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

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Abstract

Introduction: Neurogenic heterotopic ossification (NHO) is a complication of a neurological injury following traumatic brain injury (TBI) and may be present around major synovial joints. It is often accompanied by severe pain which may lead to limitation in activities of daily living. Currently the only effective treatment for NHO is surgery which carries with it many additional risks. This study was designed to assess the effect of extracorporeal shock wave therapy (ESWT) on pain in patients with TBI with chronic NHO.

Methods: A series of single case studies was undertaken on 11 patients with TBI with chronic NHO at the hip or knee. Each patient received four applications of high-energy EWST delivered to the affected joint over eight weeks. Two-weekly follow-up assessments were carried out and final assessments were made three months and six months post-intervention. Pain was measured using the Faces Rating Scale (FRS) and X-rays were taken at baseline and six-months post-intervention to physiologically measure the size of the NHO.

***Results*:** The application of high-energy ESWT was associated with overall reduction in pain in patients with TBI with NHO (TAU-0.412, 95% CI-0.672 to -0.159, P=0.002).

Conclusions: ESWT is a novel non-invasive intervention for reducing pain resulting from NHO in patients with TBI

Introduction and Background

Heterotopic ossification (HO) is defined as the formation of mature, lamellar bone inside soft-tissue structures outside normal skeletal locations [1-3]. Neurogenic heterotopic ossification (NHO) is a complication of a neurological injury, with ossification often affecting major synovial joints such as the hip or knee [2, 3]. NHO is particularly found in patients following traumatic brain injury (TBI), with an estimated prevalence of between 3% and 23% [4-6]. NHO typically develops within two to four months of the initial trauma and manifests itself clinically as swelling, erythema, warmth, and severe pain [7]. The size of the NHO tends to increase over the next few months, and is usually fully developed by one year post-injury when it is reliably seen on radiographs [1,8]. The mature NHO may greatly limit activities of daily living thereby adversely affecting quality of life of patients with TBI [7, 9-12].

To date, treatments for NHO have been pharmacological, surgical or a combination of both [13]. The pharmacological treatments, however, are not successful once NHO has formed [14]. Surgical removal is virtually the only effective treatment for the mature NHO, although it is extremely invasive and not possible for all patients following TBI [15].

Despite the extensive use of extracorporeal shock wave therapy (ESWT) in the treatment of a range of musculoskeletal conditions [16], NHO following TBI has received only limited attention [17-20]. The aim of this study was to investigate the effect of ESWT on pain in patients following TBI. In addition, the morphology of NHO was also assessed using radiographs.

Methods

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

Study design

The study design was an interventional, experimental study. A series of single case research studies was undertaken, where participants were assessed on multiple occasions, i.e. pre-, during, and post-intervention (Table 1). Four baseline assessments were conducted at two-weekly intervals prior to intervention. During the four interventions of ESWT, also conducted at two weekly intervals, assessments were again performed. Subsequent to the intervention period four further two-weekly follow-up assessments were carried out (Table 1). Final assessments were made three months and six months post-intervention (Week 26 and Week 38; Table 1). This study took place at Beit Lowenstein Hospital, Ra'anana, Israel between October 13th 2014 and February 23rd 2016.

Insert Table 1

Participants

Patients with TBI who met the selection criteria were identified from the database of the Beit Loewenstein Rehabilitation Centre, Israel. Eligible participants were aged over 18, with a history of TBI and a diagnosis of NHO around the hip or knee for a period of more than one year, and a stable serum alkaline phosphatase (SAP) level at the time of recruitment. Participants who were pregnant, suffering from rheumatoid arthritis, ankylosing spondylitis or femoral/pelvic fractures at the time of recruitment were excluded from the study. Participants were contacted by telephone and /or letter and invited to take part in the trial. All participants were asked to attend the Beit Loewenstein Rehabilitation Centre and assessed for their eligibility by the attending Medical Officer and co-investigator (YS). 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

The Minispec Extracorporeal Shock Wave instrument (Medispec Int. USA) was used to deliver four applications of EWST 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, with an energy flux density (EFD) per shock of 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].

Pain was measured using the Faces Rating Scale (FRS) as described elsewhere [23,24]. In addition, X-rays and routinely available laboratory data for serum alkaline phosphatase (SAP), which is reported to parallel the activity of ossification, were also collected to monitor the progression of NHO [25]. Normative values for SAP are 53 - 128 units per litre (U/L) in a 20 to 50 year-old man and 42 -98 U/L in a 20 to 50 year-old woman. Adults over 61 years have normative values of SAP of 51-153 U/L [26].

X-ray analysis

The NHO size was measured from plain X-rays taken at baseline and at approximately six months post-intervention. An X-ray view was set up for each patient and recorded so that it could be repeated. The view was not necessarily a standard view; each individual patient had their own particular view which was reproducible, dependent on available range of motion and pain. Prominent landmarks that were clearly visible on images from both baseline and six month post-intervention were selected. The diameter of the ossified lesion was measured at one landmark (M1) and, where possible, a second measurement at right angles was also taken (M2). Since post-intervention X-ray techniques differed slightly from baseline measure, the measurements were standardised using a correction factor calculated from measurements taken from a region of normal bone measured at the same place on the pre and post intervention X-rays.

