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Review

Extracorporeal shockwave therapy (ESWT) – First choice treatment of fracture non-unions?

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HIGHLIGHTS

- Non-healing fractures (pseudarthroses, non-unions) still are a challenging problem in orthopedics.
- ESWT is a non-invasive procedure that achieves comparable results to surgical approaches.
- Complications associated with ESWT are on rare occasions and minimal if present.
- Peer-reviewed literature shows excellent results with medium/high energy focused ESWT, with faster return to competition and athletic activity.

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ABSTRACT

Fracture non-unions are still a challenging problem in orthopedics. The treatment of non-unions remains highly individualized, complex, and demanding. In most countries the surgical approach with debridement of the non-union gap, anatomical reduction and appropriate osteosynthesis along with autologous bone grafting is considered as the standard of care. One of the very first non-urologic applications of extracorporeal shockwave treatment (ESWT) concerned non-healing fractures. Since the early 1990ties the knowledge of the working mechanism has increased enormously. The purpose of this review article is to demonstrate by peer-reviewed literature in conjunction with our own experiences that ESWT can be an efficient, non-invasive, almost complication-free and cost effective alternative to surgical treatment of non-healing fractures.

1. Introduction

In the last 40 years extracorporeal shockwave therapy (ESWT) has evolved as the standard therapy for concrement disintegration in urology. Convincing clinical aspects lead to a rapid ubiquitous dissemination of this treatment modality and include excellent efficacy, non-invasiveness and the lack of significant complications. Observing osseous thickening of the iliac bone in 1 year follow-up X-rays after employment of shockwaves in ureter or bladder stones, Gerald Haupt [1] recognized already in 1990 for the first time the dynamic interaction of ESWT with a biological tissue. During stone treatment shockwaves propagated through the bone and provoked hypertrophy whereupon the mechanism was unclear. Since the first report of Valchanov [2] in 1991 applying shockwaves for non-healing fractures the perception and understanding of this technology has grown enormously. In the beginning the hypothesis of the working mechanism was that shockwaves create micro-lesions in the treated bone (focus) without damaging the adjacent soft tissue. It was assumed that these treatment triggered micro-lesions gaining the capability to stimulate and reactivate bone healing in non-healing fractures. Tischer [3] expressed first doubts of this theory demonstrating new bone formation after shockwave application in healthy femura of rabbits without creating micro-lesions.

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In gratitude of Wang [4], one of the most accredited pioneers in shockwave therapy, the appreciation of performance completely changed when he demonstrated that shockwaves induce a significant neovascularization in the treated tissue without provoking deterioration. By means of up-regulation and expression of various pro-angiogenic and pro-osteogenic growth factors bone healing is strongly stimulated [5]. This knowledge was reason to look at the working mechanism in a different light and hypothesizing the mechanotransduction as the basis of efficacy [6]. Recent experimental studies give proof of this concept showing involvement of pathways associated in this mechanism [7,8]. In that light ESWT was considered to be a valuable alternative avoiding elaborate surgical procedures in the treatment of non-union fractures.

The purpose of this review is to analyze ESWT in regard of efficacy and efficiency based on the currently available literature. Additionally, we aim to emphasize on the rate of complications occurring after ESWT compared to surgical procedures.

2. Working mechanism of ESWT

These first seminal experiments were the basis for extensive laboratory work in recent years elucidating the biological components involved in ESWT. Currently, *Mechanotransduction* is hypothesized as the working mechanism. As a result of pressure, tensile and shearing forces delivered by shockwaves to the cells and to the extracellular matrix (ECM) messengers are liberated and activate different genes and groups of genes in the cell nucleus [9]. This impact disposes the cells to produce spatial and temporal coordinated growth factors to stimulate healing processes.

