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ORIGINAL ARTICLE

High-energy extracorporeal shockwave therapy in humeral delayed and non-unions

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Abstract

Introduction Within the last few decades, focused high-energy extracorporeal shockwave therapy (ESWT) has proven to be an effective alternative to standard of care revision surgery in delayed healing fractures or manifest non-unions in various anatomical regions.

Materials and methods A retrospective multi-variant analysis of an open prospective, single-armed clinical study was conducted. Patients receiving focused high-energy ESWT for a delayed healing or an apparent non-union of a humeral fracture between January 1999 and December 2015 at a single trauma center were included in the study. Bony healing was defined as cortical continuity in three of four cortices and pain-free force loading and evaluated using CT scans and clinical examination at three- and six-month follow-ups after ESWT.

Results A total of 236 patients were included. $N=93$ (43.8%) showed bony consolidation three months after ESWT and $n=105$ (52.5%) after six months. Sub-group analysis showed significantly better healing for the proximal metaphyseal humerus (66.7% after six months, $n=42$) compared to the diaphyseal region (48.1%, $n=133$) and distal metaphyseal humerus (48.1%, $n=25$). Regression analysis indicated significantly increased healing rates for patients of younger ages ($p=0.001$) and a fracture diastasis of less than 5 mm ($p=0.002$).

Conclusion The findings of this study indicate that ESWT can be considered as a treatment option for a well-selected patient population despite the lower healing rates compared to other anatomical regions.

Keywords Extracorporeal shockwave therapy · ESWT · Non-union · Delayed union · Humerus

Introduction

Fractures of the humeral bone account for 1–8% of all broken bones in the human body, with a steep increase in incidence rates in higher age groups. 83% of all humeral fractures occur in patients older than 50 years of age [1, 2]. With increased life expectancy, the socioeconomic importance of this type of fracture and its complications arise. Delayed healings or fracture non-union is a rare but significant complication, and therefore poses a remarkable burden on patients and their families as well as on health care systems [3]. Affected patients remain unable to return to work or perform activities of daily living independently as well as requiring medical attention for a prolonged period. Incidence rates for humeral non-unions range from 2.3 to 11.6% [4–10]. There is no uniform treatment recommendation for non-unions in current literature, but most surgeons

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recommend revision surgery with or without supplementary bone grafting [11–13].

Within the last 20 years, high-energy focused extracorporeal shockwave therapy (ESWT) has shown to be a valid and effective alternative to revision surgery for the treatment of delayed or non-healing fractures [14–16]. Since then, several studies have examined the cellular effect of ESWT, providing in vitro evidence for the upregulation of membrane proteins and adhesion molecules in osteoblasts or the increased osteogenic differentiation of mesenchymal stem cells [17]. Despite this growing understanding of biological effects and efficacy, scientific evidence from larger patient cohorts for the clinical application of ESWT in delayed and non-healing fractures is still missing.

To our knowledge, there is currently very limited literature available on the treatment of humeral fracture non-unions with extracorporeal shockwaves and this is the only study exclusively focusing on this region. The present study is aimed to evaluate the outcome of patients suffering from delayed unions or non-unions of humeral fractures treated with electrohydraulic high-energy, focused ESWT. To analyze influencing factors, sub-group analysis was performed using a multi-variant regression model.

Materials and methods

The study protocol was approved by the institutional ethics committee. Patients who had undergone ESWT treatment to the humeral bone for a single focus between January 1999 and December 2015 were retrospectively reviewed. The inclusion criteria were as follows: no contraindication for high-energy ESWT according to the German-speaking international association for extracorporeal shockwave therapy (DIGEST) guidelines, humeral non-union or delayed union due to traumatic injury. Exclusion criteria were: intraarticular fractures, fractures on multiple levels and incomplete follow-up examinations.

132/200 patients received a CT scan at the three- and six-month follow-ups appointment to accurately evaluate healing progression after ESWT. If a CT scan was not available, conventional skeletal X-rays in at least two planes were acquired. All fractures that showed stagnation of healing and hence were dedicated to ESWT were initially traumatic lesions. Initial fracture treatment included both conservative and surgical approaches. Conservative ($n=29$) strategies consisted of cast or bandage fixation for two to four weeks depending on the location of the fracture. Surgically, the majority of patients were treated with intramedullary nail fixation ($n=115$) followed by plating ($n=74$). The remaining patients were treated with inter-fragmentary screws only ($n=6$), Kirschner wires ($n=2$), a combination of inter-fragmentary screws and Kirschner wires ($n=6$), or external fixateurs ($n=4$).