Qualitative assessments of baseline and six month post-intervention NHO X-rays were performed using the Clearcanvas PACS system (*Clearcanvas Inc. Toronto ON*). The margins of the lesions were examined for clarity or fragmentation. Any trabeculation within the ossified areas was assessed for increase or decrease in number of the trabeculae; any new bone formation or any loss of bone was noted.

Reporting Adverse Events

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

Statistical analysis

Pain data were assessed from the FRS and were plotted individually and graphically for each participant allowing visual inspection of trends within baseline, intervention and post-intervention phases. The effect size estimates associated with the application of ESWT were calculated using the non-parametric non-overlap Tau-U method [27]. The resulting effect size estimates were interpreted as the magnitude of intervention effect in percentages. In particular, the Tau-U score represents the percentage of non-overlap between phases or the percentage of data showing improvement between phases [27]. Higher Tau-U scores signify greater effectiveness while lower Tau-U scores denote 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 [27]. All Tau-U score computations were performed using the Tau-U Calculator (Single Case Research™, USA).

X-Ray measurements were compared between post-intervention phase and baseline phase using the Wilcoxon signed-rank test. All computations were performed using the Stata MP/13 statistical package (StataCorp LP, USA).

Statistical significance was defined at the conventional 5% level.

Results

Patient Characteristics

Eleven patients with TBI were recruited; 4 patients presented with NHO in the affected knee and 7 in the affected hip (Table 2). Six of the 11 patients were ambulant (with or without an aid) (Table 2). TBI patients were less likely to be females (2/11; 18%), were of relatively young age (mean age 41±14 years), and had BMI scores of 25±4 kg/m^2 (Table 2). NHO tended to occur equally on both sides; 5 patients had their right affected side treated and 6 were treated on their left side (Table 2). Ten out of the 11 patients recruited were noted to have constant pain intensity on the FRS varying between 5 and 10. All participants presented with varying degrees of functional and mobility dysfunction (FIM motor score between 13 and 86; Table 2). Two participants (Cases #4 and #9) completed the four baseline measures and the four interventions and immediate post-intervention measures but were then lost to follow-up. Circulating SAP levels remained stable within normal limits in all patients with TBI who completed the full trial (Table 2). None of the participants were considered suitable at this time for surgical intervention; two of the patients recruited had had surgery several years earlier (one at the knee and one at the hip) but the NHO had regrown.

Insert Table 2

Effect of ESWT on Pain (FRS)

Nine patients completed the baseline, intervention phase, the post-intervention phase and the three and six month follow-up. Visual inspection of individual FRS pain results during the post-intervention phase, showed a reduction in FRS scores relative to the baseline phase in four patients with TBI (cases 1, 2, 3, and 6; Figure 1). Visual inspection of cases 5, 7, 8, and 10 individual results was not informative (Figure 1). There was no pain reported in case 11 during

the trial, and cases 4 and 9 did not complete the post-intervention phase (Figure 1). Overall Tau score shows that ESWT was associated with significant reduction of FRS Pain score in TBI patients post-intervention compared to the baseline (Tau-0.415, 95% CI -0.672 to -0.159, P=0.002; Table 3).

Insert Figure 1

Insert Table 3

Effect of ESWT on NHO as seen on Plain X-ray film

Nine of the 11 participants completed the full study, including repeat X-rays, taken at least 6 months post intervention. Three of the nine patients who completed had only one NHO diameter measurement (M1) taken due to the fact that the areas of NHO were too large and ill-defined to allow an accurate second measure to be taken. Overall, the smallest and the largest NHO diameters at baseline and at 6 month post-intervention were similar and showed no significant difference in all patients with TBI ($P>0.05$; Table 4).

Insert Table 4

Qualitative description of X-rays

Post-intervention X-rays showed erosion in the margin of the ossified areas and slight fragmentation of the lesion compared to the baseline radiographs (Figure 2). In addition, the clarity of the borders and loss of the "cortex" of the lesion could be seen (Figure 2).

Insert Figure 2

Pre- and post-radiographs of all nine participants who completed the trial are provided in the Supplementary Data.

Adverse effects

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

Discussion

This study reports a reduction of pain associated with the use of ESWT in patients following TBI with NHO. The results substantiate those of our previously published case report [19]. Our earlier and current results collectively demonstrate the importance of the single case research design in populations with disabling conditions such as NHO. Although we found an overall reduction in pain using ESWT, by focusing on individual patients with TBI and undertaking multiple measurements during the study, we were able to track their responses over time. This is an advantage over a randomised controlled trial design where group results only tend to be reported, and it is difficult to determine those individuals for whom a treatment may be effective or even be shown to worsen the condition. In this context, two individuals did not report pain associated with their NHO; in these participants reduced range of movement was the main effect of NHO (see companion paper). The application of ESWT was associated with a transient increase of pain post-intervention in two participants; no other participants reported an increase of pain post-intervention.

The pain presentation within the patients with TBI was variable. Some participants complained of pain only when performing a functional activity, others complained of pain only on passive movement of the affected joint and some complained of intractable pain throughout the day, suggesting the involvement of nociceptive and neuropathic mechanisms, respectively [28-30]. In this study we focussed on the pain intensity rather than the pain quality. It is doubtful that this particular patient group with TBI would have been able to provide valid descriptors of their pain since this patient group often presents with various non-compliance concerns such as cognitive problems, aggressive tendencies or impulsivity, forgetfulness, and apathy [31].

