EXOGEN THERAPY

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DISCLOSURE

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EXECUTIVE SUMMARY

Introduction

Nonunions occur in 5-10% of fractures and are characterized by the failure to heal without further intervention. To avoid the risks of surgery, several alternative treatments have been developed, including electrical stimulation, extracorporeal shock wave therapy, and low-intensity pulsed ultrasound (LIPUS). LIPUS has been found to have a beneficial effect on fracture healing by increasing the quantity and strength of bony callus and by several other biological and molecular mechanisms. Also, it is a safe and non-invasive treatment, since it uses mechanical energy of a low intensity, thereby not causing tissue damage.

Exogen, a technology from the [redacted], United States, is claimed to be the only device marketed worldwide that uses LIPUS to influence the fracture healing process. The device is intended to be used by the patient at home and is applied 20–30 minutes daily until healing occurs.

Objective/Aim

The objective of this technology review was to assess the safety, effectiveness and cost-effectiveness of Exogen therapy for the treatment of nonunion in fractures.

Results and Conclusions

There was limited but fair level of evidence to show the safety of the Exogen therapy for the treatment of nonunion in fractures. Studies included in this review showed that there were no device-related adverse events occurred. The device has USFDA approval to treat fractures that have not healed (non-unions) as well as appropriate fresh (recent) fractures. However, there was no retrievable evidence on the CE mark for this technology.

There was a lack of consistent good level of evidence from controlled trials to suggest the effectiveness of Exogen therapy for the treatment of nonunion in fractures. Most of the evidence from included studies showed that the Exogen is used after conventional therapy, and one article showed no improvement on its used in fresh fracture. There is evidence to conclude that Exogen therapy accelerated fracture healing. However, there is also poor level of evidence to suggest it used as a prophylactic measure to prevent infections in primary orthopaedic operations and as an adjuvant therapy for infected nonunions.

An economic evaluation review revealed that by adding Exogen therapy (ultrasound) for treating both nonunions and fresh fractures is a total cost savings of 20-40% per patient. However, many of the included studies were decision analysis, which are based on secondary data and require multiple assumptions to be made.

According to the manufacturer, the device costs about RM [redacted] per unit.

Methods

Electronic databases were searched, which included Medline, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon scanning databases - Centre, Birmingham, Australia and New Zealand Horizon scanning (ANZHSN), USFDA website, MHRA website and from non scientific database - Google search engine. In addition, a cross-referencing of the articles retrieved was also carried out accordingly to the topic. Relevant articles were critically appraised and evidence graded using US / Canadian Preventive Services Task Force.

EXOGEN THERAPY

1.0 INTRODUCTION

Ultrasound is sound at an ultrahigh, inaudible frequency. In healthcare these acoustic waves are used for both diagnostic and therapeutic modalities. Diagnostic ultrasound has become standard practice in several disciplines such as general surgery, trauma, urology and vascular surgery, at intensities between 0.5 and 50 mW/cm^2 with a frequency of 1-10 Mhz. Therapeutic ultrasound can be divided into two categories: high-intensity ultrasound with peak intensities from 5,000-15,000 W/cm^2 and low-intensity ultrasound with intensities of 0.5-3,000 mW/cm^2. This low-intensity ultrasound is used in physical therapy (pain reduction, heating, increasing blood flow, etc.), while the high intensity seems to have potential for treating tumours by selectively heating tissue and causing necrosis.[1]

Nonunions occur in 5-10% of fractures and are characterized by the failure to heal without further intervention. To avoid the risks of surgery, several alternative treatments have been developed, including electrical stimulation, extracorporeal shock wave therapy, and low-intensity pulsed ultrasound (LIPUS). LIPUS has been found to have a beneficial effect on fracture healing by increasing the quantity and strength of bony callus and by several other biological and molecular mechanisms. Also, it is a safe and non-invasive treatment, since it uses mechanical energy of a low intensity, thereby not causing tissue damage.[2]

Exogen, a technology from the [redacted], United States, is claimed to be the only device marketed worldwide that uses LIPUS to influence the fracture healing process. The device is intended to be used by the patient at home and is applied 20–30 minutes daily until healing occurs.[3]

This technology review was conducted following a request from the Head of Department and Senior Consultant of Orthopedic, Hospital Tengku Ampuan Afzan, Kuantan, Pahang following a query from Deputy Director General's (Medical) Ministry of Health Malaysia as regards the use of Exogen therapy for the treatment of nonunion in fractures.

