Flinders UNIVERSITY

A preliminary investigation on the effect of Extracorporeal Shock Wave Therapy as a treatment for Neurogenic Heterotopic Ossification following Traumatic Brain Injury. Part II: Effects on function

J.E. Reznik, PhD. College of Healthcare Science and Division of Tropical Health and Medicine, James Cook University, Townsville, QLD Australia 4811

E. Biros, PhD. Queensland Research Centre for Peripheral Vascular Disease, James Cook University, Townsville, QLD 4811, Australia

Y. Sacher. MD. Director, Brain Injury Unit, Loewenstein Rehabilitation Center, Sackler Faculty of Medicine, Tel Aviv University, Israel

O. Kibrik, BPT. Physiotherapist, Loewenstein Rehabilitation Center, Sackler Faculty of Medicine, Tel Aviv University, Israel

S. Milanese, PhD. Discipline of Physiotherapy, University of South Australia, Adelaide, SA 5001, Australia

S. Gordon, PhD. College of Healthcare Science, James Cook University, Townsville, QLD Australia 4811 and School of Health Sciences, Flinders University, Bedford Park, SA Australia 5042.

M.P. Galea, PhD. Department of Medicine, (Royal Melbourne Hospital) The University of Melbourne VIC 3010, and James Cook University, Townsville, QLD 4811, Australia

Corresponding author:

J.E Reznik jackie.reznik@jcu.edu.au (this may be published)

Division of Tropical Health and Medicine, James Cook University, Townsville, QLD Australia 4811
M: +61 424 546 875

Abstract

Introduction**:** Neurogenic heterotopic ossification (NHO) may occur as a complication of traumatic brain injury (TBI). No "gold standard" for treatment exists and the management of clinically significant NHO remains variable. Mature NHO results in a variety of complications limiting activities of daily living. The effect of the extracorporeal shock wave therapy (ESWT) on the range of motion at the hip and knee, and function in patients with TBI with chronic NHO was investigated.

Methods**:** A series of single-case studies applying ESWT to chronic NHO at the hip or knee of 11 patients with TBI was undertaken at a specialised rehabilitation hospital. Participants received four applications of high-energy EWST delivered to the affected hip or knee over a period of eight weeks. Two-weekly follow-up assessments were carried out and final assessments were made three months and six months post-intervention. Range of motion (ROM) and Functional Reach (FR) or Modified Functional Reach (MFR) were measured.

Results**:** The application of high-energy ESWT was associated with significant improvement in ROM (flexion) of the NHO-affected knee (Tau=0.833, 95% CI 0.391 to 1.276, P=0.002) and significant improvement of FR (Overall Tau 0.486, 95% CI 0.141 to 0.832, P=0.006), but no significant improvement in hip ROM or MFR.

Conclusions: ESWT is a novel non-invasive therapy that may improve mobility and balance of patients with TBI who have chronic NHO.

Introduction and Background

Under certain pathological conditions bone occasionally forms in tissues other than those comprising the skeleton. Neurogenic heterotopic ossification (NHO) often follows serious brain injuries [1,2]. The prevalence of clinically significant NHO in patients with traumatic brain injury (TBI) has been estimated as being between 10% and 23% [2-5]. NHO typically develops around large joints such as the hip or knee within two to four months of neurological insult and manifests itself clinically as severe pain, swelling, erythema, and warmth [2]. As the bone progressively matures it can result in a variety of complications, including decreased range of movement (ROM) of affected joints that may greatly limit activities of daily living, thereby adversely affecting the quality of life of already physically compromised patients with TBI [2,6-10]. Pharmacotherapy to date has not proven to be successful once NHO has formed [11,12], thus surgical removal remains the only treatment option for NHO but is extremely invasive and not always possible for all TBI patients [13]. The use of extracorporeal shock wave therapy (ESWT) as a treatment of NHO following TBI has received only modest attention [14-17], although it has been used in the treatment of a range of musculoskeletal conditions for over 20 years with virtually no serious side-effects [18-20]. The aim of this study was to investigate the effects of ESWT on ROM of the NHO-affected hip and knee joints in patients with TBI. The effects of ESWT on pain has been reported in the companion paper.

Methods:

The Human Research Ethics Committees of Loewenstein Rehabilitation Centre, Israel and James Cook University Townsville, Australia, Research ID granted ethics approval for this study: 0020-13-LOE. The study was also registered at ClinicalTrials.gov Identifier NCT02331628.

Study design

A series of single-case research studies was undertaken where participants were assessed for a number of physical characteristics on multiple occasions; i.e. pre-, during, and post-intervention (Table 1). Four baseline assessments were conducted at two-weekly intervals followed by four ESWT interventions and the intervention phase assessments, again at two-weekly intervals over a period of eight weeks (Table 1). Subsequently, the post-intervention phase of four two - weekly follow-up assessments was carried out (Table 1). Final assessments were carried out at three and six months post-intervention (Weeks 26 and 38). This study took place at Lowenstein Rehabilitation Centre, Israel between October 13th 2014 and February 23rd 2016.

Insert Table 1

Participants

Patients with traumatic brain injury (TBI) who met the selection criteria were identified from the database of the Loewenstein Rehabilitation Centre, Israel. Inclusion criteria were: aged over 18 years, traumatic brain injured, diagnosed with NHO around the hip or knee for a period of more than one year, and with stable serum alkaline phosphatase (SAP) level at the time of recruitment as seen in their hospital notes.. Exclusion criteria were: pregnancy, or suffering from rheumatoid arthritis, ankylosing spondylitis or femoral/pelvic fractures at the time of recruitment. All participants who met the inclusion criteria were asked to sign the consent form. In those cases where the participants had legal guardians and/or were unable to sign, the legal guardian provided informed consent.

Intervention

Using the Minispec™ Extracorporeal Shock Wave instrument (Medispec Int. USA) all participants received four applications of EWST delivered to the affected hip or knee over a period of eight weeks (one dose every two weeks ± 3 days). The patients received 3000 shocks/treatment as per the manufacturer's instructions. The energy flux density (EFD) per shock was 0.176 mJ/mm^2. This dosage is considered as high energy EWST according to the Kassel classification (High EFD>0.12mJ/mm^2) [21,22].

Reporting Adverse Events

Participants were asked at each assessment if they had any adverse events to report.

Outcome measures

The physical characteristics assessed included the ROM of knee flexion and extension, hip flexion and extension, hip abduction and adduction, and hip internal and external rotation. The knee and hip ROM measurements were performed using a universal goniometer and a standardised protocol as described elsewhere [23]. In addition, we assessed the functional reach (FR) and modified functional reach (MFR) of participants. The FR characteristic is a clinically accessible measure of balance in standing [24], while the MFR test is a reliable measure of sitting balance for those individuals unable to stand [25]. Finally, routinely available laboratory data for serum alkaline phosphatase (SAP) were also collected to monitor the progression of NHO [26]. The reference SAP values can be found elsewhere [27].