We also demonstrated erosion and marginal absorption around the NHO deposits at six month post-intervention; however, this was not associated with detectable overall changes in the size of NHO using radiographs. Thus it is reasonable to suggest that reduction of pain was

associated with mechanisms other than a simple reduction in NHO size, triggered by ESWT. It has been suggested that the application of ESWT may have an effect on gene expression, including upregulation of anti-inflammatory cytokines [32]. There is growing evidence that cytokines play an important role in mediating pain in neuropathic conditions, including suppression of pain associated with the systemic administration of the anti-inflammatory interleukin (IL)-10 cytokine in animal models [33-35]. It is possible that ESWT may have impacted on the production of anti-inflammatory cytokines which led to the observed reduction in pain. However further investigation is needed regarding the role of ESWT and cytokine production in patients with TBI.

Limitations of this study include a relatively small number of participants and of females in particular. Although the male: 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, it is important to note that only nine of the 11 patients completed the full trial.

Further limitations include the relatively low clarity of the radiographic evidence, making it difficult to reliably assess quantitative changes associated with the application of ESWT in the mature NHO. Other imaging techniques may be necessary to assess the NHO quantitatively.

This study was conducted as a series of single case research studies that allows us to draw conclusions about the effects of a specific treatment based upon the responses of single patients [36]. No “sham” trial was considered feasible with this patient group that commonly presents with a profound cognitive impairment [31] but the study design was such that each patient became their own control for the purpose of comparison [37].

Conclusions

The results of this study highlight a role for ESWT in reducing pain in patients with TBI with NHO and warrant its further investigation as a therapeutic approach that could be of potential clinical benefit.

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Conflict of Interest Statement:

The authors report no conflict of interest.

References

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

2. McCarthy EF, Sundaram M. Heterotopic ossification: A review. Skeletal Radiology 2005;34(10):609-619.

3. Simonsen LL, Sonne-Holm S, Krasheninnikoff M, Engberg AW. Symptomatic heterotopic ossification after very severe traumatic brain injury in 114 patients: Incidence and risk factors. Injury 2007;38(10):1146-1150.

4. Goldman J. Heterotopic ossification in spinal cord injuries. Physiotherapy 1980;66(7):219-220.

5. 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.

6. 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.

7. 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.

8. Garland DE. A clinical perspective on common forms of acquired heterotopic ossification. Clinical Orthopaedics and Related Research 1991(263):13-29.

9. 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.

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

11. 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.

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

13. 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.

14. Haran MJ, Bhuta T, Lee BSB. Pharmacological interventions for treating acute heterotopic ossification. Cochrane Database of Systematic Reviews 2010(5).

15. 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.

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

17. 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.

18. 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.

19. 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.

20. 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.

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. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care and Research 2011;63(SUPPL. 11):S240-S252.

24. Topolovec-Vranic J, Canzian S, Innis J, Pollmann-Mudryj MA, McFarlan AW, Baker AJ. Patient satisfaction and documentation of pain assessments and management after implementing the adult nonverbal pain scale. American Journal of Critical Care 2010;19(4):345-354.

25. 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.

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

27. 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.

28. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. The Journal of Pain 2009;10(9):895-926.

29. Merskey H, Bogduk N. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press; 1994.

30. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. Neurology 2008;70(18):1630-1635.

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

32. Chao YH, Tsuang YH, Sun JS, Chen LT, Chiang YF, Wang CC, Chen MH. Effects of Shock Waves on Tenocyte Proliferation and Extracellular Matrix Metabolism. Ultrasound in Medicine and Biology 2008;34(5):841-852.

33. Wieseler-Frank J, Maier SF, Watkins LR. Glial activation and pathological pain. Neurochemistry International 2004;45(2-3):389-395.

34. Zhang JM, An J. Cytokines, inflammation, and pain. International Anesthesiology Clinics 2007;45(2):27-37.

35. Clark AK, Old EA, Malcangio M. Neuropathic pain and cytokines: current perspectives. Journal of Pain Research 2013;6:803.

36. Portney LG, Watkins MP. Foundations of Clinical Research: Applications to Practice. Prentice Hall; 2008.

37. Kratochwill, T.R. and J.R. Levin, *Enhancing the Scientific Credibility of Single-Case Intervention Research: Randomization to the Rescue.* Psychological Methods, 2010. **15**(2): p. 124-144.

Table 1:

Timeline of outcome measures collected during this study.

Baseline				**Intervention phase (ESWT)**				**Follow-up**					
Weeks				**Weeks**				**Weeks**					
0	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**26**	**38**
FRS	FRS	FRS	FRS	FRS	FRS	FRS	FRS	FRS	FRS	FRS	FRS	FRS	FRS
SAP level					SAP level						SAP level		
X-ray													X-ray

ESWT, extracorporeal shockwave treatment; FRS, Faces Rating Scale; SAP, serum alkaline phosphatase

Table 2: Characteristics of patients included in this study.

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

U/L, units per litre; m, male; f, female; FIM, functional independence measure; FIM motor scores range from 13 (total dependence) to 91 (total independence).