Recently, it was shown that the expression of transmembrane integrins on the surface of osteoblasts, specifically $\alpha5\beta1$, which mediate the interactions between the ECM and the cells, is increased in response to ESWT [7]. Downstream, several intracellular signal transduction pathways were identified which are stimulated by ESWT. The focal adhesion kinase (FAK) complex has been implicated to be essential for transmitting extracellular signals to the cell cytoplasm and was seen to be increased phosphorylated not only by integrins [7] but also by ATP [10]. Further intracellular participants of the signaling cascade triggered by various stimuli (e.g. ATP [10–12], integrin [7], radicals [13,14]) in response to extracorporeal shockwave therapy include the p38 MAPK, ERK1/2 [11–13,15], and AKT [8] pathway. Consequently, a multitude of molecular (growth factor release and cytokine expression) as well as cellular events (e.g. cell adhesion, spreading capacity as well as migration behavior) are stimulated resulting in bone repair.

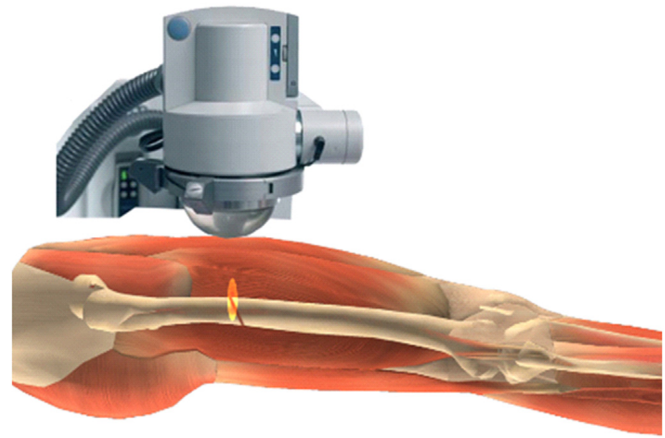

Fig. 2. The image shows the principle of shockwave treatment of a femur non-union. The therapy head is positioned above the femur in a way that the focal area of the shockwave is placed in the non-union gap.

3. ESWT in delayed or non-healing fractures - clinical results

In the late nineties of the last century several authors reported about the successful use of ESWT in the treatment of delayed or non-healing fractures [16–19]. Similarly, our group uses ESWT as the first line treatment for non-unions since 1998 and published a case series of 115 consecutive patients receiving a single session of ESWT [20]. Out of this cohort 87 non-unions (75.7%) achieved bony healing after 6 months following ESWT. Meanwhile we treated more than 3500 delayed healing fractures and pseudarthroses at different locations with an average success rate of almost 80% after six months follow-up (not published data) (Figs. 1–3). Due to our experience around 75% of referred patients suffering from a non-union fracture are suitable for ESWT. Besides the clear advantages