Statistical analysis

All individual ROM, FR and MFR data were plotted graphically for visual inspection of trends within baseline, intervention and post-intervention phases. The individual and overall effect size estimates associated with the application of ESWT were calculated using all participants

who completed the trial using the non-parametric non-overlap Tau-U method [28]. In particular, the Tau-U score represents the percentage of non-overlap between phases or the percentage of data showing improvement between phases [28]. Higher Tau-U scores represent greater intervention effect while lower Tau-U scores represent an intervention that is less effective. The Tau-U method is designed to control for baseline trend and is the preferred method to estimate effect sizes when a positive linear trend in therapeutic direction exists in baseline [28]. All Tau-U score computations were performed using the Tau-U Calculator (Single Case Research, USA). Statistical significance was defined at the conventional 5% level.

Results

Patient characteristics

Eleven patients with TBI and chronic NHO were recruited; four patients presented with NHO in the knee and seven with NHO in the hip (Table 2). Six patients were ambulant with or without an aid (Table 2). Patient with TBI were less likely to be females (2/11; 18%), with a mean age of 41±14 years and had BMI of 25±4 kg/m^2 (Table 2). NHO tended to occur equally at both sides; five patients had their right affected side treated and six out of 11 participants were treated on their left affected side (Table 2). All participants presented with varying degrees of functional and mobility dysfunction (FIM motor score between 13 and 86; Table 2). SAP levels remained within normative values [27] during the study (Table 2).

Insert Table 2

Effect of ESWT on Knee Range of Movement (ROM)

All 4 patients with NHO around the knee completed the intervention phase; however, one patient did not complete the post-intervention phase. Based on the visual inspection of

individual knee flexion data during the post-intervention phase, knee flexion improved in all 3 patients who completed the full trial compared to their respective baseline measures (Figure 1A). The visual inspection of the knee extension data indicates high variability with no obvious trend (Figure 1B). Overall Tau score shows that ESWT was associated with significantly improved flexion of the knee post-intervention compared to baseline (Tau=0.833, 95% CI 0.391 to 1.276, P=0.002; Table 3). There was no statistically significant effect associated with the application of ESWT on knee extension during the post-intervention phase compared to the baseline phase (Tau 0.000, 95% CI -0.442 to 0.442, P=1.000; Table 3).

Insert Figure 1

Insert Table 3

Effect of ESWT on Hip Range of Movement (ROM)

Six out of seven patients with NHO at the hip joint completed the intervention phase and post-intervention phase. Visual inspection of individual hip movement data during the post-intervention phase showed that the application of ESWT was associated with a trend of improved flexion (Figure 2A) and extension (Figure 2B) of the hip compared to their respective baseline phase in three patients (cases 7, 8, and 10; Figures 2A and 2B). The visual inspection indicates that case 5 had improved hip flexion only post-intervention relative to baseline, and case 6 had improved hip extension only post-intervention relative to baseline (Figure 2A and 2B). No post-intervention trend of improved hip flexion and extension relative to the baseline phase was seen in case 1 (Figure 2A and 2B). The post-intervention data were not available for case 9 (Figure 2A and 2B). Visual inspection of individual abduction and adduction data was not informative (Figures 3A and 3B), however visual inspection of individual data indicates a

decreasing trend in hip internal and external rotation during the post-intervention phase compared to baseline in all but one patient who completed the full trial (Figure 4A and 4B, respectively). Overall Tau scores based on the comparison of the post-intervention and baseline data indicate no association of ESWT with hip flexion (Tau 0.193, 95% CI -0.122 to 0.508, P=0.230; Table 4), hip extension (Tau 0.206, 95% CI -0.109 to 0.521, P=0.200; Table 4), hip abduction (Tau 0.231, 95% CI -0.084 to 0.546, P=0.151; Table 5), and hip adduction (Tau 0.191, 95% CI -0.124 to 0.506, P=0.235; Table 5). The application of ESWT was associated with the post-intervention reduction of hip internal rotation (Overall Tau -0.331, 95% CI -0.646 to -0.016, P=0.040; Table 6) and hip external rotation (Overall Tau -0.387, 95% CI -0.702 to -0.072, P=0.016; Table 6) compared to the respective baseline data. This finding was individually statistically significant in cases 5 and 6 (Table 6).

Insert Figure 2

Insert Figure 3

Insert Figure 4

Insert Table 4

Insert Table 5

Insert Table 6

Effect of ESWT on Functional Reach (FR) and Modified Functional Reach (MFR)

Five of the six ambulant patients completed the post-intervention FR testing (Table 7). Visual inspection of individual FR test results indicates that ESWT was associated with improved distance reached in four of five patients who completed the full trial compared to their respective baseline phase (cases 1, 2, 3, and 6; Figure 5A). Overall Tau score indicates that ESWT was associated with significant post-intervention improvement in FR test results in ambulant TBI patients compared to baseline (Overall Tau 0.486, 95% CI 0.141 to 0.832, P=0.006; Table 7).

Visual inspection of the MFR test results was not conclusive (Figure 5B). The patients with TBI who were unable to stand did not show any statistically significant change in distance reached post-intervention compared to baseline (Overall Tau=0.319, 95% CI -0.123to0.762, P=0.157; Table 7). One participant without any voluntary movements (Case 10), was unable to perform either the FR or the MFR test.

Insert Figure 5

Insert Table 7

Adverse effects

Minor adverse effects of a transient slight increase in pain immediately following treatment were reported in two cases.

Discussion

The purpose of this study was to examine the effects of ESWT on the ROM of large joints affected by chronic NHO, specifically the knee or hip, in patients following TBI. In addition

the effect of ESWT on function was also assessed. The results obtained from this larger study support those demonstrated in our previous case report of the effect of ESWT on hip ROM [17], and more importantly, provides additional evidence on the effects of ESWT on both hip and knee ROM in patients with TBI and chronic NHO. In particular, after the application of ESWT, flexion at the affected knee joint showed overall improvement, but not knee extension. In the affected hip joint the application of ESWT was not associated with any overall changes in flexion, extension, abduction and adduction, although the post-intervention hip rotation parameters showed an overall reduction in the range relative to the baseline. The mechanisms underlying the differential effects of the ESWT on the knee and hip ROM were not evident in the current study. The findings of no or even negative association of ESWT with hip ROM may reflect the difficulty of delivering high energy shock-waves to NHO at the hip-joint due to the thickness of the overlying tissues, particularly the adductor muscle. In addition the quality of the X-rays at the hip did not allow us to focus on the specific bony bridges possibly causing wide dissipation of the shock waves. To overcome the barrier of the specific anatomical features of the hip region, it might be necessary to apply higher dosages of ESWT to treat NHO at the hip joint or to have better defined X-rays or other imaging methods, where specific bony bridges may allow more accurate focussing of the shock waves. This issue needs further investigation.