**Pain medication ceased post-intervention* ☨ *Cases #4 and #9 did not complete post intervention assessments*

Table 3: Effect of ESWT on Pain (FRS).

Patient	Baseline vs *Intervention			Baseline vs Post-intervention		
	Tau	**CI 95%**	**P**	**Tau**	**CI 95%**	**P**
1	-0.250	-1.099 to 0.599	0.564	-0.375	-1.141 to 0.391	0.337
2	0.000	-0.849 to 0.849	1.000	-0.333	-1.099 to 0.433	0.394
3	0.500	-0.349 to 1.349	0.248	-0.667	-1.433 to 0.099	0.088
4	-0.250	-1.099 to 0.599	0.564	Lost to follow-up		
5	-0.500	-1.349 to 0.349	0.248	-0.500	-1.266 to 0.266	0.201
6	-1.000	-1.849 to -0.151	**0.021**	-0.917	-1.683 to -0.151	**0.019**
7	0.750	-0.099 to 1.599	0.083	-0.125	-0.891 to 0.641	0.749
8	0.583	-0.341 to 1.507	0.216	-0.100	-0.900 to 0.700	0.807
9	-1.000	-1.849 to -0.151	**0.021**	Lost to follow-up		
10	-0.500	-1.349 to 0.349	0.248	-0.708	-1.474 to 0.058	0.070
11	0.000	-0.849 to 0.849	1.000	0.000	-0.766 to 0.766	1.000
Overall	**-0.157**	**-0.415 to 0.101**	**0.233**	**-0.415**	**-0.672 to -0.159**	**0.002**

*During the intervention phase pain intensity was recorded after the application of ESWT

Tau, Tau scores; CI 95%, 95% confidence interval; P, P-value

Table 4: Quantitative assessment of NHO using X-ray-based measurements.

Case	Largest NHO diameter measures (mm)						Smallest NHO diameter measures (mm)					
	Baseline		Post-intervention		D%		Baseline		Post-intervention		D%	
	M1	M2	M1	M2	M1	M2	M1	M2	M1	M2	M1	M2
1	168.0	40.7	134.4	30.3	-20.0	-25.7	49.0	17.0	43.7	17.3	-9.9	1.0
2	83.0	22.8	83.0	24.9	0.0	9.2	11.0	10.0	12.8	10.6	12.3	3.9
3	174.0	20.2	149.5	20.1	-14.3	-0.5	55.0	34.0	53.8	31.4	-2.7	-8.5
5	102.0	53.5	94.3	62.4	-7.8	16.6	102.0	67.0	94.3	65.9	-7.5	-1.2
6	114.0	69.3	113.8	71.9	0.1	3.8	29.0	10.0	28.6	10.6	-2.1	1.9
7	102.0	16.1	104.6	16.7	2.6	3.7	54.0	18.0	52.4	21.3	-3.7	19.0
8	31.1	5.9	33.7	6.5	8.2	10.7	No second measure possible					
10	83.6	138.0	87.5	79.0	4.7	-42.9	No second measure possible					
11	40.9	4.3	37.2	4.85	-9.0	12.8	No second measure possible					
P	-	-	0.86	0.93	-	-	-	-	0.71	0.75	-	-

M1, measurement 1 (largest or smallest NHO diameter); M2, measurement 2 (taken at right angles to M1); P, P-value paired Wilcoxon signed-rank test; D%, percent difference between respective post-intervention and baseline M 1 and M2

§ *M1 and M2 values post intervention are the corrected values (refer to Methods).*

