Ultrasound Accelerated Fracture Healing Device

Policy Number: 1.01.05  Last Review: 8/2014

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for ultrasound accelerated fracture healing devices when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Low-intensity ultrasound treatment may be considered medically necessary when used as an adjunct to conventional management (i.e., closed reduction and cast immobilization) for the treatment of fresh, closed fractures in skeletally mature individuals. Candidates for ultrasound treatment are those at high risk for delayed fracture healing or nonunion. These risk factors may include either locations of fractures or patient comorbidities and include the following:

Patient comorbidities:
- Diabetes
- Steroid therapy
- Osteoporosis
- History of alcoholism
- History of smoking

Fracture locations:
- Jones fracture
- Fracture of navicular bone in the wrist (also called the scaphoid)
- Fracture of metatarsal
- Fractures associated with extensive soft tissue or vascular damage

Low-intensity ultrasound treatment may be considered medically necessary as a treatment of delayed union of bones, including delayed union of previously surgically-treated fractures, and excluding the skull and vertebra. (See Considerations for definition of delayed union.)

Low-intensity ultrasound treatment may be considered medically necessary as a treatment of fracture nonunions of bones, including nonunion of previously surgically-treated fractures, and excluding the skull and vertebra. (See Considerations for definition of nonunion.)

When Policy Topic is not covered
Other applications of low-intensity ultrasound treatment are investigational, including, but not limited to, treatment of congenital pseudarthroses, open fractures, fresh surgically-treated closed fractures, stress fractures, arthrodesis or failed arthrodesis.

Considerations
Fresh (Acute) Fractures
A fracture is most commonly defined as “fresh” for 7 days after the fracture occurs. Most fresh closed fractures heal without complications with the use of standard fracture care, i.e., closed reduction and cast immobilization.

Delayed Union
Delayed union is defined as a decelerating healing process as determined by serial x-rays, together with a lack of clinical and radiologic evidence of union, bony continuity, or bone reaction at the fracture site for no less than 3 months from the index injury or the most recent intervention.

Nonunions
There is not a consensus for the definition of nonunions. One proposed definition is failure of progression of fracture-healing for at least 3 consecutive months (and at least 6 months following the fracture) accompanied by clinical symptoms of delayed/nonunion (pain, difficulty weight bearing). (1)

The definition of non-union in the FDA labeling suggests that nonunion is considered established when the fracture site shows no visibly progressive signs of healing, without giving any guidance regarding the timeframe of observation. However, it is suggested that a reasonable time period for lack of visible signs of healing is 3 months. The following patient selection criteria are consistent with those proposed for electrical stimulation as a treatment of nonunions (see separate policy):

- At least 3 months have passed since the date of the fracture, AND
- serial radiographs have confirmed that no progressive signs of healing have occurred, AND
- the fracture gap is 1 cm or less, AND
- the patient can be adequately immobilized and is of an age when he/she is likely to comply with non-weight bearing.

**Description of Procedure or Service**
Low-intensity pulsed ultrasound has been investigated as a technique to accelerate healing of fresh fractures, delayed unions, and nonunions. Ultrasound is delivered with the use of a transducer applied to the skin surface overlying the fracture site.

**Background**
Ultrasound treatment can be self-administered with one daily 20-minute treatment, continuing until the fracture has healed. The mechanism of action at the cellular level is not precisely known but is thought to be related to a mechanical effect on cell micromotion/deformation causing an increase in stimulation of transmembrane cell adhesion molecules and upregulation of cyclooxygenase-2.

**Regulatory Status**
The Sonic Accelerated Fracture Healing System, SAFHS® (also referred to as Exogen 2000®) was initially cleared for marketing by the U.S. Food and Drug Administration (FDA) in October 1994 as a treatment of fresh, closed, posteriorly displaced distal radius (Colles’) fractures and fresh, closed, or grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization. In February 2000, the labeled indication was expanded to include the treatment of established nonunions, excluding skull and vertebra. According to the FDA labeling, a nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

**Rationale**
This policy was initially developed in December 1995. Since that time, the policy has been updated on a regular basis using MEDLINE literature searches. The most recent literature update was conducted through November 18, 2013.