Although a significant overall improvement was seen in functional reach (FR), similar results were not obtained for the modified FR, which has been shown to be a reliable measure of sitting balance in those patients unable to stand [25]. Visual analysis and the individual Tau scores did however indicate possible clinical improvement in two of the three non-ambulant patients who completed the trial.

The limitations of this study include the relatively small number of participants, in particular females. Although the male to female ratio is consistent with that commonly found within this

patient population, the small number of women does limit the generalizability of this study. Furthermore, this study was conducted as a single-case research design in which within-subject rather than between-subjects data are compared, e.g. between the two experimental periods [29]. Using this design we were able to demonstrate lasting positive effects on post-intervention mobility and physical function associated with the application of ESWT in patients with TBI with NHO at the hip or knee joints. No "sham" treatment was used because it was not considered feasible with this difficult patient group that frequently presents with a profound cognitive impairment following TBI such as aggressiveness, impulsivity, forgetfulness, or apathy [30].

Conclusions

The outcomes of this study show lasting improvements in knee flexion following ESWT in TBI patients with chronic NHO. Functional improvement, as demonstrated by significant overall post-intervention improvement in FR test results in ambulant patients with TBI was also noted. Further investigation of ESWT as a therapeutic approach for improving joint mobility and function in patients with NHO is warranted.

Acknowledgments

The authors would like to thank Medispec for their generosity in lending Minispec™ machine for the duration of the trial; the staff of the X-ray department of Lowenstein Hospital Rehabilitation Centre for their support in this trial; Miss Sharon Ross for her invaluable assistance in setting up the trial; the patients themselves and their families.

Conflict of Interest Statement:

The authors report no conflict of interest.

References

1. Van Kampen PJ, Martina JD, Vos PE, Hoedemaekers CWE, Hendricks HT. Potential risk factors for developing heterotopic ossification in patients with severe traumatic brain injury. Journal of Head Trauma Rehabilitation 2011;26(5):384-391.

2. Cipriano CA, Pill SG, Keenan MA. Heterotopic ossification following traumatic brain injury and spinal cord injury. Journal of the American Academy of Orthopaedic Surgeons 2009;17(11):689-697.

3. Sakellariou VI, Grigoriou E, Mavrogenis AF, Soucacos PN, Papagelopoulos PJ. Heterotopic ossification following traumatic brain injury and spinal cord injury: Insight into the etiology and pathophysiology. Journal of Musculoskeletal Neuronal Interactions 2012;12(4):230-240.

4. Bossche LV, Vanderstraeten G. Heterotopic ossification: A review. Journal of Rehabilitation Medicine 2005;37(3):129-136.

5. Reznik JE, Biros E, Marshall R, Jelbart M, Milanese S, Gordon SJ, Galea MP. Prevalence and risk factors of neurogenic heterotopic ossification in traumatic spinal cord and traumatic brain injured patients admitted to specialised units in Australia. Journal of Musculoskeletal and Neuronal Interactions 2014;14(1):19-28.

6. Akbar M, Seyler TM, Abel R, Gerner HJ. Heterotopic ossification in spinal cord injury and traumatic brain injury. Physikalische Medizin Rehabilitationsmedizin Kurortmedizin 2007;17(3):156-171.

7. Banovac K, Gonzalez F. Evaluation and management of heterotopic ossification in patients with spinal cord injury. Spinal Cord 1997;35(3):158-162.

8. Chalidis B, Stengel D, Giannoudis PV. Early excision and late excision of heterotopic ossification after traumatic brain injury are equivalent: A systematic review of the literature. Journal of Neurotrauma 2007;24(11):1675-1686.

9. Silver JR. Heterotopic ossification. A clinical study of its possible relationship to trauma. Paraplegia 1969;7(3):220-230.

10. Silver JR. A systematic review of the therapeutic interventions for heterotopic ossification after spinal cord injury. Spinal Cord 2011;49(3):482-482.

11. Aubut J-AL, Mehta S, Cullen N, Teasell RW, Research Team E. A comparison of heterotopic ossification treatment within the traumatic brain and spinal cord injured population: An evidence based systematic review. NeuroRehabilitation 2011;28(2):151-160.

12. Banovac K, Sherman AL, Estores IM, Banovac F. Prevention and treatment of heterotopic ossification after spinal cord injury. Journal of Spinal Cord Medicine 2004;27(4):376-382.

13. Melamed E, Robinson D, Halperin N, Wallach N, Keren O, Groswasser Z. Brain injury-related heterotopic bone formation: Treatment strategy and results. American Journal of Physical Medicine and Rehabilitation 2002;81(9):670-674.

14. Brissot R, Lassalle A, Vincendeau S, Polard JL, Fouché M, Ninubona D, Mahieux G, Chaperon J, Lobel B. Treatment of heterotopic ossification by extracorporeal shock wave: 26 Patients. Annales de Réadaptation et de Médecine Physique 2005;48(8):581-589.

15. Buselli P, Coco V, Notarnicola A, Messina S, Saggini R, Tafuri S, Moretti L, Moretti B. Shock Waves in the Treatment of Post-Traumatic Myositis Ossificans. Ultrasound in Medicine and Biology 2010;36(3):397-409.

16. Torrance DA, deGraauw C. Treatment of post-traumatic myositis ossificans of the anterior thigh with extracorporeal shock wave therapy. Journal of the Canadian Chiropractic Association 2011;55(4):240-246.

17. Reznik JE, Gordon SJ, Barker RN, Keren O, Arama Y, Galea MP. Extracorporeal Shock Wave Therapy (ESWT) as a treatment for recurrent Neurogenic Heterotopic Ossification (NHO). Brain Injury 2013;27(2):242-247.

18. Haake M, Wirth T, Schmitt J. Focussing of extracorporeal shock wave therapy (ESWT) in the treatment of calcifying tendinitis. Joint, Bone, Spine: Revue du Rheumatisme 2002; 69(3):344-5.

19. Speed CA. Extracorporeal shock-wave therapy in the management of chronic soft-tissue conditions. Journal of Bone and Joint Surgery-British Volume 2004;86B(2):165-171.

20. Wang CJ. Extracorporeal shockwave therapy in musculoskeletal disorders. Journal of Orthopaedic Surgery and Research 2012;7(1).

21. Siebert W. Use of laser in orthopedics. The 3rd World Congress of the International Musculoskeletal Laser-Society (IMLAS), 7-10 November 1996 in Kassel. Orthopade 1997;26(4):394-398.

22. Siebert W. How effective is extracorporeal shock wave therapy in the treatment of tennis elbow? MMW-Fortschritte der Medizin 2003;145(16):18.