The pre-treatment images were analyzed for cortical separation and fracture configuration. The sight of minimal diastasis was measured and rated as <5 mm or ≥ 5 mm. The localization of the lesion on the humeral bone on pre-treatment imaging (proximal metaphysis, diaphysis, distal metaphysis) and type of fracture were registered. The fracture type was classified as oblique, spiral, transverse, multi-fragment (three to five fragments) or comminuted fracture (more than five fragments). The patient's medical history was screened for trauma mechanism and categorized in two groups. The first group contained patients with a low-energy trauma (e.g., simple fall). The second group consisted of patients who were exposed to high energy (e.g., motor vehicle accidents, sports injuries, fall from heights).

Subgroup analysis was performed according to the time interval between initial trauma and ESWT. Lesions from time intervals between 90 and 179 days were classified as delayed union. Lesions from intervals ≥ 180 days were classified as non-unions. The primary read-out parameter of this study was healing of the humeral delayed fracture healing or non-union. Healing was defined as radiological re-establishment of cortical continuity of at least three of four cortices or more than 75% of the cortical circumference and painless force loading capacity. If no sufficient cortical healing was established, patients were referred for revision surgery. Only patients that explicitly refused or had any contraindication for surgery were offered additional ESWT using the same treatment regimen.

Extracorporeal shockwave therapy (ESWT)

All patients received regional or general anesthesia for ESWT. Shockwaves were generated with an electrohydraulic shockwave device (OrthoGold 280, MTS Medical UG, Constance, Germany). Patients were positioned in supine position on the operating table and the humeral fracture site was visualized under fluoroscopic projection in two planes. The site of the non-union was marked with a surgical skin marker according to fluoroscopic projection. Coupling gel (Aquasonic 100, Parker Laboratories, Fairfield, New Jersey) was applied to the marked area and the therapy head was accurately positioned above the fracture site. Bubbling within the coupling gel was avoided to eliminate impedance differences, which would absorb part of the energy. The system's focal point was adjusted according to the fracture conditions. ESWT trajectory was set to omit larger neurovascular structures if present. All treatments were performed with an energy flux density of 0.4 mJ/mm^2 (−6 dB) at a frequency of 4 Hz, applying 3000–4000 impulses in total. The pulses were applied to the fracture in equal parts from different directions (varying from at least two to four directions).

After removing the coupling gel, the intervention site was inspected for alterations. In few cases signs of reddening, minor swelling and rarely petechial bleedings without clinical impact were noticed. They all healed within three to four days without special treatment. No major adverse events resulting from shockwave treatment were recorded. All patients were discharged from hospital either the day of treatment, or at the latest the day after treatment according to the hospital's anesthetic care protocol.

Post-interventional measures

All patients received a Gilchrist sling fixation to immobilize the fracture site for two to four weeks after ESWT. Radiological assessment with conventional X-ray was performed upon fixation removal in most cases to exclude fracture or osteosynthesis displacement. At that time, no increase in bony bridging was expected. Patients were advised to start mobilization without external rotation up to week six. Afterwards, active physiotherapy was commenced but without weight-bearing (< 4 kg) or active external/internal rotation against resistance for another six weeks. Further radiologic evaluation of the fracture site took place by analyzing CT scans at three as well as six months after ESWT. At these appointments, clinical examination was performed for compression pain and pain-free weight-bearing capacity.

Statistical analysis

Statistical analysis was performed using IBM SPSS Version 22. Healing rates for the entire study population were calculated and subgroup analysis for different fracture criteria (localization, type of fracture, initial treatment modality, patient's age, fracture diastasis, trauma energy) were conducted. For that reason, a prediction model for the criteria healed versus not healed after three and six months following ESWT was established using a binary logistical regression model.

Model testing of the predictors was done using the backward stepwise method

Examination of qualification for operability was done using the Hosmer–Lemeshow test. All patients who were lost to follow-up were exempt from analysis.