2.0 OBJECTIVE/AIM

The objective of this technology review was to assess the safety, effectiveness and cost-effectiveness of Exogen therapy for the treatment of nonunion in fractures.

3.0 TECHNICAL FEATURES

The Exogen is a portable, lightweight unit that delivers the prescribed treatment in a convenient 20 minutes daily regimen. The system consists of three components: Main Operating Unit (MOU), Transducer and Strap (Figure 1).[3]

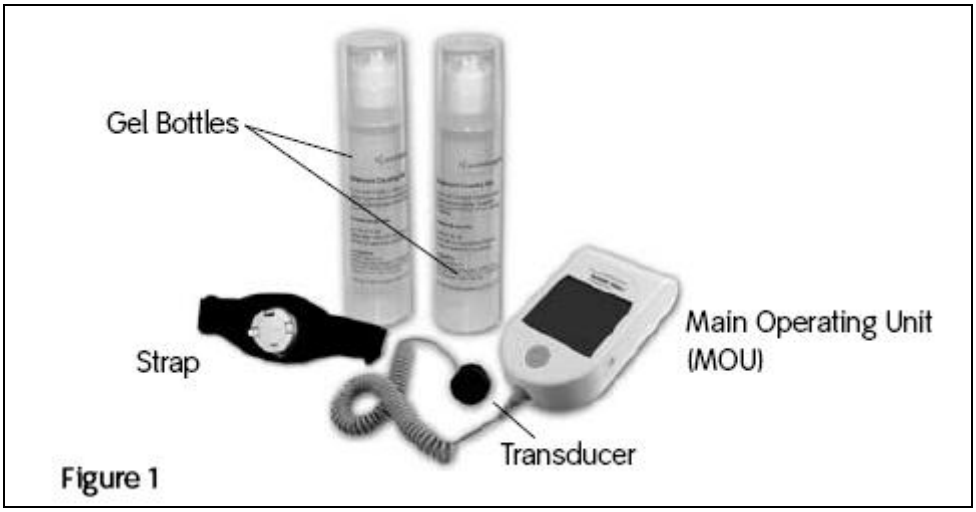
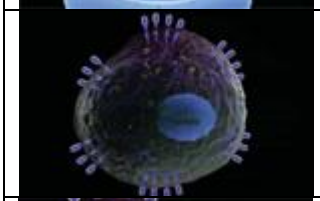


Figure 1: Exogen system

Table 1: Exogen – mechanism of actions as claimed by the manufacturer

	(1) Mechanical pressure wave transmission
	(2) Integrin signal reception
	(3) Clustered integrins
	(4) Molecules regulating gene expression are activated and migrate to the nucleus
	(5) Result: increased protein expression

The MOU is powered by a non-replaceable lithium battery. The MOU itself monitors, controls system operation during treatment, and verifies correct operation of the transducer. The device monitors the presence/absence of coupling gel on the transducer surface and alerts the patient with an audible beep if gel is not present. The MOU maintains a complete record of patient daily use of the device, which is available to the physician. The Transducer transmits low intensity pulsed ultrasound to the skin at the fracture site through a coupling medium. The Strap is designed to

hold the transducer over the fracture site. When closed, it applies light pressure to the top of the transducer to maintain skin contact. The Gel Bottles supplied with the device contain the appropriate ultrasound coupling gel.[3]

It is **claimed** that the system uses a mechanical force to stimulate mechanical receptors, producing a biological response. During the use of Exogen, mechanical pressure waves transmit through skin and soft tissue. Cell receptors known as integrins are then activated, causing molecules to cluster. This clustering then starts an intra-cellular cascade during which molecules that regulate gene expression are stimulated and move into the nucleus to perform their function. This activity results in stimulated production of a range of genes and growth factors, which are critical to the bone healing process (Table 1).[3] However, this mechanism of action is yet to be proven by scientific evidence.

4.0 METHODOLOGY

4.1. Searching

Scientific databases such as Medline, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon scanning databases - Centre, Birmingham, Australia and New Zealand Horizon scanning (ANZHSN), USFDA website, MHRA website and from non scientific database - Google search engine were searched for evidence of safety, effectiveness and cost-effectiveness of Exogen therapy for the treatment of nonunion in fractures.

The following keywords were used either singly or in combinations: Exogen, therapy, ultrasound, low-intensity, fractures.

