SPINAL CORD STIMULATION IN CHRONIC PAIN OF NEUROPATHIC OR ISCHAEMIC ORIGIN: RESPONSE TO APPRAISAL CONSULTATION DOCUMENT

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The Appraisal Committee has produced a comprehensive and detailed document on the use spinal cord stimulation in four different clinical conditions: Failed Back Surgery Syndrome (FBSS), Complex Regional Pain Syndrome (CRPS), Refractory Angina (RA) and Critical Limb Ischaemia (CLI). In the present statement the focus is on the two first conditions, with a brief comment made on RA and CLI only.

General comments

Spinal cord stimulation (SCS) has been used in clinical practice for 40 years but controlled trials are few. This is not unique in the surgical management of chronic pain in which only recently has evidence based medicine gained support. As an example, large decisive trials on the surgical management of sciatica have only been published in the last few years. There remain a large number of treatments for chronic pain for which no appropriate controlled trials have been published (e.g., microvascular decompression and ganglion-level procedures in trigeminal neuralgia and total hip replacement in advanced osteoarthritis). In these conditions, the weight of evidence supporting the use of the technology appears so overwhelming that few voices have been raised to demand a controlled trial to prove efficacy. As regards SCS, much of the current evidence has been gathered before evidence-based

medicine made its breakthrough, in the form of poorly controlled case series and a limited follow-up. Despite these weaknesses, spinal cord stimulation is steadily gaining popularity with an ever-increasing number of patients provided with the treatment. Given the long period of time over which has happened, and the fact that there are no signs of the treatment being surpassed or replaced by a more effective or popular one, SCS should be seen as an advanced clinical practice that has established its position in the armamentarium of pain clinics, despite lack of controlled trials. One has to welcome the recommendation from the Appraisal Committee that more research is needed, not the least in the form of controlled trials, but until that has been achieved, the needs of the patients must also be considered. The particular group of patients whose ongoing treatment should not be threatened are those who have enjoyed significant subjective benefit from SCS but who need a revision or battery change. To not carry out such a procedure in the light of lack of properly controlled trials would be clinically unjustifiable and ethically questionable.

SCS requires a percutaneous trial and internalisation of the system, or a separate surgical procedure (laminotomy or laminectomy), neither of which are a major operation. Reported serious adverse effects associated with SCS are very rare. Its use is limited to chronic pain, and the general acceptance on the part of the patient is excellent because it provides a drug-free alternative. Advancement of SCS, and neuromodulation therapies in general, has led to a decrease of previously common use of repeated nerve blocks and neurodestructive procedures which are not evidence based. Curtailing the use of SCS in the management of refractory pain brings about the risk of obsolete therapies being reintroduced by perplexed doctors and accepted by desperate patients.

The Appraisal Committee recommends multidisciplinary assessment of the patient's suitability for SCS and a percutaneous trial to establish efficacy before implantation of the permanent system. This is common practice and has obvious benefits. In some highly specialised centres led by very experienced clinicians this may seem superfluous. However, as SCS is becoming more technically advanced and is being adopted by an increasing number of neurosurgical and pain departments it is imperative for the maintenance of the clinical standards that patient selection and treatment choice are based on comprehensive assessment and best advice available.

The consultation document discusses two neuropathic pain conditions, FBSS and CRPS.

(1) Failed back surgery syndrome (FBSS)

The Committee has evaluated the two RCTs so far published (North et al 2005, Kumar 2007). These two studies were rated Class II by the European Federation of Neurological Sciences Task Force in 2007 (Cruccu et al 2007). Both RCTs showed superiority of SCS over either reoperation or conventional medical management, CMM. The PROCESS study (Kumar et al 2007) showed that SCS was superior to CMM at both 6 months (>50% pain relief obtained in 48% randomised to SCS and 9% randomised to CMM, respectively) and 12 months (34% and 7%, respectively). In the North study, 50% or more of pain relief was obtained by 39% of

patients who received SCCS as opposed to 12% who underwent a reoperation. The number of patients in the PROCESS study was 100, and in the North study 60. Cost effectiveness analyses carried out by the Appraisal Committee supported the use of SCS in this indication.

These two studies are of a reasonably good quality and reach similar conclusions. By and large they corroborate the suggestive evidence from a large number of case series in this indication. Cruccu et al (2007) report of pooled data of 3307 patients with FBSS, with a response rate of 62% (Class IV evidence). For a comparator trial, both studies can be commended on the long end point (12 months for the PROCESS study and 4 months for the North study).

(2) CRPS

The appraisal was based on the single Class II (EFNS Task Force definition) study by Kemler et al, with a two-year comparison of SCS with physiotherapy (PT), followed on by a non-randomised follow up for a further 3 years during which some patients received SCS (Kemler et al 2000, Kemler et al 2008). The conclusion reached by the investigators was that while at 24 months SCS is superior in pain relief to physiotherapy, this effect was lost from the 3rd year onwards. The Appraisal Committee acknowledge the treatment effect but question the use of SCS in CRPS on the basis of its cost effectiveness.