Subgroup analysis for fracture localization was performed using the Chi-Square test.

Results

A total of 236 patients between 14 and 89 years of age were included, receiving a total of 293 shockwave therapies. Most patients ($n = 189$, 80%) received one single ESWT treatment session. 38 (16%) patients had two treatment sessions. Six patients (3%) received three ESWT treatments and three patients (1.5%) had to undergo four treatment sessions. The gender distribution demonstrated an approximately even spread, with 122 male and 114 female patients. 76 patients were classified according to our definition as delayed bone healing (absence of healing by 179th day) and 160 patients with non-unions (fracture persistence longer than 180 days).

22 patients were lost to follow-up at 3 months. Another 12 of the 236 patients could not be recruited for a 6-month follow-up and were therefore excluded from further analysis. Demographic details of the study population are summarized in Table 1 and Table 2.

The most frequent fracture localization in the presented cohort was the diaphysis ($n = 161$). 46 fractures were proximal metaphyseal fractures and 29 were located in the distal metaphysis. Details of the influence of fracture localization and the initial treatment method on healing outcome are presented separately for delayed and non-healing fractures in Table 3.

Of all analyzed fractures which were treated with ESWT, $n = 93$ (43.5%) were considered healed after three months and 105 (52.5%) were considered healed after six months.

After the second ESWT application, another $n = 15$ (40.4%) of the previously non-healed fractures showed healing after three months, rising to $n = 19$ (48.7%) after six months. The respective healing rates for the delayed union six months after the second ESWT were $n = 7/16$ (43.15%)

Table 1 Demographic data of patients with delayed healing fractures—defined as absence of healing by day 179

	Healed		Not healed		Drop-out	
	3 months	6 months	3 months	6 months	3 months	6 months
$n = 76$	27	29	38	30	11	17
Avrg. age (min–max)	50.9 (19–77)	51.9 (19–79)	54.3 (22–89)	54.5 (23–89)	39.1 (22–71)	42.8 (22–77)
∑ male	14	16	18	12	9	13
∑ female	13	13	20	18	2	4
Time from injury to first ESWT (Ø)	133	133	143	141	141	141
Time from injury to first ESWT (min)	95	95	97	97	90	90
Time from injury to first ESWT (max)	176	176	178	178	176	176

Table 2 Demographic data of patients with non-unions, defined as absence of healing after 180 days or more

	Healed		Not healed		Drop-out	
	3 months	6 months	3 months	6 months	3 months	6 months
($n=160$)	66	76	83	65	11	19
Avrg. age (min–max)	49.0 (14–83)	50.1 (14–83)	56.6 (21–84)	56.6 (21–84)	50.3 (35–72)	52.4 (35–72)
∑ male	36	40	38	32	7	9
∑ female	30	36	46	33	4	10
Days from injury to first ESWT (Ø)	402	395	365	360	396	408
Days from injury to first ESWT (min)	182	182	181	181	188	188
Days from injury to first ESWT (max)	1627	1627	2798	2798	1245	1245

Table 3 Comparison of treatment method, localization and type of fracture for delayed unions and non-unions

	Healed delayed unions		Healed non-unions	
	3 months	6 months	3 months	6 months
Intramedullary	11 (33.3%)	+1	29 (38.2%)	+4
Extramedullary	6 (42.9%)	=	23 (46.9%)	+5
Screw +/wire	1 (100%)	=	5 (55.6%)	=
Conservative	8 (57.1%)	=	5 (50%)	+1
Fixateur	1 (33.3%)	+1	1 (100%)	=
Other	0	=	3 (75%)	=
Proximal metaphysis	12 (66.7%)	=	15 (62.5%)	+1
Diaphysis	13 (31.8%)	+1	42 (40%)	+8
Distal metaphysis	2 (33.3%)	+1	9 (45%)	+1
Spiral fracture	4 (36.3%)	=	7 (33.3%)	=
Transverse	7 (38.9%)	+1	15 (41.7%)	+3
Comminute	1 (100%)	=	2 (100%)	=
Multi fragment	4 (26.7%)	+1	15 (42.9%)	+2
Oblique	11 (55%)	=	27 (49.1%)	+5
Total	27 (41.5%)	+2	66 (44.3%)	+10

Absolute and relative numbers at 3 months, increase of healed cases at 6 months

and $n=12/23$ (52.2%) for non-unions. Three patients (6%) were lost to follow-up. Healing rates after a third ($n=6$) and a fourth ($n=3$) ESWT still reached 30% after six months.

