Improving extracorporeal shock wave therapy with 904 or 905 nm pulsed, high power laser pretreatment

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Extracorporeal shock wave therapy (ESWT) is a well investigated and widely used treatment modality for a number of musculoskeletal disorders. A limitation of ESWT is its potential painfulness at higher, clinically relevant energy flux density (EFD), which may limit its applicability and, thus, effectiveness. Various studies in the literature demonstrated that neither application of a higher number of extracorporeal shock waves with lower EFD nor use of local anesthesia may solve this problem. Based on the results of several other studies in the literature it is hypothesized here that in patients suffering from musculoskeletal disorders that can be treated with ESWT, pretreatment with a pulsed, high power laser with a wavelength of 904 or 905 nanometers (hereafter: "laser pretreatment") does not only allow to apply higher EFDs in subsequent ESWT but actually results in faster and/or better treatment outcome than ESWT without laser pretreatment. Accordingly, it is hypothesized here that combining ESWT with laser pretreatment leads to synergistic effects and, thus, is superior to either treatment modality alone. Confirming this hypothesis in preclinical and clinical research may raise significance and increase the use of ESWT in physical and rehabilitation medicine, with immediate benefit for patients.

Keywords: extracorporeal shock wave therapy; ESWT, laser therapy; musculoskeletal system, rehabilitation

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ABSTRACT

Extracorporeal shock wave therapy (ESWT) is a well investigated and widely used treatment modality for a number of musculoskeletal disorders. A limitation of ESWT is its potential painfulness at higher, clinically relevant energy flux density (EFD), which may limit its applicability and, thus, effectiveness. Various studies in the literature demonstrated that neither application of a higher number of extracorporeal shock waves with lower EFD nor use of local anesthesia may solve this problem. Based on the results of several other studies in the literature it is hypothesized here that in patients suffering from musculoskeletal disorders that can be treated with ESWT, pretreatment with a pulsed, high power laser with a wavelength of 904 or 905 nanometers (hereafter: "laser pretreatment") does not only allow to apply higher EFDs in subsequent ESWT but actually results in faster and/or better treatment outcome than ESWT without laser pretreatment. Accordingly, it is hypothesized here that combining ESWT with laser pretreatment leads to synergistic effects and, thus, is superior to either treatment modality alone. Confirming this hypothesis in preclinical and clinical research may raise significance and increase the use of ESWT in physical and rehabilitation medicine, with immediate benefit for patients.

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INTRODUCTION

Significance of extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) is a well investigated and widely used non-pharmacological, non-surgical treatment modality for a number of musculoskeletal disorders including rotator cuff pathology with or without calcification, tennis elbow, knee osteoarthritis, Achilles tendinopathy, plantar fasciopathy, myofascial trigger points and fracture nonunions [1-5]. The Physiotherapy Evidence Database PEDro [6] (with over 48.000 randomized controlled trials (RCTs), systematic reviews and clinical practice guidelines currently the largest independent database in the field of physical and rehabilitation medicine) has listed more than 150 RCTs on ESWT since its inception until today. For certain conditions, RCTs on ESWT are the predominant type of RCT listed in PEDro and/or obtained the highest PEDro quality scores among all investigated treatment modalities [3].

A typical treatment protocol of ESWT comprises three treatment sessions at 1-week intervals, with 2000 extracorporeal shock waves (ESWs) per treatment session applied at a certain energy flux density (EFD) (explained in the next paragraph) [3].

Basic physical principles of extracorporeal shock waves

Extracorporeal shock waves are single acoustic impulses with an initial high positive peak pressure (P_+) between 10 and 100 Megapascal (MPa) reached in less than one microsecond (μs) [7] (note that 10 MPa (100 Bar) is the pressure in a water depth of 1009 meters, and 100 MPa (1000 Bar) is the pressure in a water depth of 10.187 meters). The positive pressure is followed by a low tensile pressure (with negative peak pressure (P_-) up to -20 MPa [8]) lasting for a few μs [3,9-11]. For all that is known, both the positive (associated with stress) and negative (associated with cavitation) components of ESWs are responsible for therapeutic bioeffects [12,13]. The life cycle of an extracorporeal shock wave is approximately 5-20 μs [7-11].

