CASE REPORT

Low-intensity pulsed ultrasound treatment as an alternative to vascular bone graft surgery for a 5-year-long ulnar non-union in a patient with haemochromatosis

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Accepted 15 October 2015

SUMMARY

We present the case of a 75-year-old woman with haemochromatosis who developed a 5-year-long right ulnar non-union after a shortening osteotomy to correct a malunited Colles' fracture. Standard surgical treatment for ulnar non-unions was attempted on 19 March 2008 and again on 20 April 2009, but the non-union persisted on 8 May 2012, as confirmed by CT scan. Vascular bone grafting and refixation was then considered, but the patient declined this extensive operation, instead choosing to try non-invasive low-intensity pulsed ultrasound treatment with an Exogen device. Just 4 months later, complete union as confirmed by CT scan was achieved. This is the first case demonstrating the efficacy of ultrasound treatment for long-standing non-unions resistant to surgery in patients with haemochromatosis, a disorder where iron deposition can provide suboptimal circumstances for bone healing. Our finding suggests that low-intensity pulsed ultrasound devices could be used as a first-line treatment for stable non-unions instead of revision surgery.

BACKGROUND

Haemochromatosis is a hereditary disease characterised by a state of inappropriately increased intestinal absorption of iron that can result in tissue iron overload. This can have notable consequences on patients, such as the classical development of liver cirrhosis, heart failure and diabetes mellitus; however, it can also manifest as joint pain and problems of the bones.¹ There is evidence of an association between osteoporosis and haemochromatosis, with bone loss that may be explained by iron deposition in the bone.^{2–4} In vitro and genetic mouse model studies suggest that iron overloading may upregulate osteoclast populations, while inhibiting osteoblast metabolism and function, thereby impairing bone remodelling, as seen in animal models of iron overload.^{5–7} Although there are no studies directly assessing bone healing in patients with haemochromatosis, the evidence of impaired bone remodelling and architecture in animal models and patients, with an osteoporotic-like picture associated with the degree of iron deposition, coupled with evidence of altered osteoclast and osteoblast function in models of haemochromatosis and iron overload, may suggest that haemochromatosis and its associated iron deposition in the bone may provide suboptimal

circumstances for bone healing, and thus may complicate the healing of fractures and osteotomies, potentially contributing to the risk of developing non-unions.

A non-union can be defined as a break in the bone that has not healed in the time expected given its location, comminution, displacement and other patient factors such as age, and, furthermore, a non-union is expected not to heal at all without further intervention—the latter point differentiating it from delayed unions.⁸ For these reasons, a specific time-frame definition of non-unions cannot be given, but they are often diagnosed after 9 months without union.

Non-unions of long bones such as the ulna are typically managed with internal fixation with compression plates, with or without the use of cancellous bone grafting (typically iliac crest) in situations of severe comminution or bone loss.⁹ In situations where this has failed, the additional use of vascular bone grafts is considered following the premise that inadequate blood supply to the site of the break may contribute to the development of non-union.¹⁰ Low-intensity pulsed ultrasound treatment has been considered as a method that could non-invasively stimulate bone healing in non-unions. Studies on rat femoral fractures have shown that the treatment advances the bone healing process with increased endochondral ossification, bone bridging and bone remodelling with corresponding increased torsional torque and stiffness, compared to controls.¹¹ While the precise mechanism on a subcellular level remains uncertain, in vitro studies suggest that the treatment stimulates osteogenic transcription factor expression, including Runx2¹² and osteonectin and osteopontin.¹³ Furthermore, treatment increased osteogenic differentiation of mesenchymal stem cells¹² and activated osteogenic activity in periosteal cells.¹⁴ While clinical studies have demonstrated that low-intensity pulsed ultrasound treatment can be effective in treating some patients with established non-unions,¹⁵ no studies have currently demonstrated whether or not it can be effective in treating long-standing and previously revised non-unions in patients with haemochromatosis. This case report demonstrates, for the first time in the literature, that low-intensity pulsed ultrasound treatment can successfully treat a long-standing previously unsuccessfully revised non-union in a patient with haemochromatosis.

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To cite: Povlsen SD, Povlsen B. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211950

CASE PRESENTATION

A 75-year-old woman presented, in November 2011, with long-standing pain in her right forearm, which began after an ulnar osteotomy, approximately 5 years prior. The patient was diagnosed, over 30 years ago, as suffering from haemochromatosis with raised serum ferritin and had since been treated with regular venesection.