23. Norkin CC, White DJ. Measurement of Joint Motion: A Guide to Goniometry. F.A. Davis; 2009.

24. Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: A new clinical measure of balance. Journal of Gerontology 1990;45(6):M192-M197.

25. Katz-Leurer M, Fisher I, Neeb M, Schwartz I, Carmeli E. Reliability and validity of the modified functional reach test at the sub-acute stage post-stroke. Disability and Rehabilitation 2009;31(3):243-248.

26. Kjaersgaard-Anderson P, Pedersen P, Kristensen SS, Schmidt SA, Pedersen NW. Serum alkaline phosphatase as an indicator of heterotopic bone formation following total hip arthroplasty. Clinical Orthopaedics and Related Research 1988;234:102-109.

27. Burtis CA, Ashwood ER, Bruns DE. Tietz textbook of clinical chemistry and molecular diagnostics. Elsevier Health Sciences; 2012.

28. Parker RI, Vannest KJ, Davis JL, Sauber SB. Combining nonoverlap and trend for single-case research: Tau-U. Behavior Therapy 2011;42(2):284-299.

29. Smith JD. Single-case experimental designs: A systematic review of published research and current standards. Psychological Methods 2012;17(4):510-550.

30. Arciniegas DB, Held K, Wagner P. Cognitive impairment following traumatic brain injury. Current Treatment Options in Neurology 2002;4(1):43-57.

Table 1: Study design.

Baseline phase				**Intervention phase (ESWT)**				**Post-intervention phase**					
Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 26	Week 38
ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM
FR	FR	FR	FR	FR	FR	FR	FR	FR	FR	FR	FR	FR	FR
MFR	MFR	MFR	MFR	MFR	MFR	MFR	MFR	MFR	MFR	MFR	MFR	MFR	MFR
SAP	-	-	-	-	SAP	-	-	-	-	-	SAP	-	-

ESWT, Extracorporeal Shock Wave Therapy; ROM, Range of Movement; FR, Functional Reach; MFR, Modified Functional Reach; SAP, serum alkaline phosphatase

Table 2: Individual characteristics of TBI patients with chronic NHO included in this study

Case	Gender	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	FIM	SAP (U/L)			Affected joint	Walking
							B	I	PI		
1	m	53	85	171	29	79	79	96	96	left hip	yes
2	m	52	85	175	28	66	72	72	57	right knee	yes with cane
3	m	21	60	167	21	83	112	98	n/a	left knee	yes with cane
4	m	57	78	174	26	75	107	107	80	left knee	yes
5	m	26	68	168	24	56	156	167	128	left hip	no
6	m	62	95	173	32	86	95	98	117	right hip	yes
7	m	47	74	194	20	51	149	150	165	right hip	no
8	f	23	58	171	20	73	53	n/a	n/a	right hip	yes with crutches
9	m	35	75	185	22	25	108	111	n/a	right hip	no
10	f	44	63	166	23	13	n/a	n/a	n/a	left hip	no
11	m	36	85	189	29	37	115	115	n/a	left knee	no
Mean	**-**	**41±14**	**75±12**	**176±9**	**25±4**	**-**	**-**	**-**	**-**	**-**	**-**

m, male; f, female; SAP, Serum Alkaline Phosphatase baseline (B), intervention (I), and post-intervention (PI) values; U/L, units per litre; FIM, functional independence measure (FIM motor scores range from 13=total dependence) to 91=total independence); n/a, not available.

Table 3: Effect of ESWT on Knee Flexion and Extension.

Case	Knee	Baseline vs Intervention			Baseline vs Post-intervention		
		Tau	**CI 95%**	**P**	**Tau**	**CI 95%**	**P**
2	Flexion	0.625	-0.224 to 1.474	0.149	0.917	0.151 to 1.683	0.019
3	Flexion	-0.250	-1.099 to 0.599	0.564	1.000	0.234 to 1.766	0.011
4	Flexion	-0.188	-1.036 to 0.661	0.665	n/a	n/a	n/a
11	Flexion	0.250	-0.599 to 1.099	0.564	0.583	-0.183 to 1.349	0.136
Overall	**Flexion**	**0.109**	**-0.315 to 0.534**	**0.613**	**0.833**	**0.391 to 1.276**	**0.002**
2	Extension	0.313	-0.536 to 1.161	0.471	0.125	-0.641 to 0.891	0.749
3	Extension	-0.250	-1.099 to 0.599	0.564	0.167	-0.599 to 0.933	0.670
4	Extension	-0.125	-0.974 to 0.724	0.773	n/a	n/a	n/a
11	Extension	-0.563	-1.411 to 0.286	0.194	-0.292	-1.058 to 0.474	0.456
Overall	**Extension**	**-0.156**	**-0.581 to 0.268**	**0.471**	**0.000**	**-0.442 to 0.442**	**1.000**

n/a, not available; Tau, Tau scores; CI 95%, 95% confidence interval; P, P-value

Table 4: Effect of ESWT on Hip Flexion and Extension.

Case	Hip	Baseline vs Intervention			Baseline vs Post-intervention		
		Tau	CI 95%	P	Tau	CI 95%	P
1	Flexion	-0.250	-1.099 to 0.599	0.564	-0.042	-0.808 to 0.724	0.915
5	Flexion	0.250	-0.599 to 1.099	0.564	0.500	-0.266 to 1.266	0.201
6	Flexion	0.375	-0.474 to 1.224	0.387	-0.167	-0.933 to 0.599	0.670
7	Flexion	0.063	-0.786 to 0.911	0.885	0.333	-0.433 to 1.099	0.394
8	Flexion	-0.500	-1.424 to 0.424	0.289	0.200	-0.600 to 1.000	0.624
9	Flexion	1.000	0.151 to 1.849	0.021	n/a	n/a	n/a
10	Flexion	0.375	-0.474 to 1.224	0.387	0.333	-0.433 to 1.099	0.394
Overall	**Flexion**	**0.196**	**-0.129 to 0.521**	**0.238**	**0.193**	**-0.122 to 0.508**	**0.230**
1	Extension	0.125	-0.724 to 0.974	0.773	-0.042	-0.808 to 0.724	0.915
5	Extension	-0.500	-1.349 to 0.349	0.248	-0.125	-0.891 to 0.641	0.749
6	Extension	1.000	0.151 to 1.849	0.021	0.250	-0.516 to 1.016	0.522
7	Extension	0.375	-0.474 to 1.224	0.387	0.500	-0.266 to 1.266	0.201
8	Extension	-0.250	-1.174 to 0.674	0.596	0.500	-0.300 to 1.300	0.221
9	Extension	0.750	-0.099 to 1.599	0.083	n/a	n/a	n/a
10	Extension	-0.250	-1.099 to 0.599	0.564	0.167	-0.599 to 0.933	0.670
Overall	**Extension**	**0.184**	**-0.141 to 0.509**	**0.268**	**0.206**	**-0.109 to 0.521**	**0.200**

n/a, not available; Tau, Tau scores; CI 95%, 95% confidence interval; P, P-value

Table 5: Effect of ESWT on Hip Abduction and Adduction.