The logistic regression model applied for variables three months after ESWT indicated that patients of younger ages demonstrate increased fracture healing rates [$p=0.001$, OR = 0.967, 95% CI (0.95; 0.99)]. Similarly, a fracture fragment diastasis of less than 5 mm is correlated with better healing outcomes ($p=0.002$, OR 0.226).

All other tested covariates (gender, trauma energy, type of fracture, type of initial treatment) did not demonstrate a significant impact on healing rates. The same logistic regression model was carried out for the six months parameter after ESWT. The calculations revealed that a younger age correlates with higher healing rates [$p=0.013$, OR = 0.98; 95% CI (0.96, 0.995)]. Moreover, a smaller diastasis of fracture fragments exhibited a higher rate of bony consolidation [$p=0.001$, OR 0.22, 95% CI (0.09, 0.55)]. In addition, the proximal metaphyseal localization of the lesion demonstrated better healing rates opposed to the diaphysis ($p=0.030$, OR = 0.41). No significant difference in healing could be found between proximal and distal fracture localization ($p=0.130$). The remaining analyzed covariates (gender, trauma energy, type of fracture, type of treatment) did not show further significant correlations.

Subgroup analysis

Within the first three months after ESWT, healing rates for the proximal humeral metaphysis (64.3%, $n=27$) were significantly better ($p=0.009$), compared to the diaphysis (37.7%, $n=55$) and the distal humeral metaphysis (42.3%, $n=11$) (Fig. 1). Follow-up results at 6 months after the first shockwave application yielded similar results to those at 3 months. Likewise, in cases a second ESWT was deemed appropriate, results showed a comparable picture at both time points of follow-up ($p=0.110$). The diaphyseal region showed the highest increase in healing rates between the three- and six-month follow-ups (Fig. 1).

Six months after performing ESWT for delayed or not-healing humeral fractures, healing rates of 66.7% ($n=42$) could be found for the proximal metaphysis, for the diaphysis 48.1% ($n=133$) and 48.1% ($n=25$) at the distal metaphysis (Fig. 1).

Comparing the healing rates for delayed unions (according to our definition less than 179 days) and non-unions (fracture persistence longer than 180 days), similar bony consolidation rates were achieved by applying focused high-energy shock waves. Thus, indicating that the time lag between trauma and ESWT only plays a subordinate role.

Discussion

To the best of our knowledge, this is the first study conducted on healing rates for humeral delayed unions and non-unions treated with ESWT in a patient group of this size. In

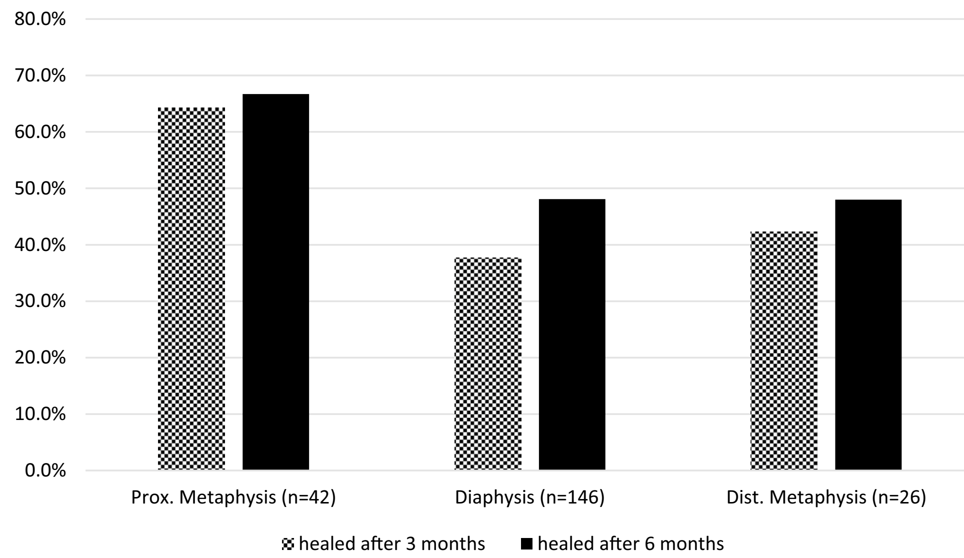

Fig. 1 Stacked bar chart of healing rates for delayed and non-unions in different humeral localizations in % 3 and 6 months after first ESWT