A key characteristic of ESWs is their energy flux density (EFD), which is calculated as the integral of pressure over time [7-11]. The EDF related to the positive pressure is EFD_+, the EFD related to the negative pressure is EFD_-, and the total EFD is the sum of EFD_+ and EFD_- [7,8,10,11]

Radial ESWs differ from focused ESWs in the penetration depth into the tissue, a number of physical characteristics and the technology for generating them [3]. Radial ESWs are not real shock waves in the strict physical sense [14]. Focused ESWs may or may not be real shock waves in the strict physical sense, depending on their pressure characteristics and the way they are generated [14,15]. Compared to measurements performed in water, penetration of focused ESWs through biological tissue was demonstrated to cause a reduction in both P_+ and P_- as well as an increased rise time (i.e., the time between 10% of P_+ and 90% of P_+) [16]. In consequence, one should keep in mind that those focused ESWs that are real shock waves in the strict physical sense

when measured in water may lose this characteristic in biological tissue. On the other hand, the rise time of the applied ESWs is possibly rather insignificant for the effectiveness of ESWT [17].

Mode of action of extracorporeal shock waves on musculoskeletal tissue

The release of substance P (one of the body's neurotransmitter of pain and heat), calcitonin gene-related peptide and other inflammation mediators from afferent nerve fibers is generally referred to as neurogenic inflammation [18-20]. The latter was demonstrated being involved in the pathogenesis of tendinopathies such as tennis elbow and Achilles tendinopathy [21,22]. A key working mechanism of ESWs on musculoskeletal tissue is overstimulation of substance P nerve fibers, which depletes presynaptic substance P [23]. As a result, the nerves are apparently unable to report pain for an extended period of time, which leads to reduction in sensation of pain and blockade of neurogenic inflammation. Furthermore, ESWs can lead in the treated tissue to a stronger expression of growth factors such as bone morphogenetic proteins (BMPs), endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF) and proliferating cell nuclear antigen (PCNA) [24-26] as well as to activation of cells that are involved in tissue regeneration [27-29].

Current limitations of extracorporeal shock wave therapy

Several studies (RCTs, meta-analyses and a recent systematic review) demonstrated superiority of ESWT performed at higher EFD compared with ESWT performed at lower EFD [3,30-32]. Unfortunately, due to its action on substance P nerve fibers ESWT may become very painful at higher, clinically relevant EFD, which may limit its applicability and, thus, effectiveness.

A key study on focused extracorporeal shock wave therapy (fESWT) for chronic calcifying tendonitis of the shoulder demonstrated that two treatment sessions with 6000 focused ESWs each with $EFD_+ = 0.08$ mJ/mm^2 resulted in worse clinical outcome than two treatment sessions with 1500 focused ESWs each with $EFD_+ = 0.32$ mJ/mm^2 (in both cases the cumulative EFD_+ was 0.96 J/mm^2) [33]. In line with these results, a very recent study on radial extracorporeal shock wave therapy (rESWT) for knee osteoarthritis demonstrated that four treatment sessions with 4000 radial ESWs each with $EFD_+ = 0.12$ mJ/mm^2 resulted in worse clinical outcome than four treatment sessions with 2000 radial ESWs each with $EFD_+ = 0.24$ mJ/mm^2 (in both cases the cumulative EFD_+ was 1.92 J/mm^2) [34]. Accordingly, applying a higher number of ESWs with lower EFD does not solve the problem that ESWT may become very painful at higher EFD, potentially limiting its applicability and, thus, effectiveness.

In several recent studies this problem was circumvented by applying the individual, maximum EFD a patient could tolerate [35-37]. However, this may result in increased interindividual differences in the amount of shock wave

energy applied in the same study, with potential impact on interindividual differences in treatment success.

Other authors have approached this problem by applying ESWT with local anesthesia [32,38-40]. However, it turned out that local anesthesia may block the action of ESWs on substance P nerve fibers [41], and repetitive ESWT without local anesthesia was demonstrated being more effective than repetitive ESWT with local anesthesia in the treatment of chronic plantar fasciopathy [42,43].