Case	Hip	Baseline vs Intervention			Baseline vs Post-intervention		
		Tau	CI 95%	P	Tau	CI 95%	P
1	Abduction	-0.188	-1.036 to 0.661	0.665	0.292	-0.474 to 1.058	0.456
5	Abduction	-0.250	-1.099 to 0.599	0.564	-0.583	-1.349 to 0.183	0.136
6	Abduction	0.500	-0.349 to 1.349	0.248	0.875	0.109 to 1.641	0.025
7	Abduction	0.063	-0.786 to 0.911	0.885	0.042	-0.724 to 0.808	0.915
8	Abduction	0.000	-0.924 to 0.924	1.000	0.350	-0.450 to 1.150	0.391
9	Abduction	-0.250	-1.099 to 0.599	0.564	n/a	n/a	n/a
10	Abduction	0.875	0.026 to 1.724	0.043	0.417	-0.349 to 1.183	0.286
Overall	**Abduction**	**0.108**	**-0.217 to 0.433**	**0.513**	**0.231**	**-0.084 to 0.546**	**0.151**
1	Adduction	0.313	-0.536 to 1.161	0.471	0.292	-0.474 to 1.058	0.456
5	Adduction	0.125	-0.724 to 0.974	0.773	-0.250	-1.016 to 0.516	0.522
6	Adduction	0.625	-0.224 to 1.474	0.149	0.500	-0.266 to 1.266	0.201
7	Adduction	-0.500	-1.349 to 0.349	0.248	0.083	-0.683 to 0.849	0.831
8	Adduction	-0.333	-1.257 to 0.591	0.480	0.100	-0.700 to 0.900	0.807
9	Adduction	0.625	-0.224 to 1.474	0.149	n/a	n/a	n/a
10	Adduction	-0.375	-1.224 to 0.474	0.387	0.417	-0.349 to 1.183	0.286
Overall	**Adduction**	**0.073**	**-0.252 to 0.398**	**0.659**	**0.191**	**-0.124 to 0.506**	**0.235**

n/a, not available; Tau, Tau scores; CI 95%, 95% confidence interval; P, P-value.

Table 6: Effect of ESWT on Hip Internal and External Rotation.

Case	Hip	Baseline vs Intervention			Baseline vs Post-intervention		
		Tau	CI 95%	P	Tau	CI 95%	P
1	IR	0.438	-0.411 to 1.286	0.312	-0.167	-0.933 to 0.599	0.670
5	IR	-0.688	-1.536 to 0.161	0.112	-0.917	-1.683 to -0.151	0.019
6	IR	-0.625	-1.474 to 0.224	0.149	-0.292	-1.058 to 0.474	0.456
7	IR	-0.375	-1.224 to 0.474	0.387	-0.417	-1.183 to 0.349	0.286
8	IR	0.250	-0.674 to 1.174	0.596	-0.100	-0.900 to 0.700	0.807
9	IR	0.500	-0.349 to 1.349	0.248	n/a	n/a	n/a
10	IR	-0.063	-0.911 to 0.786	0.885	-0.083	-0.849 to 0.683	0.831
Overall	**IR**	**-0.084**	**-0.409 to 0.241**	**0.611**	**-0.331**	**-0.646 to -0.016**	**0.040**
1	ER	-0.500	-1.349 to 0.349	0.248	-0.583	-1.349 to 0.183	0.136
5	ER	-0.625	-1.474 to 0.224	0.149	-0.750	-1.516 to 0.016	0.055
6	ER	-0.250	-1.099 to 0.599	0.564	-1.000	-1.766 to -0.234	0.011
7	ER	0.750	-0.099 to 1.599	0.083	-0.125	-0.891 to 0.641	0.749
8	ER	-1.000	-1.924 to -0.076	0.034	-0.450	-1.25 to 0.35	0.270
9	ER	-0.813	-1.661 to 0.036	0.061	n/a	n/a	n/a
10	ER	0.125	-0.724 to 0.974	0.773	0.583	-0.183 to 1.349	0.136
Overall	**ER**	**-0.323**	**-0.648 to 0.003**	**0.052**	**-0.387**	**-0.702 to -0.072**	**0.016**

IR, Internal Rotation; ER, External Rotation; n/a, not available; Tau, Tau scores; CI 95%, 95% confidence interval; P, P-value

Table 7: Effect of ESWT on Functional Reach and Modified Functional Reach.

Case	Test	Baseline vs Intervention			Baseline vs Post-intervention		
		Tau	CI 95%	P	Tau	CI 95%	P
1	FR	-0.375	-1.224 to 0.474	0.387	0.125	-0.641 to 0.891	0.749
2	FR	1.375	0.526 to 2.224	0.002	1.250	0.484 to 2.016	0.001
3	FR	1.000	0.151 to 1.849	0.021	1.000	0.234 to 1.766	0.011
4	FR	0.125	-0.724 to 0.974	0.773	n/a	n/a	n/a
6	FR	0.063	-0.786 to 0.911	0.885	0.083	-0.683 to 0.849	0.831
8	FR	0.333	-0.591 to 1.257	0.480	-0.050	-0.850 to 0.750	0.903
Overall	**FR**	**0.227**	**-0.159 to 0.614**	**0.249**	**0.486**	**0.141 to 0.832**	**0.006**
5	MFR	0.375	-0.474 to 1.224	0.387	0.417	-0.349 to 1.183	0.286
7	MFR	0.188	-0.661 to 1.036	0.665	0.292	-0.474 to 1.058	0.456
9	MFR	-0.500	-1.349 to 0.349	0.248	n/a	n/a	n/a
10	MFR	n/a	n/a	n/a	n/a	n/a	n/a
11	MFR	0.500	-0.349 to 1.349	0.248	0.250	-0.516 to 1.016	0.522
Overall	**MFR**	**0.141**	**-0.2837 to 0.565**	**0.516**	**0.319**	**-0.123 to 0.762**	**0.157**

FR, Functional reach; MFR, Modified Functional Reach; n/a, not available;
Tau, Tau scores; CI 95%, 95% confidence interval; P, P-value