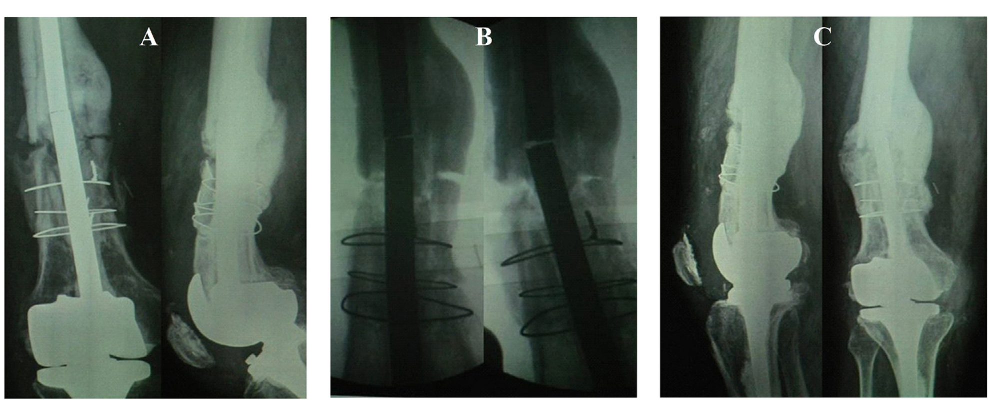

Fig. 1. Case report of a 58 year old male who received total knee replacement (TKR) due to osteoarthritis demonstrating the biological potential of ESWT for the treatment of challenging fracture non-unions. After 4 years he suffered a periprosthetic supracondylar fracture. He was surgically revised with changing the femoral TKR component to a long stem with bone cement and double plating. Regarding the blood supply it has to be considered that the bone cement applied intramedullary is impeding practically all endosteal and the plates on the medial and lateral aspect at least 50% of the periosteal blood supply. Already two months later one plate broke and one loosened thus re-plating was necessary. Further two months later the plates failed again necessitating removal and two wire cerclages were used in a desperate attempt to stabilize the fracture. Four months later the patient was referred to our clinic (A). Dynamic X-rays demonstrate the mobility of the hypertrophic non-union (B). Following ESWT stabilization of the non-union with an external fixator was scheduled. Due to the impaired quality of the bone a satisfying stabilization of the screws was not achievable. Hence, immobilization was realized by a plaster cast (including the pelvis) for four weeks. (C) depicts the outcome after 6 months with the broken implant *in situ*, a slight varus malalignment but a sufficient bony bridging enabling the patient to full weight bear without pain.

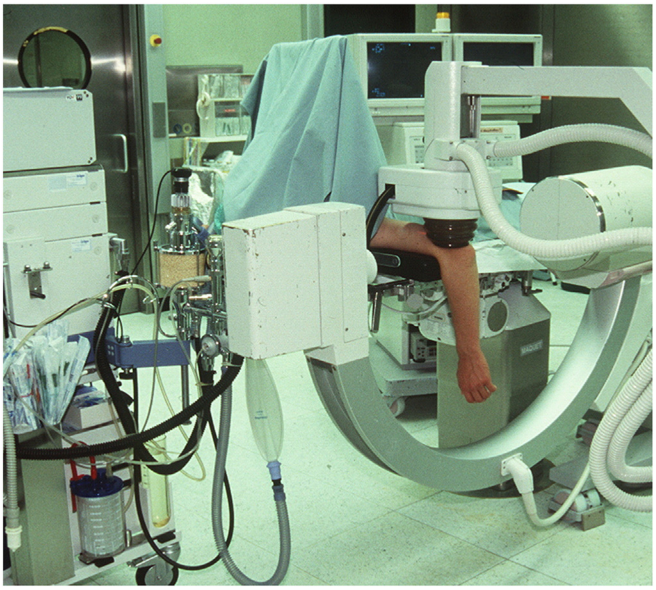

Fig. 3. The picture shows the positioning of the patient during the shockwave treatment of a supracondylar humerus non-union under X-ray control by the C-arm.

for the patient not undergoing major surgery with the associated risks and complications, also the financial effort of different treatment options is increasingly recognized by the health care systems worldwide. Savings of around 65%–85% (depending on different assurance modalities) are achieved in Austria treating non-union fractures with ESWT in place of surgery.

3.1. Studies comparing ESWT with surgery

Our group [21] compared retrospectively two patient collectives suffering from non-unions on the base of the fifth metatarsal bone (Jones fracture). One group (23 patients) received a single session of high-energy electrohydraulic shockwave therapy (2000–4000 impulses; 0.35 mJ/mm^2 energy flux density per impulse), and the surgical control group (20 patients) was treated with closed reduction and intramedullary screw fixation. The number of fractures which healed at three and six months follow-up in each group was determined, and treatment complications recorded. Twenty out of the twenty-three non-unions in the shockwave group and eighteen out of the twenty non-unions in the screw fixation group showed osseous healing at three months after treatment. One of the three non-unions that had not healed by three months in the shockwave group was consolidated by six months. Only one complication in the shockwave group (post-treatment petechiae) was observed whereas eleven complications in the screw-fixation group (one re-fracture, one case of cellulitis and nine cases of symptomatic hardware) were registered (Table 1). The authors conclude that both intramedullary screw fixation and shockwave therapy are effective treatments for fracture non-union in the metaphyseal-diaphyseal region of the fifth metatarsal. However, screw fixation is more often associated with complications that frequently result in additional surgery irrespective of scheduled hardware removal.