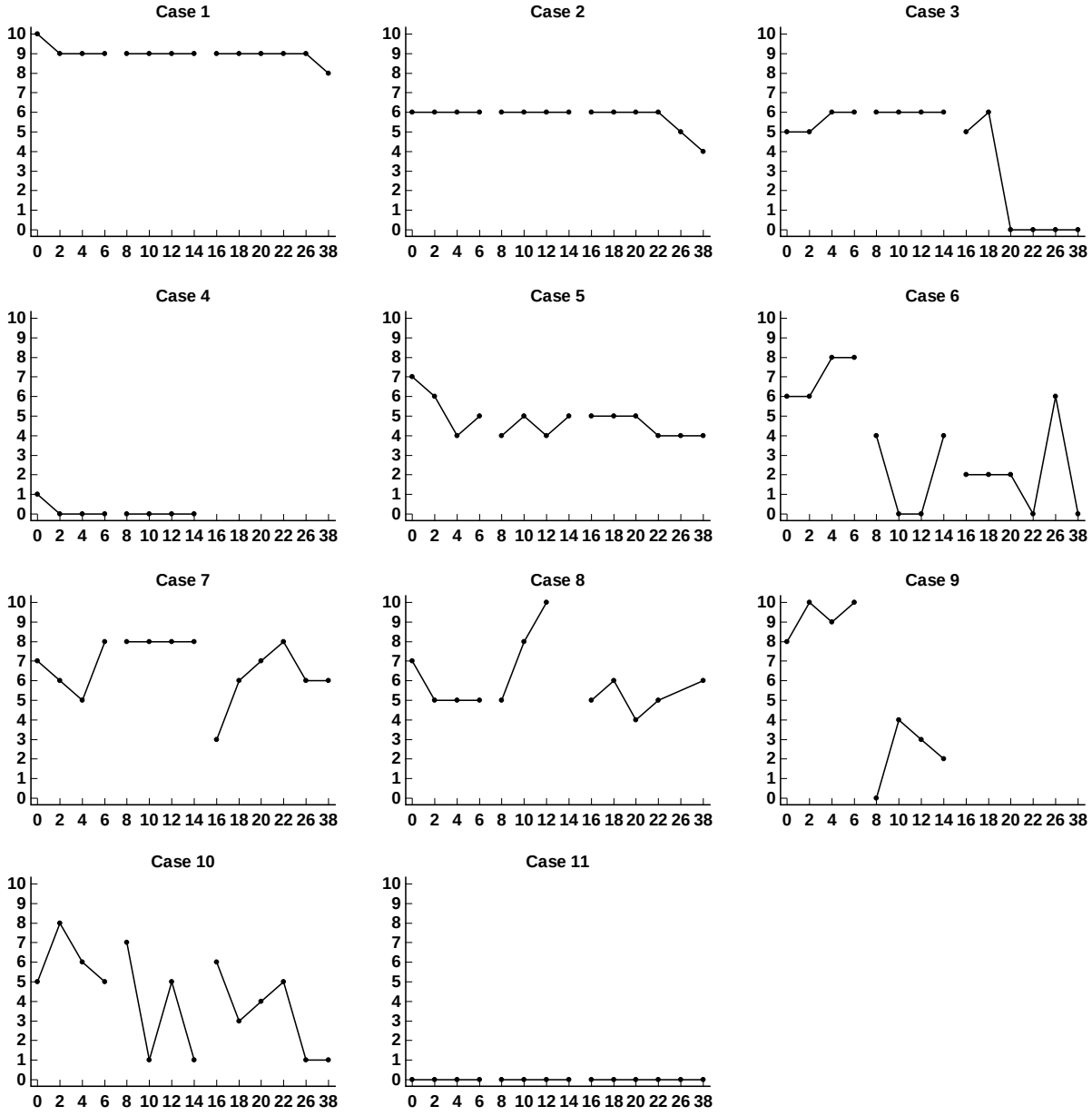

Figure 1: Effect of ESWT on Pain (FRS).

Pain intensity was recorded after the application of ESWT during the intervention phase. Horizontal axes, time in weeks (time points are not proportional); Weeks 0 to 6, baseline phase; Weeks 8 to 14, intervention phase; Weeks 16 to 38, post-intervention phase; Vertical axes, FRS Pain scores. (Patient#11 FRS score 0 throughout)

Reznik et al. Supplementary data

Individual Commentaries (provided by an independent radiologist):

Case #1: No qualitative changes detected; no erosions or loss of bone (Plate 1).

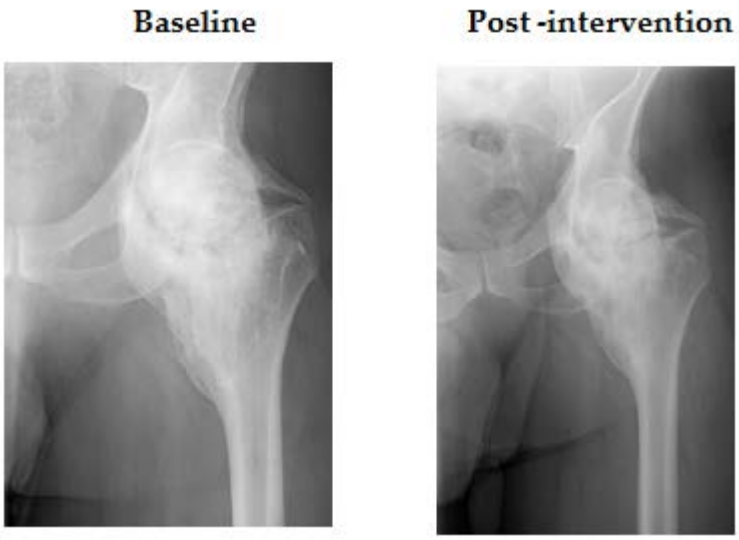

Plate 1: Baseline and post-intervention X-rays.

Case #2: Post- intervention X-rays showed erosion in the margin of the ossified areas and slight fragmentation of the lesion. In addition of clarity of the borders and loss of the cortex of the lesion could be seen (Plate 2).