**Literature Review**

**Fresh Fractures**
The policy regarding fresh fractures is based in part on a 1995 TEC Assessment that concluded that ultrasound fracture healing met the TEC criteria for the indications labeled by the U.S. Food and Drug Administration (FDA) as a treatment of closed, fresh fractures of the tibial or distal radius (ie, Colles’) fractures.(2) Since the TEC Assessment, there have been numerous randomized controlled trials (RCTs) and systematic reviews of clinical trials on the use of ultrasound to improve healing in fresh fractures.

Systematic Reviews. A 2002 meta-analysis conducted by Busse et al(3) supported the use of low-intensity ultrasound as a technique for fractures treated nonoperatively. This systematic review was updated in 2009 and included RCTs of low-intensity pulsed ultrasonography for any type of fracture.(4) Thirteen trials were included; in 5 of them, patients were managed conservatively, and in 8 studies, patients had ultrasound therapy after operative management (distraction osteogenesis in 3 studies, bone graft for nonunion in one, and operative treatment of fresh fractures in 4). Ultrasound therapy significantly accelerated radiographic healing of fractures in all 3 RCTs of conservatively managed fresh fractures that assessed this outcome. (These trials are described in more detail next.)

The trials of operatively managed (open) fresh fractures outcomes were inconsistent; 4 trials provided low-quality evidence for acceleration of healing by ultrasound therapy. Pooled results of 2 trials showed a nonsignificant mean reduction in radiographic healing time of 16.6%.

A 2012 Cochrane review on ultrasound and shockwave therapy included 11 studies on ultrasound; 8 of the studies were RCTs.(5) The included studies were limited in methodologic quality, with all having some evidence of bias. There was very limited evidence on functional outcomes, and the available data showed no significant difference between ultrasound and placebo control on functional outcomes. There was a significant effect of ultrasound on time to healing when all types of fractures were pooled (standardized mean difference -0.69; 95% confidence interval [CI], -1.31 to -0.07). This effect on time to healing was not present when upper or lower limb fractures were examined separately and was not robust in sensitivity analyses performed as a “worst case analysis”. There was also no significant treatment effect found in pooled analyses for treatment of nonunion or delayed union. This review did not distinguish between closed and open fractures.

RCTs of Closed Fractures. In a 1997 multicenter RCT by Kristiansen et al, 60 patients with dorsally angulated fractures of the distal radius treated with manipulation and cast were randomly assigned to 10 weeks of daily treatment with a pulsed ultrasound device or an inactive device.(6) All patients started ultrasound within 7 days after having sustained the fracture. Blinded radiographic and clinical examinations showed faster healing in the ultrasound group (61 days) than in the control group (98 days) (p<0.001). Each radiographic stage of healing also was significantly accelerated in the treatment group.

Heckman et al performed a double-blind RCT comparing ultrasound treatment (n=33) with a placebo-control device (n=34) in closed or grade-I open fractures of the tibial shaft.(7) Treatment was started within 7 days after the fracture and consisted of one 20-minute period each day. Time-to-healing was 86 days in the treatment group versus 114 days in the control group (p=0.01), and time to overall (clinical and radiographic) healing was 96 days in the active-treatment group compared to 154 days in the control group (p<0.001). Scaphoid fractures were treated with ultrasound in a study done in Germany.(8) Fifteen patients were randomly assigned to treatment and 15 to placebo device groups. Healing was assessed by computed tomography (CT) scans every 2 weeks. Fractures treated with ultrasound healed in 43.2 days versus 62 days in the control group (p<0.01). Pooled data from these studies demonstrated a mean reduction in radiographic healing time of 36.9% (95% CI, 25.6% to 46.0%).