Notarnicola et al. [22] compared in a retrospective analysis ESWT in patients suffering from non-unions of the carpal scaphoid with surgery. They could include in their study a total of 118 individuals of whose 58 were assigned to shockwave treatment and 60 patients decided to undergo surgery. All patients were initially treated conservatively with a plaster cast (range from 4 to 12 weeks). In the case of failing osseous consolidation on X-rays for at least 6 months after immobilization and persistence for a further 3 months the fracture was judged as not healed (non-union) and included into the study. In the ESWT group patients had three sessions at a 72 h interval, receiving 4000 impulses at a mean energy flux density of 0.09 mJ/mm^2 at each session, conducted with an electromagnetic device. Subsequent immobilization was realized by a brachio-metacarpal cast embedding the thumb as well for 60 consecutive days. Surgery was performed according to the Matti-Russe procedure with a cortico-cancellous bone graft. Post-surgery immobilization was identical to the ESWT group. At the 12 month follow-up period bony consolidation did not differ between the study groups being 79.3% in the ESWT group and 78.3% in the surgical group. Similarly, the clinical status assessed by the Mayo wrist score revealed no statistical significant differences between the studied treatment modalities (excellent/good outcome: ESWT - 56.9%; surgery - 60%). It is noteworthy, that no complications were registered neither in the ESWT group nor in the group receiving surgery.

Cacchio et al. [23] performed a prospective, randomized controlled multi-center trial (evidence level I) comparing ESWT to “standard of care” surgery in the treatment of long bone non-unions. One hundred and twenty-six patients with a long-bone non-union were randomly assigned to receive either ESWT (Groups 1 and 2) or surgical treatment (Group 3). The patients in

Table 1
Studies comparing ESWT with surgery.

	Furia et al. [21]	Notarnicola et al. [22]	Cacchio et al. [23]
Indication	5th Metatarsus	Carpal scaphoid	Long bone
Device	Electrohydraulic	Electromagnetic	Electromagnetic
ESWT	2000–4000 impulses 0.35 mJ/mm^2 Single session	4000 impulses 0.09 mJ/mm^2 3 sessions	4000 impulses Group 1: 0.4 mJ/mm^2 Group 2: 0.7 mJ/mm^2 4 sessions
Number of pts (n)	23 vs 20 ESWT vs surgery	58 vs 60 ESWT vs surgery	36 vs 38 vs 37[a] ESWT group 1 vs 2 vs surgery
Union rate	*6 month FU* 91% vs 90% ESWT vs surgery	*12 month FU* 79.3% vs 78.3% ESWT vs surgery	*24 month FU* 94% vs 92% vs 95% ESWT group 1 vs 2 vs surgery
Complications	1 vs 11 ESWT vs surgery	None	23 vs 3 ESWT group1+2 vs surgery
Type of complication	*ESWT*: petechiae *Surgery*: re-fracture, cellulitis, symptomatic hardware		*ESWT*: Petechiae, hematoma *Surgery*: wound infection, temporary paresis

[a] Number of patients completing the 24 month FU.

the ESWT-groups received four treatments with 4000 impulses of electromagnetic shockwaves with an energy flux density of 0.40 mJ/mm^2 (Group 1) or 0.70 mJ/mm^2 (Group 2). The patients in the three groups had similar demographic characteristics, duration of non-union, and duration of follow-up. Radiography (primary outcome parameter) as well as clinical results (secondary outcome parameter) were determined before and three, six, twelve, and twenty-four months after treatment. The radiographic findings did not differ significantly among the three study groups. At six months, 70% of the non-unions in ESWT Group 1 (0.40 mJ/mm^2), 71% of the non-unions in ESWT Group 2 (0.70 mJ/mm^2), and 73% of the non-unions in Group 3 (surgical treatment) had healed. Three and six months after treatment, the clinical outcome parameter visual analog scale (VAS), Lower Extremity Functional Scale (LEFS) and Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH-score) in the two shockwave groups were statistically significant better than those in the surgical group ($p < 0.001$). Only after twelve and twenty-four months following treatment, there were no more differences among the three groups, except the DASH score at 12 months being significant better for the ESWT groups compared to the surgical group (Group 1 vs 3 $p = 0.038$; Group 2 vs 3 $p = 0.021$). In the two shockwave groups local effects such as petechial bleeding and hematoma, which lasted from four to six days were observed in 23 patients (27%); this problem resolved spontaneously after a few days. No other neuromuscular, systemic, or device-related adverse effects were observed in these two shockwave groups. The rate of adverse effects in the surgical group was 7% (three of forty-two). Two cases of wound infection and one temporary paresis of a radial nerve were observed. The authors concluded ESWT being as effective as surgery in stimulating bony consolidation of long-bone hypertrophic non-unions and yields better short-term clinical outcomes. Moreover, ESWT usually show less and more importantly less severe complications compared to surgery.