The patient initially sustained a Colles' fracture after a fall in 1995, which was initially managed conservatively with manipulation and placing in a cast, but subsequent X-rays, taken in 1996, showed the fracture to have slipped, requiring a radial osteotomy with bone grafting and external fixation to correct.

However, the patient later developed ulna impaction syndrome as a consequence of malunion and was treated with a radial closing wedge and ulnar shortening osteotomy with internal fixation in July 2007, and the arm was placed in a splint.

By January 2008, X-rays showed no evidence of union at the ulnar osteotomy site, and so, in March 2008, the patient underwent reoperation with plate removal, resection at the non-union site, grafting iliac crest bone around the non-union site and internal fixation with a five-hole locking compression plate. The patient remained in a cast for the next 3 months. Unfortunately, X-rays taken in January 2009 showed that the ulnar osteotomy had again failed to unite, requiring further reoperation with plate removal, non-union excision, iliac crest bone grafting in between the ends of the ulnar non-union with additional BMP (bone morphogenetic protein) application to the site, with internal fixation using a six-hole locking compression plate, and the patient placed in a below-elbow cast.

CT scans in May 2010 again demonstrated that the ulnar non-union had resisted this surgical management, prompting discussion of alternative surgical options, namely vascularised bone grafting and refixation. However, the patient declined to go through with yet another surgery, and opted to go without treatment for the next 2 years despite ongoing severe ulnar-sided right forearm pain.

INVESTIGATIONS

When the patient presented again in November 2011, reporting the same ongoing pain in her right forearm, an X-ray was initially taken, noting incomplete bridging ossification with some mature callus formation over the osteotomy site (figure 1). In order to quantify the extent of bridging of the osteotomy site, a CT scan was performed (figure 2). Mature trabecular callus formation was noted centrally, with additional hypertrophic marginal calluses in the dorsal and volar regions of the osteotomy site. However, a bridging trabecular callus was only seen in the dorsal 20% of the fracture, leaving 80% of the osteotomy in a state of non-union.

DIFFERENTIAL DIAGNOSIS

Given the patient's forearm pain coinciding with her persistent ulnar non-union, of which the radiological evidence was very clear, it was determined that the non-union was the cause of the pain. Soft tissue irritation caused by her plate in situ could have additionally contributed to her forearm pain.

TREATMENT

Since her initial fall in 1995, which resulted in a right-sided Colles' fracture, all four operations she underwent resulted in either soft tissue or bony damage over any symptomatic improvement. With these surgical failures in mind, the patient

chose not to undergo a further invasive procedure—a vascularised bone graft with refixation. Instead, she chose the wholly non-invasive option of low-intensity pulsed ultrasound treatment, with the use of an Exogen device, worn as a wristwatch and placed over the osteotomy site for 20 min a day over the next 4 months. The device uses a 1.5 MHz frequency ultrasound wave at a power of 117 mW to radiate an area of 3.88 cm². Indeed, by November 2012, after this period of use, X-rays (figure 3) confirmed complete bony union of this osteotomy that had been present for the previous 5 years, and resistant to two conventional surgeries for the treatment of non-unions.

OUTCOME AND FOLLOW-UP

The achievement of complete union was accompanied by a significant decrease in patient-reported forearm pain to a level where the patient desired no further medical treatment. The patient had previously described tenderness over areas of her plate in situ. However, given the symptomatic improvement brought about after ulnar union was achieved, she requested that the plate not be removed, as she did not want to undergo any further surgeries.

DISCUSSION

This case report provides the first radiological support that low-intensity pulsed ultrasound devices can be used to stimulate bone growth in non-unions of patients with haemochromatosis, despite the non-union having persisted for 5 years and having resisted two attempts at standard surgical treatment of ulnar non-unions—refixation with iliac crest bone grafting. Given the failures of these two procedures in the patient, the next standard surgical treatment option—refixation with vascularised bone grafting—was considered, but the patient declined to undergo yet another invasive procedure given her history of

Figure 1 X-ray of the right forearm showing non-union—9 November 2011—before low-intensity pulsed ultrasound treatment.

Figure 2 CT of the right forearm showing non-union—10 November 2011—before low-intensity pulsed ultrasound treatment.

complications since her initial fall in 1995, where she sustained a Colles' fracture after which she underwent five surgical procedures (2 radial osteotomies, 1 ulnar osteotomy and 2 failed revisions of non-union of ulnar osteotomies).