Authors of another study included in the 2009 systematic review observed that the clinical relevance of accelerated radiologic healing has not been described and examined the effect of low-intensity pulsed ultrasound on fracture healing issues such as pain, function, and resumption of professional and personal activities.(9) They performed a multicenter double-blind RCT of ultrasound treatment of fresh
clavicle fractures. Patients were taught to use the ultrasound devices for 20 minutes each day for 28 days and to record daily their subjective feeling as to whether the fracture healed or not (the primary outcome measure), pain on visual analog scale (VAS), level of daily activities once a day expressed as hours of activity (work, household work, sport), and analgesic use. A total of 120 patients (61 active and 59 placebo) started study treatment. Nine patients in the active group and 10 in the placebo group were excluded from analysis because of incomplete follow-up or early withdrawal from the study. The day that the fracture clinically healed according to patient perception was determined in 92 patients (47 active and 45 placebo), and mean duration of time to clinical healing was 26.77 days in the active group versus 27.09 days in the placebo group. Between-group differences in analgesic use and mean VAS were not significant.

RCTs of Open Fractures and Surgically Treated Closed Fractures. For the treatment of open fractures, the data are conflicting regarding the efficacy of ultrasonic accelerated fracture healing system, specifically those treated surgically with placement of an intramedullary nail. For example, Emami et al conducted a study that randomly assigned 32 patients with a fresh tibial fracture that was fixed with an intramedullary rod to undergo additional treatment with an active or inactive ultrasound device.(10) The time-to-healing was not significantly different in the 2 groups, and the authors concluded that there was no benefit in operatively treated fractures. In contrast, Leung et al reported on the results of a study that randomly assigned 30 fractures in 28 patients with complex tibial fractures treated with internal or external fixation to receive or not receive additional treatment with low-intensity ultrasound.(11) Based on radiologic assessment, the time to callus formation was significantly less in those in the ultrasound group. Due to the inconsistent results in the 2 small randomized studies, and the negative results of the meta-analysis, low-intensity ultrasound is considered investigational for open fractures.

In 2011 Dijkman et al reported data from a substudy of 51 patients of a larger RCTs that enrolled patients with open or closed tibial shaft fractures that were treated surgically with an intramedullary nail. (12) According to the posting on online site www.ClinicalTrials.gov (NCT00667849), “the study was terminated due to futility”, suggesting lack of benefit for this indication.

Section Summary

There is some RCT evidence that ultrasound treatment improves radiographic healing for closed fresh fractures, but this finding is not consistent for studies of open fresh fractures. A 2009 systematic review and meta-analysis of RCTs found moderate- to very low-quality evidence for low-intensity pulsed ultrasonography in accelerating functional recovery among patients with fracture. The systematic review concluded that large trials of high methodologic quality focusing on patient important outcomes such as quality of life and return to function are needed to determine whether ultrasound fracture healing devices provide important benefits to patients. A 2012 Cochrane review that did not distinguish between closed and open fractures reported that there was an improvement in time to healing when all studies were pooled but that this finding was not robust on further analyses. The Cochrane review did not find any evidence that ultrasound improves functional outcomes.

Nonunions

The policy regarding nonunion of fractures is based on data presented to FDA as part of the approval process for Sonic Accelerated Fracture Healing System (SAFHS®) as a treatment of fracture nonunions. The following data were reported and are included in the package insert for the device(13):

- Data were collected on 74 cases of established nonunion with a mean fracture age of nearly 3 years. The principal outcome measure was the percentage of patients with healed nonunions, as determined clinically and by radiographic analysis. Each case served as its own control, based on the definition of nonunion that suggests that nonunions have a 0% probability of achieving a healed state without an intervention.
- A total of 64 of 74 cases (86%) were healed with use of low-intensity ultrasound. The time-to-healing was 173 days. The healed rate of scaphoid bones was lower, at 33% (2 of 6 cases), which
was partially responsible for a significant difference between the healing rates of long bones (92%) versus other bones (67%).

