appropriate medical care will be arranged for the patient. Abnormal tests will be repeated until they return to baseline levels or an adequate explanation of the abnormality has been found.

<u>In the Event of Pregnancy</u>

A female patient must be stopped from the treatments and immediately inform the Principal Investigator if she becomes pregnant during this study. The medical monitor will be contacted immediately to break the blind. The Principal Investigator will counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient will continue until conclusion of the pregnancy.

Pregnancies will be formally reported as SAEs.

10.5. Safety update

Electro Medical Systems will notify investigators of all AEs that are serious or unexpected and very likely, probably or possibly related to the investigational products. The Principal Investigator must retain such notice with the Investigator's Brochure and immediately submit a copy of this information to the Ethics Committee of the Universidad Abierta Interamericana (Buenos Aires, Argentina).. The Ethics Committee of the Universidad Abierta Interamericana (Buenos Aires, Argentina).will determine if the informed consent requires revision. The Principal Investigator should also comply with the procedures of the Ethics Committee of the Universidad Abierta Interamericana (Buenos Aires, Argentina). for reporting any other safety information.

10.6. Potential unwanted side effects

Potential unwanted side effects of rESWT may be petechial bruises of the skin at the location of application of rESWs and temporary numbness. These unwanted side effects normally vanish within one or two days. In case of petechial bruises of the skin at the location of application of rESWs they will be photographed and documented in the patient's record. Temporary numbness will also be documented in the patient's record. In the exceptional case that these unwanted side effects would really persist for longer than one or two days, (i) the corresponding patient would no longer be treated with rESWT or sham-rESWT but would be kept in the study for follow-up analysis, (ii) petechial bruises would be treated with, e.g., ice until they disappear, and (iii) patients with persistent numbness would be presented to a neurologist.

11. Statement on Confidentiality

All data collected from participants will not have any personal identifiers. They will instead be given a specific research ID to respect the privacy and confidentiality of participants. The Principal Investigator will keep a separate Patient Identification List with complete identification information (name, address, contact number) and randomization number on each patient. All data collected will be stored in a computer that is protected by a password at the clinic of the Principal Investigator. Only investigators and study team members will have access to the study data. This limits the access to study data to the minimum number of individuals necessary for quality control, audit and analysis. Participants will not be given access to any personal information and study data collected during this study.

12. Data Protection

All data collected will be stored in a computer that is protected by a password at the clinic of the Principal Investigator. Only investigators and study team members will have access to the study data. Study data will be stored for a duration of five years after completion of this study. All data will be destroyed thereafter.

13. Publication Policy

The investigators shall have the right to publish or permit the publication of any information or material relating to or arising from this study. All study data will be reported in a collective manner without any personal identifiers to protect the confidentiality of the participants.

14. Conflict of Interest

The rESWT equipment to be used in this study (Swiss DolorClast) is purchased from Electro Medical Systems (Nyon, Switzerland).

Dr. Christoph Schmitz serves as paid consultant for and receives benefits from Electro Medical Systems. However, Electro Medical Systems will have no any role in patient recruitment, treatment of patients, data collection and analysis, decision to publish, or preparation of corresponding manuscripts. Furthermore, Dr. Christoph Schmitz will have no any role in patient recruitment, treatment of patients and data collection.

No other potential conflicts of interest relevant to this study have been reported.

15. References

Askling CM, Tengvar M, Tarassova O, Thorstensson A. Acute hamstring injuries in Swedish elite sprinters and jumpers: a prospective randomised controlled clinical trial comparing two rehabilitation protocols. Br J Sports Med 2014;48:532-539.

Barnett AJ, Negus JJ, Barton T, Wood DG. Reattachment of the proximal hamstring origin: outcome in subjects with partial and complete tears. Knee Surg Sports Traumatol Arthrosc 2015;23:2130-2135.

Bayer ML, Magnusson SP, Kjaer M; Tendon Research Group Bispebjerg. Early versus Delayed Rehabilitation after Acute Muscle Injury. N Engl J Med 2017;377:1300-1301.

Biedermann R, Martin A, Handle G, Auckenthaler T, Bach C, Krismer M: Extracorporeal shock waves in the treatment of nonunions. J Trauma 2003;54:936-942.

Blobaum P. Physiotherapy Evidence Database (PEDro). J Med Libr Assoc 2006, 94(4): 477–478.

Brucker PU, Imhoff AB. Functional assessment after acute and chronic complete ruptures of the proximal hamstring tendons. Knee Surg Sports Traumatol Arthrosc 2005;13:411-418.