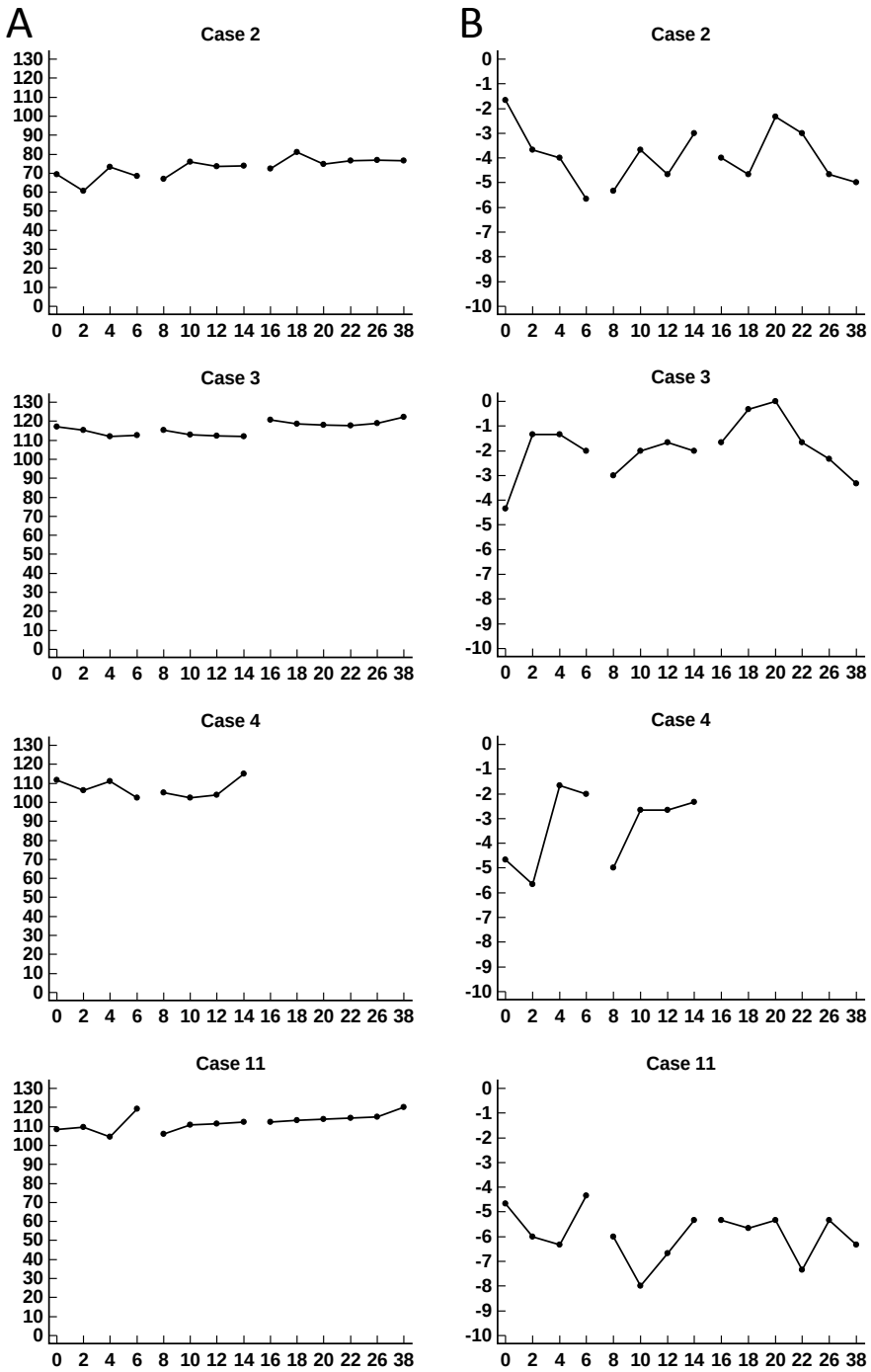

Figure 1: Effect of ESWT on Knee Flexion (A) and Extension (B).

Horizontal axes, time in weeks (weeks 0 to 6, baseline phase; weeks 8 to 14, intervention phase; weeks 16 to 38, post-intervention phase; (time-points are not proportional); Vertical axes, angle in degrees measured by a universal goniometer.

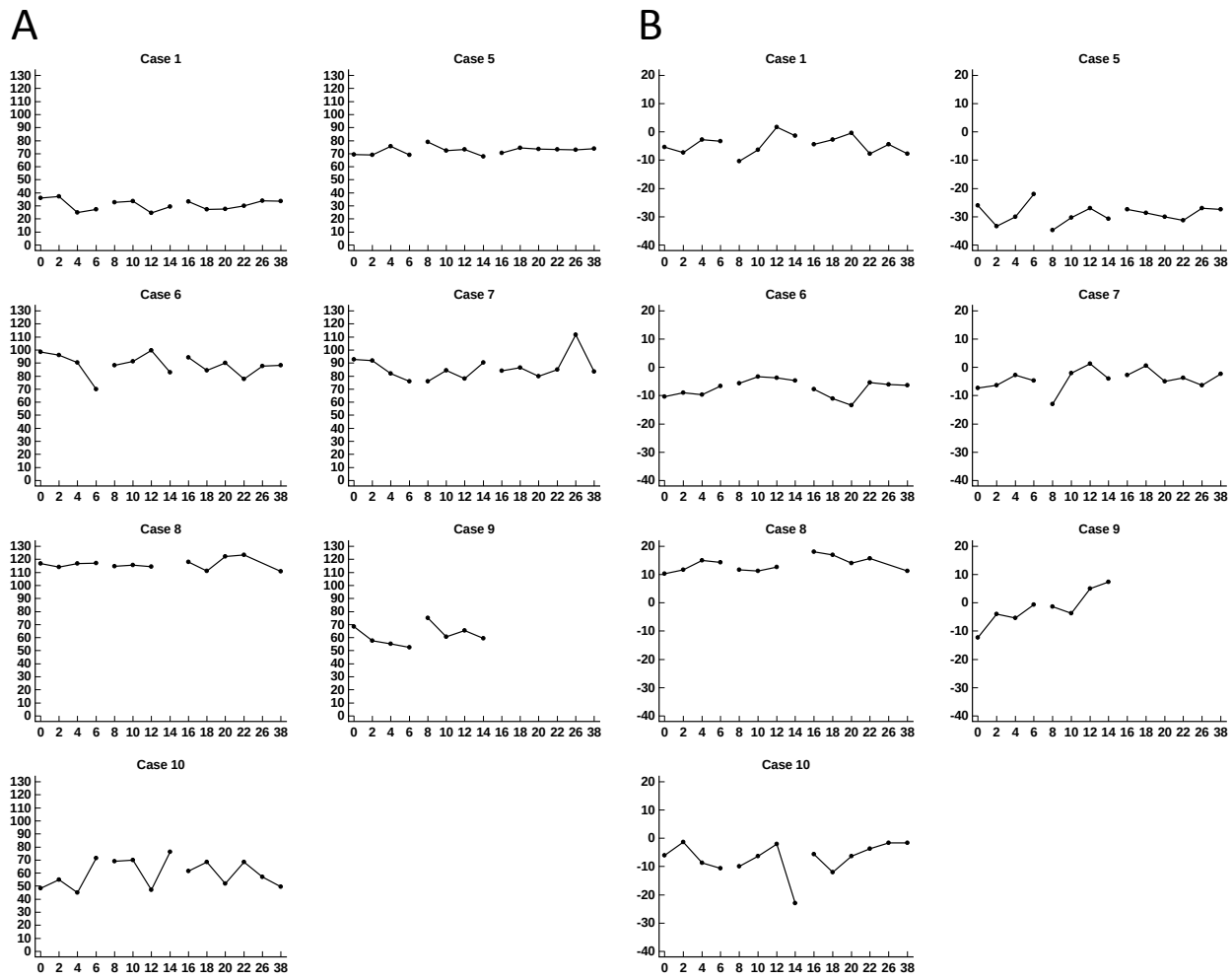

Figure 2: Effect of ESWT on Hip Flexion (A) and Extension (B).