- Fracture age also affected healing rates, with fractures over 5 years old having a healing rate of 50% compared to a healing rate of 95% in those present for no more than 1 year.

A study used prospectively defined criteria for analysis of all Dutch patients (96 participating clinics) who had been treated with ultrasound for established nonunion of the tibia (characterized by a total stop of all fracture repair processes).(14) Included in the analysis were 71 patients who were at least 3 months from the last surgical intervention and did not show any healing improvements in the 3 months before ultrasound treatment (average fracture age, 257 days; range: 180-781). All patients were followed up (average, 2.7 years) by questionnaire, or by phone, if needed. There was an overall healing rate of 73%, at an average 184 days to healing (range, 52-739). No difference in healing rate for open or closed fractures was observed.

Delayed Union

In 2010, Schofer et al. reported an industry-sponsored multicenter randomized double-blinded sham-controlled trial of low-intensity pulsed ultrasound in 101 patients with delayed union of the tibia.(15) Delayed union was defined as lack of clinical and radiologic evidence of union, bony continuity, or bone reaction at the fracture site for no less than 16 weeks from the index injury or the most recent intervention. Roughly one-third of the patients had an open fracture. Fifty-one patients were randomized to daily treatment with ultrasound, and 50 were assigned to an inactive sham device (20 minutes daily for 16 weeks). The primary outcome measure was the change in bone mineral density (BMD) over the 16 weeks, assessed by CT attenuation coefficients, or Hounsfield units. Gap area at the fracture site was a secondary end point. The primary analysis was intention-to-treat with imputation of missing values (24% of sham-treated subjects and 9.8% of active-treated subjects were missing posttreatment values). The mean improvement in BMD was 1.34 (90% CI, 1.14 to 1.57) times greater for ultrasound-treated subjects compared to sham. Analysis of ‘completers’ showed a medium effect size (0.53) of the treatment. A mean reduction in bone gap area also favored ultrasound treatment, with a mean change of log gap area of -0.131 mm² for the active treatment and -0.097 mm² for sham (effect size,-0.47; 95% CI, -0.91 to -0.03). Untransformed data showed a difference between groups of -0.457 mm² (90% CI, -0.864 to -0.049), which was statistically significant by a 1-sided test. The clinical significance of this difference is unclear. There was a trend (p=0.07) for more subjects receiving low-intensity pulsed ultrasound to be judged to be healed by the participating physicians by the end of the 16-week study period, 65% (33 of 51) of ultrasound versus 46% (23 of 50) sham subjects. While there was not a statistically significant improvement in the rate of healing, the improvements in intermediate outcomes and the corroborating evidence from trials of patients with similar indications, eg, fracture nonunion, make it very likely that this treatment is efficacious for delayed union.

Osteotomy Sites

In 2013, Urita et al. published a small (n=27) quasirandomized study (alternating assignment) of low-intensity pulsed ultrasound after ulnar shortening osteotomy for ulnar impaction syndrome or radial shortening osteotomy for Kienbock disease.(16) Patients in the ultrasound group received once-daily 20-minute ultrasound treatments for at least 12 weeks postoperatively. Blinded evaluation of radiographic healing showed that ultrasound reduced the mean time to cortical union by 27% (57 vs 76 days) and endosteal union by 18% (121 vs 148 days). At the time of endosteal healing (mean, 121 or 148 days), the 2 groups had similar results on the Modified Mayo Wrist Score and no pain at the osteotomy site. Limitations of this study include the lack of a sham control and the long interval between the 16 and 24 week assessments, which may have increased group differences. In addition, clinical outcomes appear to have been assessed only at the time of radiographic healing and did not show any differences at this time point. Additional study is needed to determine with greater certainty the effect of low-intensity pulsed ultrasound on healing of osteotomy sites.