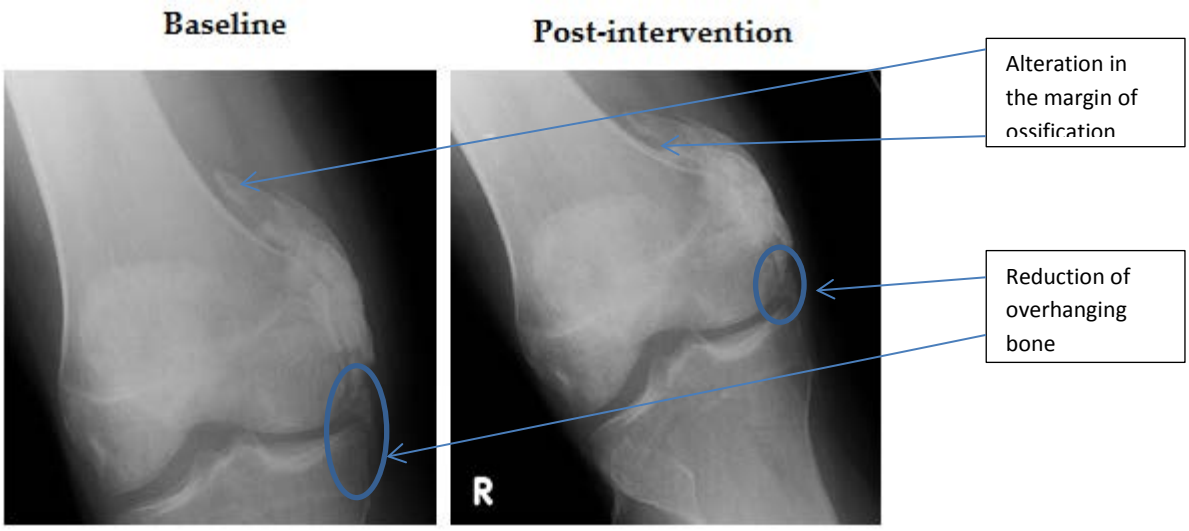

Plate 2: Baseline and post-intervention X-rays.

Case #3: The visual impression was that the lesion had increased in size between the two studies (Plate 3).

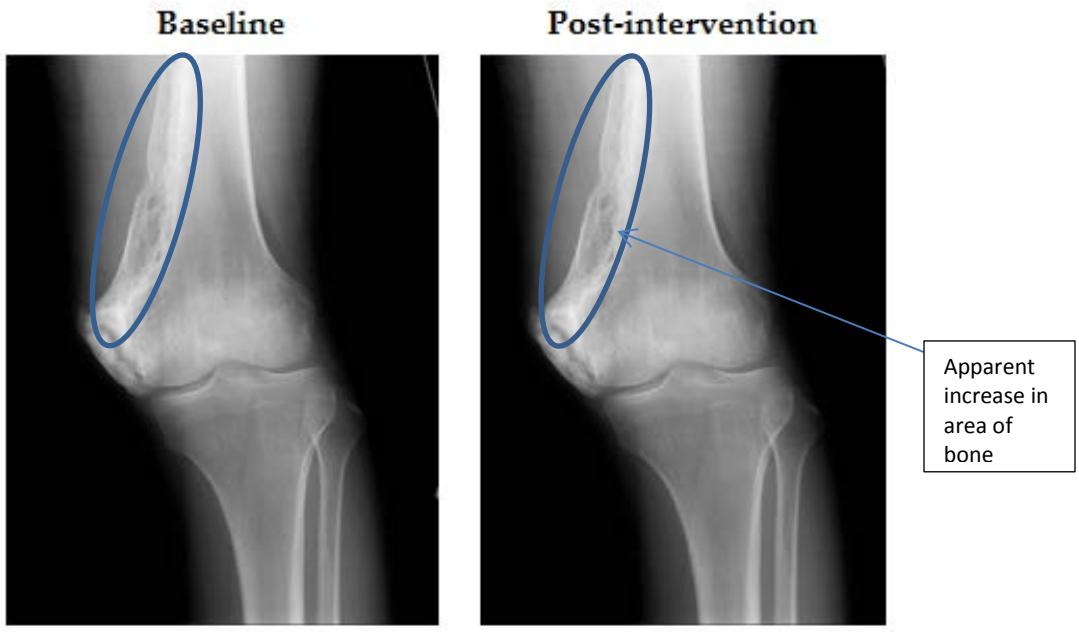

Plate 3: Baseline and post-intervention X-rays.

Case #5: Very similar techniques for both baseline and post-intervention X-rays. A definite irregularity of the upper border of the lesion under the femoral neck on the post intervention X-ray was noted. Lower border of the lesion was fragmented suggesting possible erosion of the lesion (Plate 5).

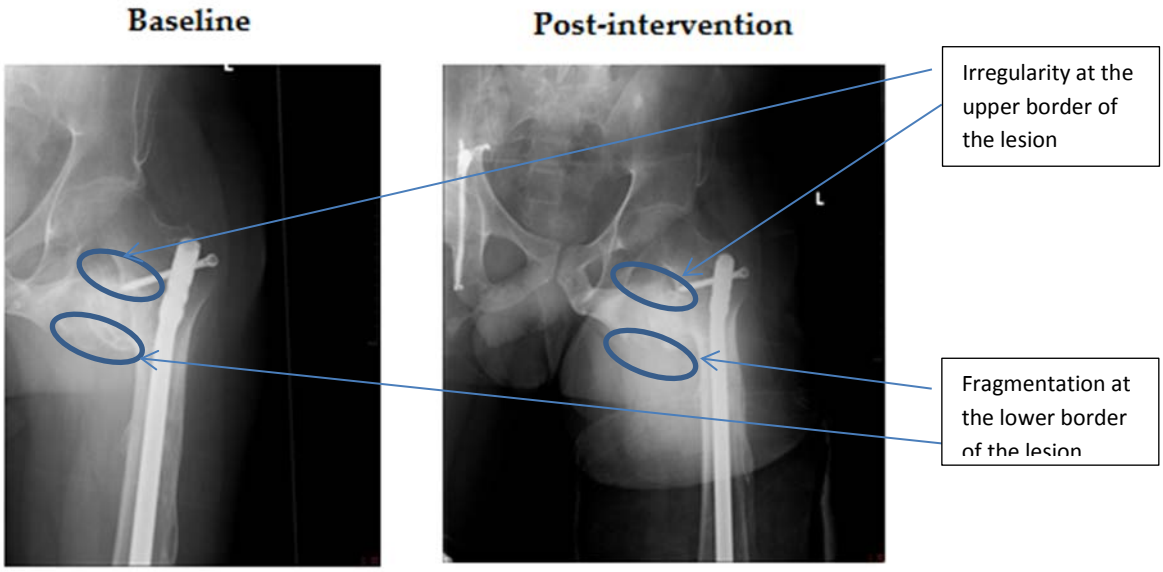

Plate 5: Baseline and post-intervention X-rays.