3.2. Recommendations applying ESWT in delayed or non-healing fractures

The current peer-reviewed literature clearly shows that treatment of fracture non-unions with electrohydraulic and electromagnetic shockwave sources possessing wide focusses (big devices) delivering high energy flux densities is effective. As these devices are used at high energy levels for non-union treatments usually sedation or general- or regional anesthesia is required. Electrohydraulic systems are used in a single session whereas electromagnetic devices are recommended to be applied from two to four sessions. To be suitable for ESWT the non-union should be in correct anatomical position. According to the literature atrophic and oligotrophic non-unions have an inferior probability of bony healing after ESWT than hypertrophic non-unions. However, according to our experience we could not see a significant difference in the outcome between these non-union types. Nevertheless, we could determine a non-union gap of being larger than 5 mm in long bones as a negative predictor for outcome, thus surgical options should be considered in these cases.

As ESWT is initiating healing inter alia by angiogenesis where capillaries are crossing the non-union gap it increases success when avoiding micro movements for four to six weeks after the treatment. If necessary this can be achieved by orthosis, plaster cast and/or no weight bearing for this period of time. In very instable non-unions especially in the lower limb it might be necessary to apply an external fixator in the same session to ensure sufficient stability. Reproducible results for the treatment of non-union fractures can be expected when using ESWT in conformity with above mentioned standards.

4. Discussion

Currently, there are more than 20 peer reviewed publications available reporting about the use of ESWT in bone healing disturbances (in addition to already cited articles [24–30]). All these publications including the review of Zelle et al. [31] comparably show significant healing rates of fracture non-unions with practically no appreciable side effects.

Most of these articles are retrospective cohort studies with low evidence. This might be owed to the fact that the development of non-unions has an extreme high number of different origins such as location of the fracture, initial soft tissue damage, time to first aid and surgery, quality of surgery, concomitant injuries, compliance of the patient, extend of the external forces causing the fracture, and infection. Along, the patients' age, comorbidities such as diabetes or osteoporosis, use of corticosteroids, metabolic disorders, smoking or alcohol have a strong influence on bone healing. Due to this fact it is almost impossible to create two comparable cohorts of patients suffering from non-unions in approximately the same anatomical region with similar previous surgical procedures to evaluate different treatment options for study purposes.

Surgery is still considered as the “golden standard” for the treatment of fracture non-unions. Usually, the previous implant is removed followed by decortication of the fracture site and removal of interposed soft tissue. In long bones the intramedullary space is recanalized and the fracture reduced. A very critical point of this surgery, which needs long experience, is to judge the vitality of the bone fragments in the vicinity of the fracture. Stabilization is ensured by appropriate osteosynthetic material (intramedullary nails, plates, screws etc.). The gap is substituted with autologous cancellous bone usually harvested from the iliac crest. Sometimes, especially in the elderly both iliac crests have to be exposed to get a sufficient amount of autologous cancellous bone for grafting. In most of the cases immobilization and partial or no weight bearing is required after surgery. Such surgical procedures on two different sites (non-union and donor site) often exceed several hours and are potentially associated with the corresponding risks. Regularly, antibiotic prophylaxis is administered and the patients need to stay for approximately one week in the hospital.

Contrary, ESWT can be performed as an outpatient procedure or alternatively admission overnight in the hospital. The procedure itself only takes between 25 and 45 min, is easy to be performed and has a short learning curve. Minor side effects include reddening and swelling and occasionally petechial bleedings and hematomas without clinical impact. However, no major side effects are reported.

5. Conclusion

As ESWT has been proven to be as effective as surgical procedures but being more economic and practically free of side effects it should be considered progressively as “therapy of first choice” for the treatment of suitable non-union fractures.

Ethical approval

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Author contribution

All authors contributed substantially and equally in the literature review, concept of the manuscript, writing and manuscript review.

Conflict of interest

None.

Guarantor

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