Distraction Osteogenesis
The 2009 systematic review by Busse et al found 3 trials of distraction osteogenesis that used a variety of surrogate outcome measures with inconsistent results and provided very low-quality evidence of accelerated functional improvement.(4) In 2011, a small (n=36) nonblinded RCT of low-intensity pulsed ultrasound found no significant differences between the active and control groups in efficacy measures, although the treatment period (fixator gestation period) was decreased by more than a month.(17) Double-blind trials with a larger number of subjects are needed to evaluate the health benefits of this procedure.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2008

In response to requests for input from physician specialty societies and academic medical centers for the 2008 policy update, input was received from 1 physician specialty society while this policy was under review. Physician input obtained through the American Academy of Orthopaedic Surgeons agreed with the positions regarding the criteria for medical necessity and the conditions that are considered investigational (eg, delayed union and open/unstable grade II or III fractures).

2011

In response to requests, input was received through 2 physician specialty societies and 1 academic medical center for the policy review in January 2011. Input supported the use of ultrasound for nonunion and for fresh closed fractures at high risk for delayed fracture healing or nonunion as described in the policy. One reviewer supported including chemotherapy, immunosuppressive agents, history of infection, Charcot neuroarthropathy, and fractures of the tibial shaft or clavicle as additional risk factors, and a different reviewer supported including fractures of the talus and sesamoids as additional risk factors.

2012

In response to requests, input was received through 4 academic medical centers for the policy review in December 2012. Input supported the use of low-intensity ultrasound in delayed union and nonunion of bones excluding the skull and vertebra, and in fresh closed fractures at high risk for delayed fracture healing or nonunion. Input agreed that other applications of low-intensity ultrasound treatment are investigational, including, but not limited to, treatment of congenital pseudoarthroses, open fractures, stress fractures, arthrodesis or failed arthrodesis. Additional risk factors were noted, including: use of anticoagulants, immunosuppressive drugs or chemotherapy; infection at the fracture site; severe anemia; obesity; and fracture locations more prone to nonunion such as tibial and distal radial fractures.

Ongoing and Terminated Clinical Trials

The Trial to Evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) (NCT00667849) was a trial of low-intensity ultrasound for tibial fractures. This was a double-blind trial with sham ultrasound control, and was scheduled to enroll 500 patients with open or closed tibial fracture amenable to intramedullary nail fixation. The primary outcome measure was radiographic healing at up to 1 year, and a secondary outcome was the rate of fracture nonunion. According to the posting on the online site www.Clinicaltrials.gov, “the study was terminated due to futility”.

An industry-sponsored randomized sham-controlled trial of low-intensity pulsed ultrasound for lumbar spine fusion (NCT00744861) was terminated after interim analysis. The primary outcome measure was
radiographic fusion success at up to 1 year, and a secondary outcome was pain/disability. The study had a targeted enrollment of 310 patients with completion expected in 2012.

Summary
There is evidence from published studies that ultrasound improves healing rates in closed fresh fractures, delayed union, and fracture nonunion. As a result, ultrasound may be considered medically necessary for these indications. For treatment of open, fresh fractures, the evidence is less consistent across randomized controlled trials, and systematic reviews do not report strong conclusions on efficacy of ultrasound for improving healing when data on closed and open fresh fractures are combined. Most fresh closed fractures heal without complications with the use of standard fracture care, ie, closed reduction and cast immobilization. Therefore, the most appropriate candidates for ultrasound treatment may be those with closed fractures at high risk for delayed fracture healing or nonunion. Based on the available evidence and support from clinical input, low-intensity ultrasound treatment may be considered medically necessary for fresh fractures (closed), delayed union of fractures, and nonunion of fractures.

Evidence is insufficient to evaluate health outcomes with use of low-intensity ultrasound as a treatment of congenital pseudarthroses, arthrodesis of the appendicular skeleton, or spinal fusions. Use of ultrasound for these conditions is considered investigational. Based on 1 small trial with results showing no benefit to use of ultrasound treatment in the treatment of stress fractures, this is considered investigational.