Case #6: On subjective assessment there appeared to be some erosion of the lesion on the post intervention study. (Plate 6)

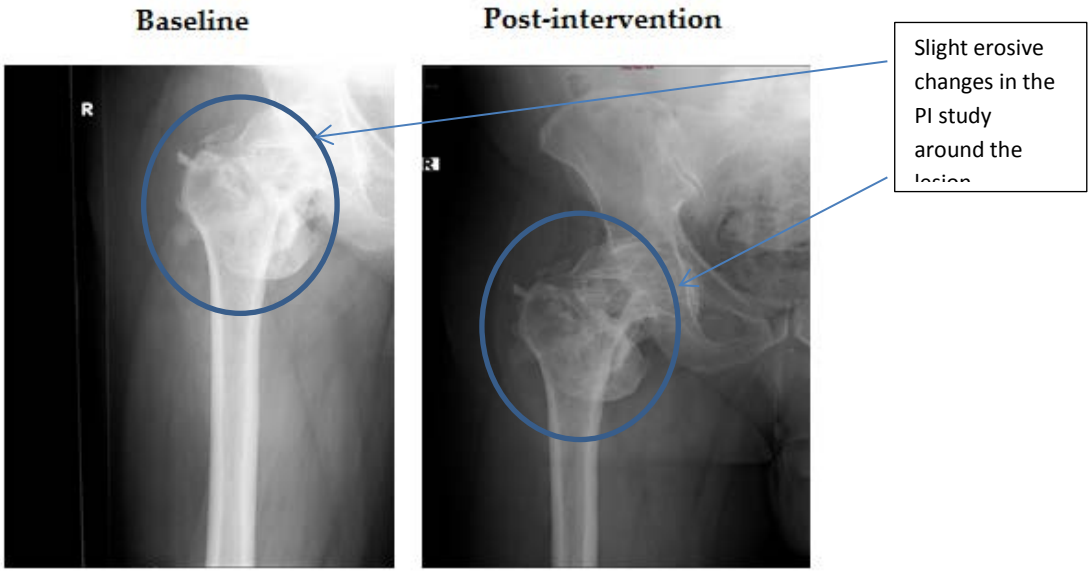

Plate 6: Base-line and post-intervention X-rays.

Case # 7: On the post-intervention (PI) study of the right hip the margins of the lesions were definitely less well defined inferiorly and around the femoral neck. This was also the case around the inferior margin of the gluteal ossification. This is of interest because the technical differences of the PI study give the image more contrast and a higher definition of the areas mentioned than would have been expected. (Plate 7).

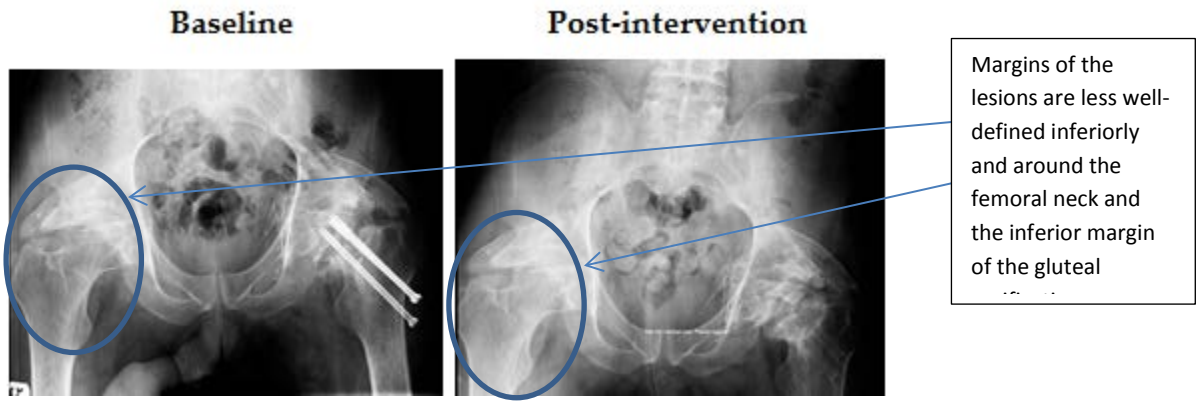

Plate 7: Baseline and post-intervention X-rays.

Case # 8: No qualitative changes between the two images were noted (Plate 8).