4.2. Selection

All published articles related to safety, effectiveness and cost-effectiveness of Exogen therapy were included. Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence was graded according to US/Canadian Preventive Services Task Force (Appendix 1).

5.0 RESULTS AND DISCUSSION

The search strategies yielded an article on the USFDA related to Exogen therapy. There were four articles related to both safety and effectiveness and two articles related to only the effectiveness of this technology. There was only an article on economic evaluation associated with this device.

5.1 Safety

The Exogen therapy is approved by USFDA for treating fractures that have not healed (non-unions) as well as appropriate fresh (recent) fractures.[4] However, there was no retrievable evidence on the CE mark for this technology.

Schofer MD *et al*. 2010 conducted a multi-centre, randomized, controlled trial at six hospitals in Germany to determine the effectiveness of low-intensity pulsed ultrasound (LIPUS), Exogen 2000/2000+ (Smith & Nephew GmbH, Schenefeld, Germany), involving 101 patients with delayed unions of tibia. Patients were randomly allocated to treatment with either an active LIPUS device (n=51) or an inactive sham device (n=50). From this study group, there were no device-related adverse events occurred.[5 Level I]

A randomised double blind, placebo-controlled multi-centre trial in 101 adult patients with a non-operatively treated fresh clavicle shaft fracture was conducted by Lubbert P *et al*. 2008 at the Emergency Departments of the participating hospitals in Netherlands, comparing an active transducer ultrasound stimulation, Exogen 2000® (n=52) treatment with a placebo transducer (n=49). Some of the secondary outcomes measures were painkiller use, pain assessment using Visual Analogue Scale (VAS), and adverse events. The study showed that in the active group, 37.21 tablets of painkiller were used whereas 32.88 tablets in placebo group (p=0.66). Pain score measured by daily VAS was not different between groups (p=0.9). There were no allergic reactions to either the transducer gel or the transducer itself.[1 Level I]

Hemery X *et al*. 2011 evaluated a retrospective series of 14 patients treated using the Exogen® 2000 as part of management of surgically treated long-bone non-union between September 2006 and January 2008. The study revealed that no postoperative complications occurred. Associated sepsis or atrophy did not significantly impact treatment efficacy.[6 Level III]

A case report was evaluated by Lerner A, Stein H and Soudry in 2004. They reported 17 patients with 18 severe compound high-energy limb injuries and varying degrees of bone comminution and soft-tissue loss, underwent complex treatment with the use of low intensity pulsed ultrasound between 1997 and 2001. The study found no local or systemic side effects of the ultrasound supplementation.[9 Level III]

5.2. Effectiveness

Schofer MD *et al*. 2010 conducted a multi-centre, randomized, controlled trial at six hospitals in Germany to determine the effectiveness of low-intensity pulsed ultrasound (LIPUS), Exogen 2000/2000+ (Smith & Nephew GmbH, Schenefeld, Germany), in acceleration of the healing process in delayed unions of the tibial shaft. 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. One hundred one subjects (age range: 14 to 70 years) with delayed unions of the tibia, enrolled between January 2002 and December 2005, were randomly allocated to treatment with either an active LIPUS device (n=51) or an inactive sham device (n=50). The primary outcomes of this study were bone mineral dencity (BMD) and gap area at the fracture site, assessed by computed tomography (CT) scanning. The study demonstrated that the mean (SD) changes from pre-treatment to 16 weeks follow-up in log BMD were 0.87 (0.67) HU and 0.57 (0.38) HU (Hounsfield units) for active- and sham-treated groups, respectively (t-test, p=0.014). The corresponding mean changes (SD) in log gap area were -0.131 (0.072) mm^2 and -0.097 (0.070) mm^2 for active and sham groups, respectively (p=0.034) resulting in a standardized effect size of comparable absolute value (ES = - 0.47, 95% CI -0.91 to -0.03). Based on log transformed data, the adjusted mean improvement in BMD was 1.34 (90% CI 1.14 to 1.57) times greater for

LIPUS-treated subjects compared to sham (p=0.002). A mean reduction in bone gap area also favored LIPUS treatment (p=0.014). At the completion of the 16 weeks study period, 65% (33 of 51) of LIPUS and 46% (23 of 50) of sham subjects were judge to be healed by the participating physicians (p=0.07). The authors concluded that this trial provides Level-1 evidence that use of LIPUS accelerates the healing process and likely improves the odds of achieving solid union in patients with delayed unions of the tibia.[5 Level I]