total, 236 patients were included of which 200 patients were followed up for six months after treatment. Analysis showed that bony union could be achieved in 52.5% ($n=105$) at the end of follow-up. Subgroup analysis revealed that healing rates of 64.3% ($n=27$) were achieved for proximal metaphyseal delayed healings and non-unions. The largest late healing effect between the 3- and 6-month follow-up was found for the diaphyseal region, whereas limited changes were observed in the proximal and distal metaphyseal region. Regression analysis showed significantly better healing rates for younger patients and a fracture diastasis of less than 5 mm. No significant effect could be detected for other variates (gender, trauma energy, type of fracture, type of initial treatment).

Non-union rates for proximal humeral fractures range from 2.3 to 8.9% [4–6] in surgically treated patients and from 1.1 to 10% in conservatively treated patients [18–20].

Healing rates differ mildly between treatment methods. Whether a patient receives surgical or conservative treatment may be subject to a selection bias, since patients with a higher degree of fracture dislocation or open fractures are more likely to be operated upon. Nandra et al. determined non-union rates to be 4.2% for conservative treatment, 4.2% for plate fixation, 11.6% for antegrade intramedullary nailing and 4.5% for retrograde intramedullary nailing [7].

Distal humerus fractures account for up to 7% of all humeral fractures [21]. Undislocated fractures can be treated conservatively with healing rates of 96% and good functional outcomes [8]. In surgically treated distal humerus fractures, non-union rates range between 2 and 11% [9, 10].

There is no uniform treatment recommendation for non-unions. Most surgical treatment modalities, such as open revision and plating with bone grafts, show healing rates between 75 and 98.1% [22–24]. Healing rates of 93% were found be Aytac et al. for non-unions of the proximal metaphysis and proximal third of the diaphysis treated with revision plating with bone grafting [22]. Pollon et al. treated humeral shaft non-unions with bone grafting and plating and were able to achieve healing in only 75% of their shaft non-union cases ($n=16$) [24]. Helfet et al. describe union rates of 98.1% after open revision of distal humeral non-unions but with 29% of patients requiring additional surgery (ranging from hardware removal to compartment release) [23].

Within the last 20 years, extracorporeal shockwave therapy has proven to be a valid alternative to revision surgery in many cases of disturbed fracture healings.

Within current literature, the definitions of delayed unions and non-unions are still debated and a high variability in routine clinical application can be found [25]. In this study, the following definitions were applied, which are routinely used at our center and are the most common in clinical practice [25]. A delayed union was defined as a fracture that failed to show proof of healing 90 days after trauma and did not yet meet the criteria of a non-union. A non-union was defined as a fracture failing to show cortical continuity six months after surgical or conservative treatment initiation and no radiologic progress of healing for 3 months. It is commonly accepted that a non-union will not heal without further therapeutic intervention. ESWT offers these patients the benefit of an extremely low risk of adverse events and shorter hospital stays [14]. Willems et al. performed a literature review on delayed fracture healings and non-unions of different anatomic regions treated with ESWT, finding average healing rates of 86% for delayed unions and 73% for non-unions [26].

Our analysis of this open prospective, single-armed clinical study showed inferior effects for ESWT in humeral delayed fracture healings or non-unions compared to previous studies, which were conducted on lesions in different anatomical regions. Xu et al. analyzed healing rates in different long bone non-unions after ESWT including the humeral bone [27]. Bony consolidation of the humeral bone was found in 8/13 (62%) cases six months after ESWT. The small patient count in this population indicates similar healing rates to our findings but may be susceptible to statistical error. The precise fracture localization on the humeral bone is not described in the above-mentioned publication and might be another explanation for the somewhat divergent healing rates.