In summary, the problem that the desire for higher EFDs in ESWT is opposed by the painfulness of the treatment has remained unsolved.

Mode of action of pulsed lasers with wavelength of 904 nanometers on musculoskeletal tissue

Already more than 30 years ago it was demonstrated that treatment with a pulsed laser with a wavelength of 904 nanometers (hereafter: "904 nm pulsed laser treatment") (GaAlAs semiconductor laser; peak power, 2 W; pulse width, 200 ns; frequency, 3040 Hz) is able to influence the firing rate of nociceptors and, thus, may have an analgesic effect [44]. To this end, the authors of [44] placed a thermostatically controlled thermal probe on the tongue of anesthetized cats and recorded activities of heat nociceptors in the tongue. Increasing the temperature from $30°$ C to $53°$ C ($\Delta = 23°$ C) caused more firing of the nociceptors than increasing the temperature from $33°$ C to $47°$ C ($\Delta = 14°$ C). Laser pretreatment for respectively (i) one minute, (ii) three minutes, (iii) five minutes or (iv) ten minutes (i) had no effect on the firing rate of the nociceptors, (ii) reduced the firing rate of the nociceptors in the $\Delta = 14°$ C experiment but not the $\Delta = 23°$ C experiment, (iii) substantially reduced the firing rate of the nociceptors in both experiments and (iv) had no additional effect compared to laser pretreatment for five minutes [44].

Furthermore, prostaglandin E2 (PGE_2) plays a central role in inflammation and feeling pain via inflammatory nociception [45]. Already 14 years ago it was demonstrated that 904 nm pulsed laser treatment (GaAs laser; peak power, 10 W; pulse width, 200 ns; frequency, 5000 Hz) can influence the concentration of peritendinous PGE_2 in humans [46]. To this end, the authors of [46] placed a microdialysis membrane in the peritendinous tissue parallel to both Achilles tendons of subjects suffering from bilateral Achilles tendinitis. Then, both Achilles tendons were pretreated with the laser for three minutes. However, only one Achilles tendon each received active treatment, whereas the other Achilles tendon each received sham treatment. Immediately hereafter the subjects performed pain inducing exercises that aggravated their symptoms, and PGE_2 concentrations in the peritendinous tissue were measured. On the side of sham laser pretreatment the following mean relative PGE_2 concentrations were obtained in the seven, subsequent 15-min time intervals (I1-I7) after starting the exercises: I1, 100%; I2, 95%, I3, 100%; I4, 125%, I5, 139%, I6, 136%, I7, 131%. In contrast, on the side of active laser pretreatment the following mean relative

PGE_2 concentrations were found: I1, 100%, I2, 102%, I3, 118%, I4, 102%; I5, 89%, I6, 87%, I7, 73%. Thus, active laser pretreatment reduced the relative PGE_2 concentration in peritendinous tissue compared to baseline even during exercises that increased the PGE_2 concentration in the same tissue after sham laser pretreatment.

Treatment of musculoskeletal disorders with 904 or 905 nm pulsed, high power laser therapy alone

As of today (December 27, 2020) 23 RCTs listed in the PEDro database described treatment of musculoskeletal disorders with 904 or 905 nm pulsed, high power laser therapy alone, including rotator cuff pathology, tennis elbow, carpal tunnel syndrome, knee osteoarthritis, myofascial pain syndrome, acute cervical pain, chronic nonspecific low back pain and fibromyalgia) [47-69] (Table 1). Twenty out of these 23 studies (87%) reported that laser therapy was superior to sham treatment or another treatment modality. Of note, both the total number of treatment sessions as well as the number of treatment sessions per week reported in these studies were substantially higher than the corresponding numbers reported for ESWT [3]. This may limit the attractiveness of 904 or 905 nm pulsed, high power laser therapy alone in treatment of musculoskeletal disorders to both therapists and patients. However, these studies indicate that ESWT and 904 or 905 nm pulsed, high power laser treatment may have synergistic effects that are currently unexplored.