Buchbinder R, Ptasznik R, Gordon J, Buchanan J, Prabaharan V, Forbes A. Ultrasound-guided extracorporeal shock wave therapy for plantar fasciitis: a randomized controlled trial. J Am Med Assoc 2002;288:1364-1372.

Cacchio A, Giordano L, Colafarina O, Rompe JD, Tavernese E, Ioppolo F, Flamini S, Spacca G, Santilli V: Extracorporeal shock wave therapy compared with surgery for

hypertrophic long-bone nonunions. J Bone Joint Surg (Am) 2009;91:2589-2597.
Chalmers TC, Smith H Jr, Blackburn B. A method for assessing the quality of a randomized control trial. Control Clin Trials 1981,2(1):31-49.
Chaussy C, Brendel W, Schmiedt E: Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980;2:1265-1268.
Chu SK, Rho ME. hamstring injuries in the athlete: diagnosis, treatment, and return to play. Curr Sports Med Rep 2016;15:184-190.
Crema MD, Guermazi A, Tol JL, Niu J, Hamilton B, Roemer FW. Acute hamstring injury in football players: Association between anatomical location and extent of injury-A large single-center MRI report. J Sci Med Sport 2016;19:317-322.
Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52(6):377–384.
European Medicines Agency. Guideline on missing data in confirmatory clinical trials. 2010; www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf (assessed for the last time on August 13, 2015).
Fiorentino NM, Blemker SS. Musculotendon variability influences tissue strains experienced by the biceps femoris long head muscle during high-speed running. J Biomech 2014;47:3325-3333.
Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions, 3rd edition. Hoboken: Wiley-Interscience, 2003.
Folsom GJ, Larson CM. Surgical treatment of acute versus chronic complete proximal hamstring ruptures: results of a new allograft technique for chronic reconstructions. Am J Sports Med 2008;36:104-109.
Fournier-Farley C, Lamontagne M, Gendron P, Gagnon DH. Determinants of return to play after the nonoperative management of hamstring injuries in athletes: a systematic review. Am J Sports Med 2016;44:2166-2172.
Hamilton B, Tol JL, Almusa E, Boukarroum S, Eirale C, Farooq A,Whiteley R, Chalabi H. Platelet-rich plasma does not enhance return to play in hamstring injuries: a randomised controlled trial. Br J Sports Med 2015;49:943-950.
Heiderscheit BC, Sherry MA, Silder A, Chumanov ES, Thelen DG. Hamstring strain injuries: recommendations for diagnosis, rehabilitation, and injury prevention. J Orthop Sports Phys Ther 2010;40:67-81.
Hoskins W, Pollard H. The management of hamstring injury--Part 1: Issues in diagnosis. Man Ther 2005;10:96-107.
Jadad AR, Moore RA, Carrol D. Assessing the quality of reports of randomised clinical trials. is blinding necessary? Control Clin Trials 1996,17(1):1-12.
Kearney CJ, Prevost T, Socrate S, Cleveland RO, Spector M. Pressure-time profiles of a focused and a radial shockwave device: Measurements in tissue, ex vivo, and in a water bath. J Acoust Soc Am 2010;128:2364.
Kellermann M, Lutter C, Hotfiel T. Healing response of a structural hamstring injury - perfusion imaging 8 weeksfollow-up. J Sport Rehabil 2017;5:1-13.
Kelsey JL, Whittemore AS, Evans AS, Thompson WD. Methods in Observational Epidemiology, 2nd edition. New York, Oxford: Oxford University Press, 1996.
Koulouris G, Connell D. Hamstring muscle complex: an imaging review. Radiographics 2005;25:571-586.
Lang TA, Secic M. How To Report Statistics in Medicine (2nd ed.). American College of Physicians, 2006.
Linklater JM, Hamilton B, Carmichael J, Orchard J, Wood DG. Hamstring injuries: anatomy, imaging, and intervention. Semin Musculoskelet Radiol. 2010;14:131-161.
Lohrer H, Nauck T, Korakakis V, Malliaropoulos N. Validation of the FASH (Functional Assessment Scale for Acute Hamstring Injuries) questionnaire for German-speaking football players. J Orthop Surg Res 2016;11:130.
Manduca ML, Straub SJ. Effectiveness of PRP injection in reducing recovery time of acute hamstringinjury: a critically appraised topic. J Sport Rehabil 2017;17:1-19.