Previous ESWT studies in various body regions found inferior healing rates for lesions with a fracture gap larger than 4 mm this is in line with results of the present study and should thus be considered as an exclusion criteria for ESWT [14, 15, 28]. According to our data, additional negative predictive factors for a successful ESWT outcome were older age and fracture localization in the diaphysis or distal metaphysis of the humerus.

The authors can only speculate on reasons for the generally inferior healing rates compared to other anatomical regions. One possible explanation might be the biomechanical instability due to strong axial and rotational forces paired with the difficulty of proper immobilization. Thus, the humeral diaphysis is especially vulnerable for the development of non-unions [29]. The same reasons might be responsible for the poor outcome after ESWT.

Pollon et al. determined that all of their persistent non-union cases revealed technical errors in the initial treatment attempt (poor reduction, insufficient fixation, intra-focal hardware) [24]. These shortcomings are sometimes hard to detect but should be ruled out prior to ESWT. Another reason for persistent non-unions are fracture site infections. Since healing rates for the presented patients initially treated conservatively or surgically did not differ significantly this effect seems to be negligible. ESWT might even be useful in patients with low-grade infections due to a suspected bactericidal effect as shown by Gerdesmayer et al. in a vitro model [30]. Nevertheless, patients must be screened and in case of suspected infections, ESWT should not primarily be used.

In this study, healing rates declined at the second (40.4%), third (30%) and fourth (30%) application. This might be explained by persisting biomechanical problems that already prevented healing after the first application. A negative selection bias for patients undergoing ESWT can be presumed especially for the second, third and fourth ESWT, since patients unfit for surgery due to other medical conditions underwent ESWT as a less-invasive treatment option.

Causes for non-unions are multifactorial including age, type of fracture (open or closed, simple or comminuted), local changes in homeostasis and blood circulation, fracture site infection, fracture diastasis with potential interposition of soft tissues, soft tissue damage and systemic factors like comorbidities, such as diabetes, hypertension, chronic renal failure and others as well as smoking or inadequate calorie intake [21].

In most clinics, the treatment of choice for these complicated cases remains to be revision surgery yielding results similar to the studies mentioned above. While considering these (in some cases) excellent results, one still needs to take socioeconomic and patient related factors into account. Revision surgery requires a high degree of experience and long operating times. Complication rates are inevitably higher in revision surgery compared to initial operations. Patients suffer from surgical pain and if bone grafting is necessary from donor site morbidity in up to 44% of cases [31].

This study has several limitations. First, it was a retrospective analysis of an ongoing single-armed prospective study without control group or randomization with the according risks of bias. Another limitation is the size of the study population, limiting statistical power for subgroup analysis. Nevertheless, the current study presents, by far, the most extensive analysis of ESWT treatment in patients with humeral delayed unions and non-unions. The relatively high lost to follow-up rate of 14.8% after 6 months also represents a limitation of this study. This can partially be explained by the long commute patients had to endure to get treatment at this trauma center as 104/236 (43%) of patients reside in a different state than the hospital.

Further investigations are necessary to explain differences in ESWT efficacy compared to other fracture localizations and optimize patient selection. The biomechanical situation and diastasis at the fracture site should be thoroughly assessed prior to ESWT. Thus, treatment decisions should be made by experienced trauma surgeons. According to our results, ESWT can only be recommended in selected cases of humeral delayed fracture healings or non-unions but should be considered as a valid alternative to surgery for these patients.

Conclusion

This study of 200 humeral delayed fracture healings or non-unions found healing rates of 52.5% six months after ESWT without notable complications. The proximal metaphyseal region appeared more responsive with healing rates of 66.7%. Statistical analysis revealed significantly better healing for fracture diastasis of less than 5 mm and deteriorating healing rates with older age. Taking these factors into consideration, ESWT is a reasonable alternative for a well-selected patient cohort with humeral delayed fracture healings or non-unions where biomechanical problems of the previous therapeutic concept have been ruled out.

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Data availability and material Data will be made available upon reasonable request.

Declarations

Conflict of interest W.S. is holding ESWT related patents. F.D. has no conflict of interest. X.F. has no conflict of interest. S-M.V: has no conflict of interest. N.H. has no conflict of interest. C.F. has no conflict of interest. R.M. has no conflict of interest.

Consent for publication All authors have approved the final version of the manuscript fur publication.

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