Applicability of extracorporeal shock wave therapy with increased energy flux density after 905 nm pulsed, high power laser pretreatment

Colleagues in Germany, Switzerland and Spain who have started to perform 905 nm pulsed, high power laser pretreatment before performing rESWT have reported the possibility to increase the EFD of radial ESWs by up to 50% when waiting five minutes between laser pretreatment and rESWT, and up to 100% when waiting one hour between laser pretreatment and rESWT, compared to rESWT without laser pretreatment (Alexander Ablass, Thomas Maier, James P.M. Morgan, Antoni Morral, Peter Stiller, Felix Zimmermann; personal communications). This experience was obtained using a DolorClast high power laser (wavelength, 905 nm; peak power, 300 W; pulse width, 100 ns; frequency, 40 KHz) (Electro Medical Systems, Nyon, Switzerland) and a DolorClast rESWT device (Electro Medical Systems).

HYPOTHESIS

It is hypothesized here that in patients suffering from musculoskeletal disorders that can be treated with ESWT, pretreatment with a 904 or 905 nm pulsed, high power laser does not only allow to apply higher EFDs in subsequent ESWT but actually results in faster and/or better treatment outcome than ESWT without laser pretreatment. Accordingly, it is hypothesized here that (unlike local anesthesia) the combination of ESWT with 904 or 905 nm pulsed, high power

laser pretreatment leads to synergistic effects and, thus, is superior to either treatment modality alone.

Table 1 | RCTs on 904 or 905 nm pulsed, high power laser treatment of various musculoskeletal disorders listed in the PEDro database [6].
Abbreviations: TS, treatment sessions; n.r., not reported; ATDG, arthralgic temporomandibular degenerative joints; PMFT; pulsed magnetic field therapy. Notes: [a], laser > sham laser, better outcome after laser therapy than after sham laser therapy; laser = sham laser; no better outcome after laser therapy than after sham laser therapy. [b], better outcome after laser therapy only in range of motion, not in pain.

Indication	Study	No. of TS	No. of TS per week	Control treatment	Outcome[a]
Rotator cuff tendinopathy	[47]	6	3	Sham laser	Laser > sham laser
Shoulder pain	[48]	10	5	Sham laser	Laser > sham laser[b]
Tennis elbow	[49]	10	2-3	Sham laser	Laser = sham laser
Tennis elbow	[50]	15	5	Sham laser	Laser = sham laser
Tennis elbow	[51]	10	2-3	Sham laser	Laser > sham laser[b]
Cervical myofascial pain	[52]	10	5	Sham laser	Laser = sham laser
Cervical myofascial pain	[53]	10	5	Sham laser	Laser > sham laser
Cervical myofascial pain	[54]	12	3	Sham laser	Laser > sham laser
Shoulder myofascial pain	[55]	10	5	Sham laser, ultrasound	Laser > ultrasound > sham laser
Myofascial pain	[56]	n.r.	n.r.	Sham laser	Laser > sham laser
Various tendinitis	[57]	6	1-2	Sham laser	Laser > sham laser
ATDG	[58]	9	3	Sham laser	Laser > sham laser
Acute cervical pain	[59]	10	5	Sham laser	Laser > sham laser
Chronic low back pain	[60]	10	5	Sham laser	Laser > sham laser
Chronic low back pain	[61]	20	5	Laser without exercise	Laser with exercise > laser without exercise
Carpal tunnel syndrome	[62]	18-24	3	Sham laser	Laser > sham laser
Carpal tunnel syndrome	[63]	10	5	Ultrasound	Laser > ultrasound
Carpal tunnel syndrome	[64]	20	5	PMFT	Laser > PMFT
Nonspecific knee pain	[65]	12	3	Sham laser	Laser > sham laser
Knee osteoarthritis	[66]	12	3	Sham laser	Laser > sham laser
Knee osteoarthritis	[67]	9	3	Sham laser	Laser > sham laser
Knee osteoarthritis	[68]	10	5	Sham laser	Laser > sham laser
Fibromyalgia	[69]	10	5	Sham laser	Laser > sham laser

DISCUSSION

The hypothesis outlined above may serve as basis for a variety of preclinical and clinical studies in the future.

Preclinical studies should address the questions (i) why 904 or 905 nm pulsed, high power laser pretreatment may not cause antagonistic effects to ESWT, as local anesthesia does, and (ii) which synergistic, molecular and cellular mechanisms can be expected when combining ESWT with 904 or 905 nm pulsed, high power laser pretreatment.