Practice Guidelines and Position Statements
The United Kingdom’s National Institute for Health and Clinical Excellence (NICE) updated their guidance on low-intensity pulsed ultrasound for the treatment of nonunion and delayed fracture healing in 2013.(18) NICE reached the following conclusions:

1.1 The case for adopting the EXOGEN ultrasound bone healing system to treat long-bone fractures with nonunion (failure to heal after 9 months) is supported by the clinical evidence, which shows high rates of fracture healing.

1.2 The EXOGEN ultrasound bone healing system to treat long-bone fractures with nonunion is associated with an estimated cost saving of £1164 per patient compared with current management, through avoiding surgery.

1.3 There is some radiological evidence of improved healing when the EXOGEN ultrasound bone healing system is used for long-bone fractures with delayedhealing (no radiological evidence of healing after approximately 3 months). There are substantial uncertainties about the rate at which bone healing progresses without adjunctive treatment between 3 and 9 months after fracture, and about whether or not surgery would be necessary. These uncertainties result in a range of cost consequences, some cost-saving and others that are more costly than current management.

The American Academy of Orthopaedic Surgeons (AAOS) published 2009 guidelines on the treatment of distal radius fractures.(19) AAOS provided a weak recommendation for use of ultrasound for adjuvant treatment of distal radius fractures. This recommendation was based results from 2 studies that used nonvalidated patient outcome measures.

Medicare National Coverage
Effective January 1, 2001, ultrasonic osteogenic stimulators are covered as medically reasonable and necessary for the treatment of nonunion fractures (20) Nonunion fractures of the skull, vertebrae, and those that are tumor-related are excluded from coverage. Ultrasonic osteogenic stimulators may not be
used concurrently with other noninvasive osteogenic devices. Ultrasonic osteogenic stimulators for fresh fractures and delayed unions remain noncovered.

References

Billing Coding/Physician Documentation Information
20979 Low intensity ultrasound stimulation to aid bone healing
E0760 Osteogenesis stimulator
**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

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<thead>
<tr>
<th>Date</th>
<th>Change Description</th>
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<tr>
<td>8/1/02</td>
<td>New policy titled <em>Bone Growth Stimulation</em>.</td>
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<tr>
<td>8/1/03</td>
<td>No policy statement changes.</td>
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<tr>
<td>8/1/04</td>
<td>Policy statement revised to indicate ultrasound bone growth stimulation for infantile non-union (congenital pseudoarthoses) is considered investigational.</td>
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<tr>
<td>8/1/05</td>
<td>Policy updated to split Bone Growth Stimulation into three separate policies: Ultrasound Accelerated Fracture Healing Device, Noninvasive Electrical Bone Growth Stimulation of the Appendicular Skeleton, and Electrical Stimulation of the Spine as an Adjunct to Spinal Fusion Procedures)</td>
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<td>8/1/06</td>
<td>No policy statement changes.</td>
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<td>8/1/08</td>
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<tr>
<td>8/1/09</td>
<td>No policy statement changes.</td>
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<tr>
<td>8/1/10</td>
<td>Use in stress fractures added as investigational; intent of the policy remains unchanged.</td>
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<tr>
<td>8/1/11</td>
<td>Policy statements modified by moving information from policy guidelines to policy statements about risk factors for nonunion.</td>
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<tr>
<td>8/1/12</td>
<td>Policy statement revised to indicate treatment of delayed unions may be considered medically necessary. Fresh fracture defined.</td>
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<tr>
<td>8/1/13</td>
<td>Arthrodesis added to investigational statement; definition of delayed unions revised to 3 months for consistency with definition of nonunion.</td>
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<tr>
<td>8/1/14</td>
<td>Clarification of delayed union and nonunion of previously surgically treated fractures; fresh surgically treated closed fractures added to investigational and medically necessary statements.</td>
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