Mason DL, Dickens V, Vail A. Rehabilitation for hamstring injuries. Cochrane Database Syst Rev 2007;1:CD004575.
Mattyasovszky SG, Langendorf EK, Ritz U, Schmidtmann I, Wagner D, Drees P, Rommens PM, Schmitz C, Hofmann A. Exposure to radial extracorporeal shock waves modulates viability and gene expression of human skeletal muscle cells in vitro. Submitted for publication.
Mendiguchia J, Brughelli M. A return-to-sport algorithm for acute hamstring injuries. Phys Ther Sport 2011;12:2-14.
Mendiguchia J, Martinez-Ruiz E, Edouard P, Morin JB, Martinez-Martinez F, Idoate F, Mendez-Villanueva A. A multifactorial, criteria-based progressive algorithm for hamstring injury treatment. Med Sci Sports Exerc 2017;49:1482-1492.
Müller-Wohlfahrt, HW, Ueblacker P, Haensel L, Garrett J WE. Muscle Injuries in Sports. Thieme, Stuttgart, 2013.
Pas HI, Reurink G, Tol JL, Weir A, Winters M, Moen MH. Efficacy of rehabilitation (lengthening) exercises, platelet-rich plasma injections, and other conservative interventions in acute hamstring injuries: an updated systematic review and meta-analysis. Br J Sports Med 2015;49:1197-1205.
Petersen J, Thorborg K, Nielsen MB, Hölmich P. Acute hamstring injuries in Danish elite football: a 12-month prospective registration study among 374 players. Scand J Med Sci Sports 2010;20:588-592.
Petersen J, Thorborg K, Nielsen MB, Skjødt T, Bolvig L, Bang N, Hölmich P. The diagnostic and prognostic value of ultrasonography in soccer players with acute hamstring injuries. Am J Sports Med 2014;42:399-404.
Rassweiler JJ, Knoll T, Köhrmann KU, McAteer JA, Lingeman JE, Cleveland RO, Bailey MR, Chaussy C: Shock wave technology and application: an update. Eur Urol 2011;59:784-796.
Reurink G, Goudswaard GJ, Tol JL, Verhaar JA, Weir A, Moen MH. Therapeutic interventions for acute hamstring injuries: a systematic review. Br J Sports Med 2012;46:103-109.
Reurink G, Goudswaard GJ, Moen MH, Weir A, Verhaar JAN, Bierma-Zeinstra SMA, Maas M, Tol JL, Dutch Hamstring Injection Therapy (HIT) Study Investigators. Platelet-rich plasma injections in acute muscle injury. New Engl J Med 2014a;370:2546-2547.
Reurink G, Tol JL, de Vos RJ. Acute hamstringblessures bij sporters [Acute hamstring injuries in athletes] [Article in Dutch]. Ned Tijdschr Geneeskd 2014b;159:A8152.
Robinson M, Hamilton B. Medical interventions in the management of hamstring muscle injury. Eur J Sport Sci 2014;14:743-751.
Rompe JD, Furia J, Maffulli N. Eccentric loading compared with shock wave treatment for chronic insertional achilles tendinopathy. A randomized, controlled trial. J Bone Joint Surg Am 2008;90(1):52-61.
Schmitz C, Császár NBM, Milz S, Schieker M, Maffulli N, Rompe JD, Furia JP. Efficacy and safety of extracorporeal shock wave therapy for orthopedic conditions: a systematic review on studies listed in the PEDro database. Brit Med Bull 2015:116:115-138.
Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. PLoS Med 2010;7(3):e1000251.
Sherry MA, Best TM. A comparison of 2 rehabilitation programs in the treatment of acute hamstring strains. J Orthop Sports Phys Ther 2004;34:116-25.
Speed C. A systematic review of shockwave therapies in soft tissue conditions: focusing on the evidence. Br J Sports Med 2014;48:1538-1542.
Valle X, L Tol J, Hamilton B, Rodas G, Malliaras P, MalliaropoulosN, Rizo V, Moreno M, Jardi J. Hamstring muscle injuries, a rehabilitation protocol purpose. Asian J Sports Med 2015;6:e25411.
van der Horst N, van de Hoef S, Reurink G, Huisstede B, Backx F. Return to play after hamstring injuries: a qualitative systematic review of definitions and criteria. Sports Med 2016;46(6):899-912.

Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998;51(12):1235-1241.

Zanon G, Combi F, Combi A, Perticarini L, Sammarchi L, Benazzo F. Platelet-rich plasma in the treatment of acute hamstring injuries in professional football players. Joints 2016;4:17-23.

Zissler A, Steinbacher P, Zimmermann R, Pittner S, Stoiber W, Bathke AC, Sänger AM. Extracorporeal shock wave therapy accelerates regeneration after acute skeletal muscle injury. Am J Sports Med 2017;45:676-684.