With regard to the first question it is of note that a single exposure of the right distal femur of normal rabbits to 1500 focused ESWs with $EFD_+ = 0.9$ mJ/mm^2) resulted in the periosteum of the exposed femur (compared to the periosteum of the unexposed left femur) in no alteration of the mean PGE_2 concentration at six hours (H6), H24 and six weeks (W6) post exposure, but an increased mean substance P concentration at both H6 and H24 and a reduced mean substance P concentration at W6 post exposure [23]. Furthermore, the same animals had on average statistically significantly fewer neurons immunoreactive for substance P in the right dorsal root ganglion (DRG) L5 (exposed side) than in the left DRG L5 (unexposed side) at W6 post exposure, with no alteration in the mean total number of neurons in this DRG [70]. In contrast, treatment of a rat model of neuropathic pain (chronic constriction injury of the sciatic nerve with increased substance P levels in DRG L4-L6) with laser therapy (904 nm,

GaAs laser; peak power, 70 mW; pulse width, 60 ns; frequency, 9500 Hz; 10 treatment sessions; interval between treatment sessions, 2 days; stimulation of nine points lasting 18 seconds each per treatment session) reduced the mean substance P level in DRGs L4-L6 to levels that were found in control animals but not further [71] (similar results were reported in [72]). Together with the fact that exposure of musculoskeletal tissue to ESWs can be very painful, whereas treatment with a 905 nm pulsed, high power laser is usually not painful (A. Ablass, T. Maier, J.P.M. Morgan, A. Morral; P. Stiller, F. Zimmermann, personal communications), these data indicate that ESWs and 904 or 905 nm pulsed, high power lasers may act on different molecular and cellular targets in the treated tissue which prevents negative mutual interaction.

With regard to the second question it should be mentioned that both radial ESWs and focused EWSs can stimulate fibroblasts [28,73] and activate satellite cells in skeletal muscle [29,74], whereas in a rat model of gastrocnemius muscle injury (single impact blunt trauma) early treatment with a 904 nm laser reduced the inflammatory response as well as overexpression of inducible nitric oxide synthase and increased collagen production induced by trauma [75]. Accordingly, the effects of ESWs may primarily accelerate regeneration of damaged muscle [29,74], whereas the effects of 904 or 905 nm laser treatment may primarily prevent the formation of scar tissue after muscle trauma in a synergistic

manner. Clinical studies should determine potential short-term and long-term benefits of the combination of ESWT with 904 or 905 nm pulsed, high power laser pretreatment. Short-term benefits may include faster improvement of subjective (pain etc.) and objective (range of motion etc.) clinical endpoints as well as patients' satisfaction with the treatment procedure (less pain during ESWT); long-term benefits may include further improvement of subjective (pain etc.) and objective (range of motion etc.) clinical endpoints and/or longer lasting improvement (e.g., in treatment of knee osteoarthritis).

Conclusions
Combining ESWT with 904 or 905 nm pulsed, high power laser pretreatment may raise ESWT and its significance in physical and rehabilitation medicine to a new, previously unattained level, with immediate benefit for patients.

Abbreviations
DRG, dorsal root ganglion; EFD, energy flux density; EFD_+, positive energy flux density; EFD_-, negative energy flux density; ESWs, extracorporeal shock waves; ESWT, extracorporeal shock wave therapy; fESWT, focused extracorporeal shock wave therapy; H, hours; MPa, Megapascal; µs, microsecond; P_-, negative peak pressure; P_+, positive peak pressure; RCT, randomized controlled trial; rESWT, radial extracorporeal shock wave therapy; W, weeks.

Availability of data and materials
All datasets used and analyzed in this study are presented in this report.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Alexander Ablass, Thomas Maier, James P.M. Morgan, Antoni Morral, Peter Stiller and Felix Zimmermann have agreed to have their names included in personal communications in this paper.

Competing interests
The author has received research funding at LMU Munich and consulted (until December 31st, 2017) for Electro Medical Systems (Nyon, Switzerland). However, Electro Medical Systems had no role in study design, data collection, data analysis, data interpretation and writing of the report.

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