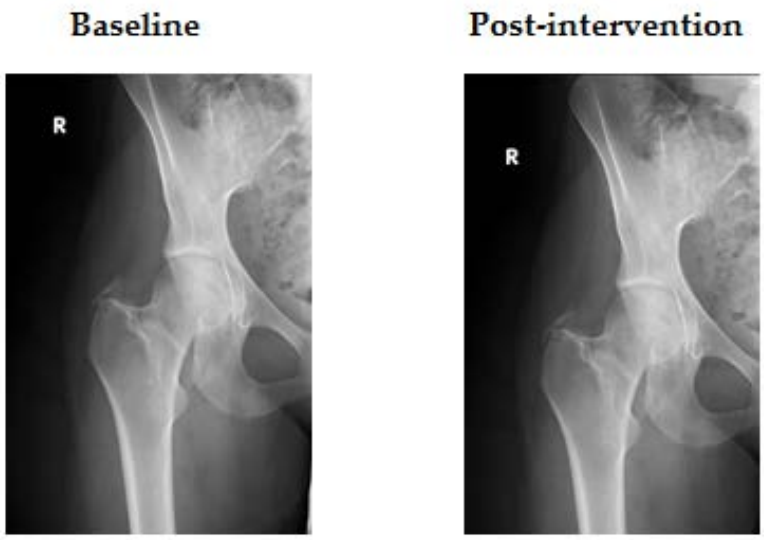

Plate 8: Baseline and post-intervention X-rays.

Case#10: A big difference in apparent ossification between the two studies. This apparent ossification was most probably due to technical factors, most likely of which was different exposures (Plate 10).

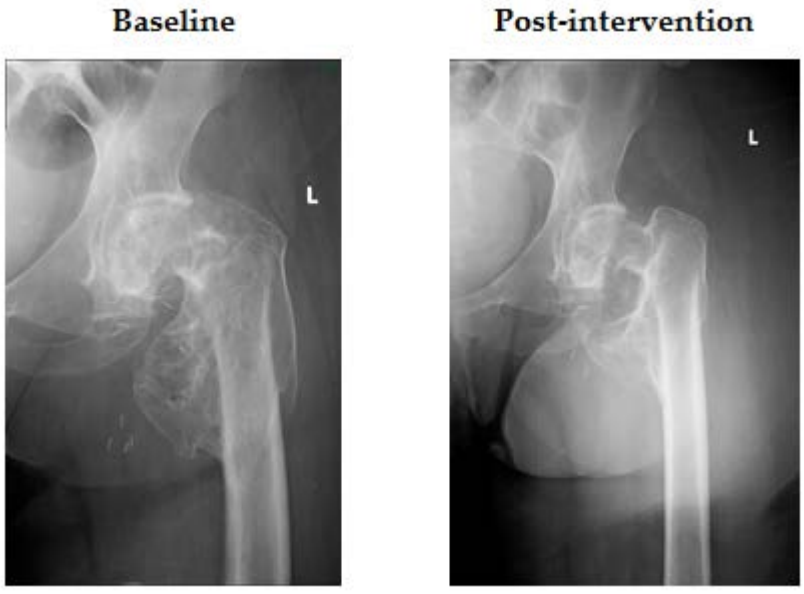

Plate 10: Baseline and post-intervention X-rays.

Case #11: The spike of bone appeared significantly less dense than previously, although this could be a technical radiographic factor (Plate 11).

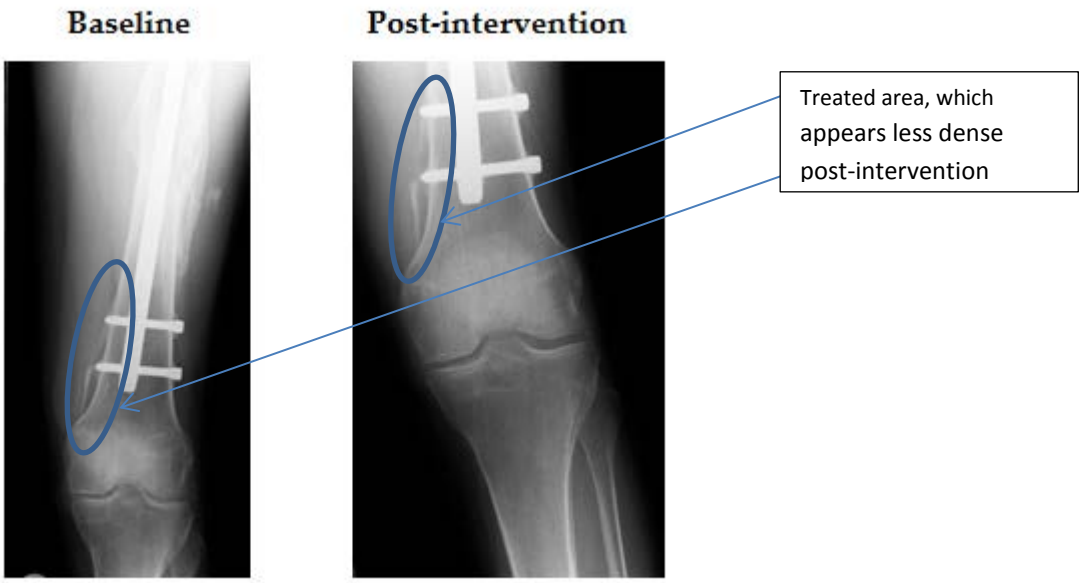

Plate 11: Baseline and post-intervention X-rays.