Horizontal axes, time in weeks (weeks 0 to 6, baseline phase; weeks 8 to 14, intervention phase; weeks 16 to 38, post-intervention phase;(time-points are not proportional); Vertical axes, angle in degrees as measured by a universal goniometer.

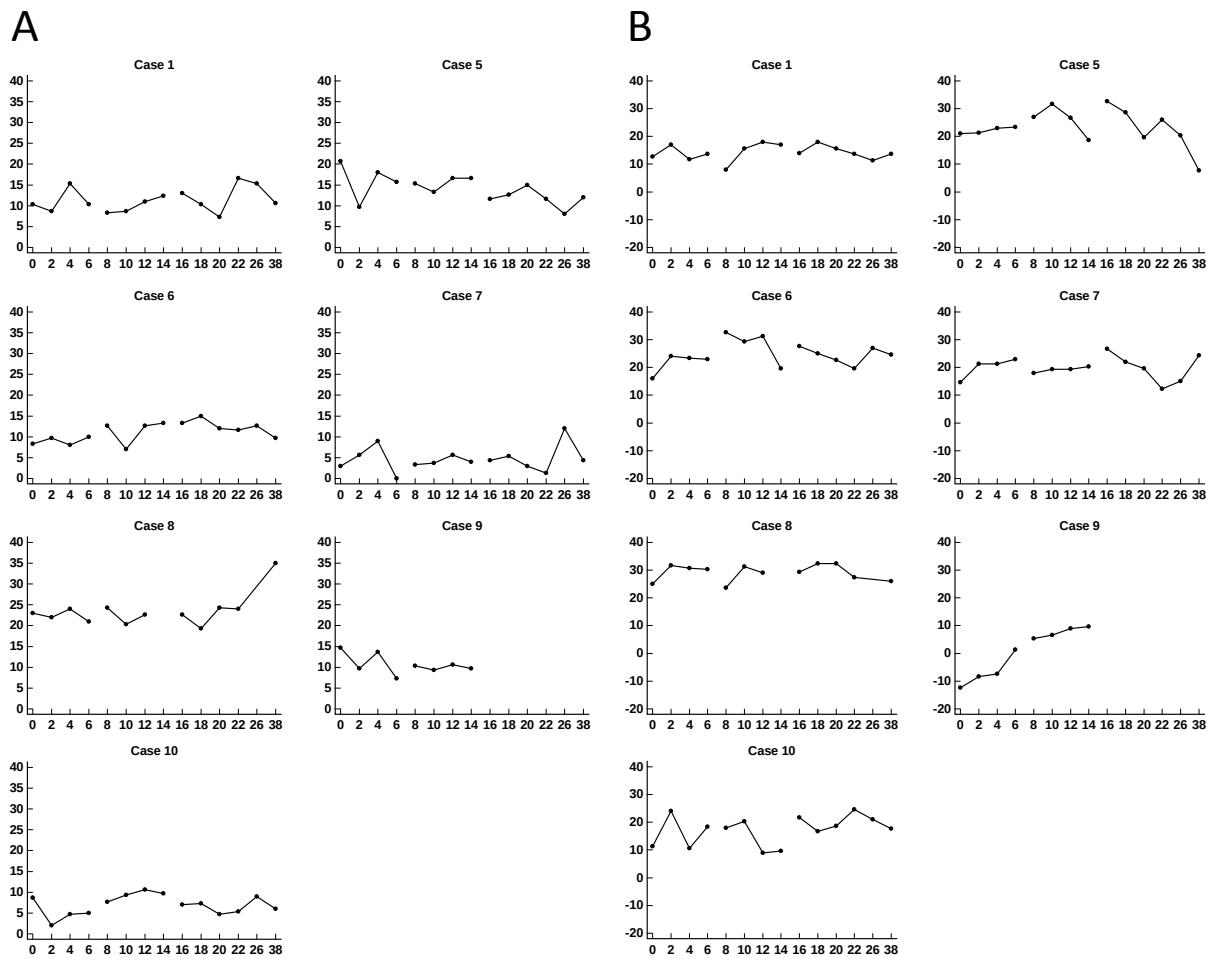

Figure 3: Effect of ESWT on Hip Abduction (A) and Adduction (B).

Horizontal axes, time in weeks (weeks 0 to 6, baseline phase; weeks 8 to 14, intervention phase; weeks 16 to 38, post-intervention phase; (time-points not proportional); Vertical axes, angle in degrees as measured by a universal goniometer.