Another randomised double blind, placebo-controlled multi-centre trial was conducted by Lubbert P *et al*. 2008 at the Emergency Departments of the participating hospitals in Netherlands between 1 March 2001 and 31 December 2003. One hundred one adult patients with a non-operatively treated fresh clavicle shaft fracture, were randomly allocated to treatment with either an active transducer with ultrasound stimulation, Exogen 2000® (n=52) or a placebo transducer (n=49). Primary outcome measure was fracture consolidation according to the patient. Secondary outcome measures were possible operation, painkiller use, pain assessment using Visual Analogue Scale (VAS), adverse events, and resumption of sport and professional or household activities. The study revealed that mean duration of time to clinical fracture healing was 26.77 days (active) and 27.09 days (placebo) (p=0.91). Time to operation was 112 days for the active group and 228 for the placebo group (p=0.13). Resumption of activities was not significant between groups (household, p=0.16; professional work, p=0.38; sports, p=0.07). Based on the findings, the authors did not confirm that LIPUS accelerates clinical healing time of fresh clavicle shaft fractures due to study limitations.[1 Level I]

Hemery X *et al*. 2011 evaluated a retrospective series of 14 patients treated using the Exogen® 2000 as part of management of surgically treated long-bone non-union between September 2006 and January 2008. Fourteen patients underwent surgery, and the non-union site was mechanically and radiologically stable in all cases (osteosynthesis by intramedullary nailing, plate or external fixator). They received 20 minutes stimulation daily over a period of three months. Regular clinical and radiological follow-up checked treatment efficacy. It showed that bone consolidation was obtained in 11 of the 14 cases (79%): within three months of beginning Exogen® treatment in 27% (3/11), within six months in 27% (3/11) and within nine months in 46% (5/11). There was no significant correlation between interval to initiation of ultrasound treatment and bone consolidation. The authors concluded that low-intensity pulsed ultrasound is a non-invasive procedure that seemed to promote consolidation in case of non-union. However, a larger series will be needed to validate the application of this device in the management of non-union.[6 Level III]

Gold SM and Wasserman R conducted a study to assess whether the use of non-invasive, pulsed low intensity ultrasound (Exogen™) reduced external fixation time for bone transport patients with large, segmental tibial defects. This was a prospective study compared to a previously treated control group. Eight patients (male, mean age 34 years; range 18-50) with large tibial segmental defects, acute or chronic, were studied. All patients were treated with single-level bone transport, started five to 10 days after a metaphyseal corticotomy and progressed with one-quarter milimeter advancement two to four times per day. Exogen was applied to the regenerate site in the second postoperative week and to the docking site after docking was complete. The treatment was used for 20 minutes daily at each site. The patients were followed weekly for the first four week. They were then followed bimonthly for two months and then monthly until consolidation had occurred. The two main outcome measures

used were the external fixation time (EFT) measured in months and the external fixation index (EFI) measured in months per cm. The study demonstrated that the mean follow-up from frame removal to the time of the last clinic visit was 12.4 months (range 4-32). The mean EFT was 13.91 months (range 8.25-25.25), while the mean EFI was 1.34 months per cm transported for the Exogen group and 2.02 months per cm for the control group. Although not statistically significant because of small numbers, the EFI was reduced by 17.21%. The authors concluded that these data further confirm already published data on acceleration of fracture healing by low--intensity pulsed ultrasound and, in their case, regenerate consolidation.[7 Level II-3]

Lerner A, Stein H and Soudry in 2004 reported a case of 17 patients with 18 severe compound high-energy limb injuries and varying degrees of bone comminution and soft-tissue loss, underwent complex treatment with the use of low intensity pulsed ultrasound between 1997 and 2001. All ultrasound treatment was performed according to the protocol of a 20 minutes period each day applied by the patients at home. The ultrasound treatment was continued until the appearance of clinical and radiographic signs of solid bone union. The study revealed that 16 of the 18 (88.9%) treated fractures united with solid bone union within 13-52 weeks after starting the ultrasound supplementation. The authors concluded that this method may be useful in the combined treatment of high-energy limb injuries.[8 Level III]