Given the eventual success of low-intensity pulsed ultrasound treatment in providing a wholly non-invasive cure for the long-standing multioperated ulnar non-union in a patient with haemochromatosis, this case calls into question the logic of revision surgery as a first-line option for the treatment of stable

non-unions. This may be of added importance in patients with haemochromatosis, where iron deposition may provide suboptimal circumstances for bone growth and healing.^{2–7} However, more research is needed to confirm the extent to which haemochromatosis might complicate fracture and osteotomy healing. Nevertheless, given that National Institute for Health and Care Excellence guidelines support the use of the Exogen ultrasound bone healing system for long-bone fractures with non-union or delayed healing,¹⁶ we recommend that it should be offered as first-line treatment as an alternative to surgical intervention in all patients with stable non-unions.

Figure 3 X-ray of the right forearm showing union—31 October 2012—after low-intensity pulsed ultrasound treatment.

Learning points

- ▶ Low-intensity pulsed ultrasound can be a successful, non-invasive method for treating non-unions in patients with haemochromatosis.
- ▶ Revision surgery may not be the best first-line treatment for non-unions in patients with haemochromatosis.
- ▶ Offering first-line treatment with low-intensity pulsed ultrasound treatment to all patients with non-unions as an alternative to surgical intervention should be considered.

Contributors BP found the patient and obtained patient consent. SDP wrote the first draft and worked together with BP to reach the submitted version.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Guggenbuhl P, Brissot P, Loréal O. Haemochromatosis: the bone and the joint. *Best Pract Res Clin Rheumatol* 2011;25:649–64.

- 2 Valenti L, Varenna M, Fracanzani AL, *et al.* Association between iron overload and osteoporosis in patients with hereditary hemochromatosis. *Osteoporos Int* 2009;20:549–55.
- 3 Guggenbuhl P, Deugnier Y, Boisdet JF, *et al.* Bone mineral density in men with genetic hemochromatosis and HFE gene mutation. *Osteoporos Int* 2005;16:1809–14.
- 4 Weinberg ED. Iron loading: a risk factor for osteoporosis. *Biometals* 2006;19:633–5.
- 5 Yamasaki K, Hagiwara H. Excess iron inhibits osteoblast metabolism. *Toxicology Letters* 2009;191:211–15.
- 6 Guggenbuhl P, Fergelot P, Doyard M, *et al.* Bone status in a mouse model of genetic hemochromatosis. *Osteoporos Int* 2011;22:2313–19.
- 7 de Vernejoul MC, Pointillart A, Golenzer CC, *et al.* Effects of iron overload on bone remodelling in pigs. *Am J Pathol* 1984;116:377–84.
- 8 de Buren N. Causes and treatment of non-union in fractures of the radius and ulna. *JBS* 1962;44B:614–25.
- 9 Cleveland KB. Chapter 56—Delayed union and nonunion of fractures. *Canale & Beaty: Campbell's Operative Orthopaedics*. 11th edn e-book. Mosby, An Imprint of Elsevier, 2007.
- 10 Soucacos PN, Dailiana Z, Beris AE, *et al.* Vascularised bone grafts for the management of non-union. *Injury* 2006;37(Suppl 1):S41–50.
- 11 Azuma Y, Ito M, Harada Y, *et al.* Low-intensity pulsed ultrasound accelerates rat femoral fracture healing by acting on the various cellular reactions in the fracture callus. *J Bone Miner Res* 2001;16:671–80.
- 12 Lai CH, Chen SC, Chiu LH, *et al.* Effects of low-intensity pulsed ultrasound, dexamethasone/TGF- β 1 and/or BMP-2 on the transcriptional expression of genes in human mesenchymal stem cells: chondrogenic vs. osteogenic differentiation. *Ultrasound Med Biol* 2010;36:1022–33.
- 13 Sena K, Leven RM, Mazhar K, *et al.* Early gene response to low-intensity pulsed ultrasound in rat osteoblastic cells. *Ultrasound Med Biol* 2005;31:703–8.
- 14 Leung KS, Cheung WH, Zhang C, *et al.* Low intensity pulsed ultrasound stimulates osteogenic activity of human periosteal cells. *Clin Orthop Relat Res* 2004;418:253–9.
- 15 Nolte PA, van der Krans A, Patka P, *et al.* Low-intensity pulsed ultrasound in the treatment of nonunions. *J Trauma* 2001;51:693–703.
- 16 EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing. *NICE medical technology guidance [MTG12]*. 2013. <https://www.nice.org.uk/guidance/mtg12> (accessed 28 Jun 2015).

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