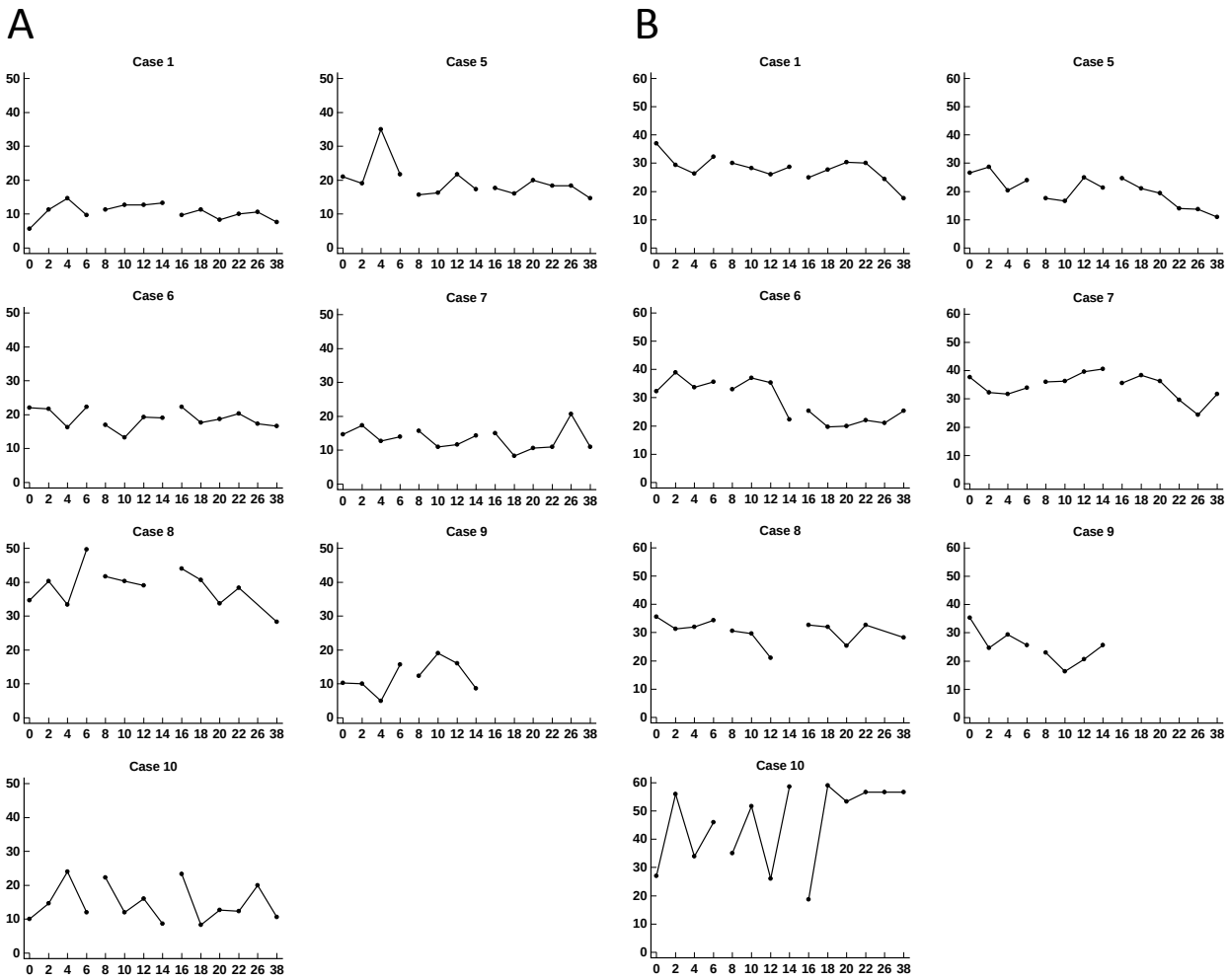

Figure 4: Effect of ESWT on Hip Internal (A) and External (B) Rotation.

Horizontal axes, time in weeks (weeks 0 to 6, baseline phase; weeks 8 to 14, intervention phase; weeks 16 to 38, post-intervention phase; time-points are not proportional); Vertical axes, angle in degrees measured by a universal goniometer.

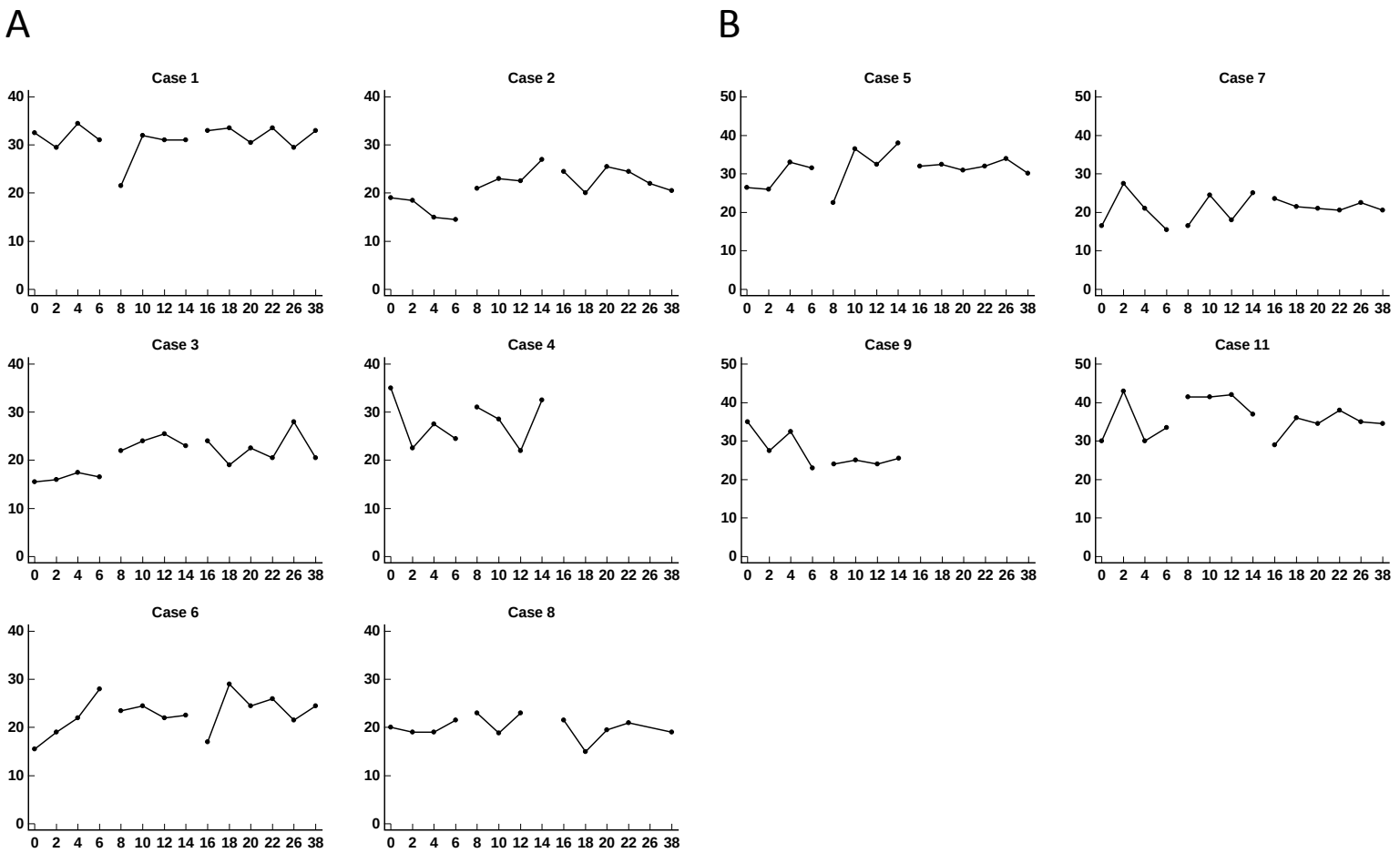

Figure 5: Effect of ESWT on Functional Reach (A) and Modified Functional Reach (B).*Horizontal axes, time in weeks (weeks 0 to 6, baseline phase; weeks 8 to 14, intervention phase; weeks 16 to 38, post-intervention phase; time-points are not proportional); Vertical axes, distance in cm as measured by FRT in standing.*