Ayan I *et al*. 2008 investigated the effect of low-intensity pulsed sound waves delivered by the Exogen device, which was recommended for the treatment of delayed union and nonunion in orthopaedic surgery, on the colony number, antimicrobial susceptibility, bacterial morphology, and genetics of *Staphylococcus aureus*, which is a frequent pathogen in orthopaedic infections. Thirty tubes containing 0.5 McFarland suspensions of *S. Aureus* were used. Fifteen tubes forming the test group were subjected to low-intensity sound waves by the Exogen device for 20 minutes. The remaining 15 tubes were untreated as control. The two groups were then compared with respect to colony number, antibiotic susceptibility, and genotypic properties. The tubes were examined histologically by electron microscopy. The study demonstrated that in the test group, there was a significant reduction in viable bacteria count due to ultrasound treatment with approximately 5 log 10 CFU/ml to 3.66 log 10 CFU/ml ($p<0.001$). No resistance to penicillin, oxacillin, teicoplanin, erythromycin, clindamicine, levofloxacine, vancomycin, or ciprofloxacin was encountered in antimicrobial susceptibility test. It was found that LIPUS application did not cause any genetic differences detectable by AP-PCR process. Electron microscopical histologic evaluation yielded the following results: Bacterial cell wall structure in the control group was of normal appearance, whereas partial destruction and break-up were observed in the test sample. Bacterial cell wall thickness was significantly higher in the test group compared to the control group (41.54 nm and 24.27 nm, respectively; $p<0.001$). The authors concluded that low-intensity sound waves may be beneficial as a prophylactic measure to prevent infections in primary orthopaedic operations and as an adjuvant therapy for infected nonunions.[9 Level III]

5.3. Economic evaluation

Button M *et al*. conducted a systematic review of the current literature to identify economic analyses evaluating the costs and effectiveness of ultrasound, electrical stimulation, or extracorporeal shock waves in the treatment of fresh fractures or non-unions. Articles were included if they met the following criteria: (1) assessed ultrasound, electrical stimulation, and extracorporeal treatment in terms of economic

impact; (2) inclusion of patients presenting with fresh fractures or non-unions; and (3) reporting the effect of ultrasound, electrical stimulation, or extracorporeal shock waves on bone healing. Interim or subset analyses of final trials were excluded. The authors identified studies, in English, by a systematic search of EMBASE, PubMed, Cochrane, and Medline databases from 1997 to November 2008. The search resulted in 1,536 potentially eligible studies; 21 articles were retrieved in full text, and seven studies met their inclusion criteria and were included in the final review. Unfortunately, no economic analyses concentrating on electrical stimulation or shock waves modalities were identified. By using ultrasound as a treatment for non-unions, costs per patient were reduced by USD $[redacted] for patients receiving the surgical treatment, USD $[redacted] for patients receiving the conservative treatment, and USD $[redacted] for overall patient costs when compared to patients receiving other modalities as treatment. Similar results were found for patients receiving ultrasound as a treatment option for fresh fractures. Costs savings ranged from USD $[redacted] to $[redacted] per patient. The results suggest that the ultrasound is a viable alternative for bone stimulation; however, the impacts of the other modalities are left unknown due to the lack of research available. Methodological limitations leave the overall economic and clinical impact of these modalities uncertain. Large, prospective, randomized controlled trials that include cost-effectiveness analyses are needed to further define the clinical effectiveness and financial burden associated with bone stimulation modalities.[10 Level I]

According to the manufacturer, the device costs about RM [redacted] per unit.[11]

6.0 CONCLUSION

6.1. Safety

There was limited but fair level of evidence to show the safety of the Exogen therapy for the treatment of nonunion in fractures. Studies included in this review showed that there were no device-related adverse events occurred. The device has USFDA approval to treat fractures that have not healed (non-unions) as well as appropriate fresh (recent) fractures. However, there was no retrievable evidence on the CE mark for this technology.

6.2. Effectiveness

There was a lack of consistent good level of evidence from controlled trials to suggest the effectiveness of Exogen therapy for the treatment of nonunion in fractures. Most of the evidence from included studies showed that the Exogen is used after conventional therapy, and one article showed no improvement on its used in fresh fracture. There is evidence to conclude that Exogen therapy accelerated fracture healing. However, there is also poor level of evidence to suggest it used as a prophylactic measure to prevent infections in primary orthopaedic operations and as an adjuvant therapy for infected nonunions.

6.3. Economic evaluation

An economic evaluation review revealed that by adding Exogen therapy (ultrasound) for treating both nonunions and fresh fractures is a total cost savings of 20-40% per patient. However, many of the included studies were decision analysis, which are based on secondary data and require multiple assumptions to be made.

7.0 REFERENCES

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8.0 APPENDIX

8.1 Appendix 1

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)