It is unfortunate that only one serious attempt at a controlled trial has been published on this indication. The conclusions that can be reached from this study are hampered by methodological flaws. One relates to power calculations that were inadequate and led to the study becoming underpowered. The authors based their calculations on a previous pilot data (Kemler et al 1999). In that uncontrolled study, 18/23 (78%) patients went on to have a permanent stimulator implanted following a successful percutaneous trial. At one month, the baseline mean of 7.9 (range 6.5-1.0) on a visual analogue scale (VAS) of 0-10 had dropped to 4.2 (range 1-7) (Kemler et al 1999). This large treatment effect (~3.7) appears to be the basis of their power calculations. However, from the same report it appears that at a follow up of a (mean of) 32 months (range 6-79 months) the mean VAS score was 5.4 (range 1.0-8.4) in the 15 patients in whom the data were available where as in the 23 who did not have a SCS implanted the score had come down from 7.3(baseline) to 6.8 (2.3-9.3). The authors do not present the figure for the adjusted mean difference (between pain scores in the implanted vs. non-implanted groups) but it is likely to be around 2, still a very substantial difference in comparison with any approved pharmacological agent in neuropathic pain. It should be noted that the authors specify a target of 3.5 (3.5 cm on a 10 cm visual analogue scale presumably) at six months for the basis of their power calculations regarding the RCT, which is extraordinarily large. It of course allows far fewer patients to be recruited into the study, a sensible aim if one is concerned about shot term efficacy. It should be noted that the above-mentioned power calculations were based on a 6 month perspective (Kemler et al 1999). If the authors had planned a long-term follow-up study from the outset they would have been compelled to consider entering far more patients, the estimate based on their own 32 month

data from the pilot study (Kemler et al 1999). Taking these data at face value one would predict that 22% of patients allocated to the SCS+PT group fail the percutaneous trial (based on their pilot study), and aim at a treatment difference of 2.0. In this way one would get a more realistic target for the group difference of 1.6. Using their reported SD of 2.34 (with alpha 0.05 and beta 0.90) one would need 90 patients to enter.

It should be also noted that the power calculations did not include drop-outs. In the five-year follow-up study (Kemler et al 2008) the completed patients totalled 31 in the SCS+PT group and 13 in the PT group (less than the 34 +17 needed based on their original calculations). An attrition percentage of 15 would increase the sample size to over 100.

The five-year assessment also suffers from methodological ambiguity (Kemler et al 2008). The ITT evaluation was not pursued rigorously throughout the study, and a patient with a special implant was excluded from the SCS+PT group analysis. No data are given as to any confounding factors during the 3 years of extended study, other than SCS provided for 4 patients in the PT group, such as other interventions that might alter the course of the pain problem (e.g. use of medication). This is especially pertinent to the PT group. These flaws withstanding, there was no statistical group-wise difference detected in any measures. As is customary in studies in which crossing over to another treatment modality is allowed, a sub group analysis of the 5-year pain status was carried out between the patients with SCS versus those who were offered PT in the first place, had no trial, and no SCS. Such an analysis led to a significant group difference of approximately 1.5 in favour of SCS (P=0.06) – an impressive result from an underpowered study and compatible with results from 12-week only drug trials in neuropathic pain. Despite some post hoc analyses based on LOCF values (no data shown), the authors appear not to have compared two further groups, those who actually received SCS and were not lost to follow up (20 in the randomised and 4 who crossed over) versus those who received PT alone (13 in the group assigned to PT at the outset and 9 who failed the trial). Such a comparison would better reflect clinical practice and inform the clinician what additional value to the management of CRPS to conventional treatment available SCS could provide.

Further scrutiny of the results show that there was limited increase in reported pain scores form year 2 to 5 so in the SCS+PT group and reduction of pain levels in the PT group during the same period. Because 4(22%) of 18 patients randomised to this group actually received SCS and were excluded from the analysis, this may have caused a significant bias, not captured by the LOCF analysis.

It would seem premature to conclude anything definitive on the long-term (5-year) effectiveness of SCS on the basis of this single small study.

In discussing the long term effect of SCS the Committee expressed unease about the uncertainty of the duration of effect of SCS. However, several long-term follow up studies have been published that by and large are in agreement with a sustained effect of SCS, especially in the CRPS group. Kumar et al reported a case series spanning over 22 years of 410 patients, 328 of whom received a permanent implant, and reported a long term success

rate of 74%. The mean follow-up in this case series was 96 months. Of the 32 patients with CRPS (both types) 23(72%) benefited long-term. Similar results were reported by Quigley et al in 21 patients with CRPS and a mean follow-up of 4.2 years.

For their cost effectiveness analysis, the Appraisal Committee estimated the device longevity at 4 years. It is not clear that this is based on the actual longevity of the devices implanted today observing the best clinical practice. Although Kumar et al report in their last case series that on average, the internal pulse generator (IPG) had to be changed in the fourth year (Kumar et al 2006), the results were biased because of use of the now discontinued Pisces-Sigma in the early part of the case series, and limited use of the new multichannel and multipolar electrode systems that have a longer survival time (Kumar et al 2006). In Kemler's study (2008) in half of the patients the IPG was replaced in the fifth year. As rechargeable IPGs are appearing with a claimed life span of 7-10 years (Kumar et al 2006), the chosen longevity of 4 years for the cost effectiveness analyses seems unduly short. As was acknowledged by the Committee, the clinical specialists made the point in this regard and also highlighted the role of the individual's pain characteristics.

The Committee also recognised (page 23) that the economic modelling based on the assumption that the effect of SCS is stable over 15 years may be overoptimistic with subsequent underestimation of ICERs. However, it must be emphasised that there are no data suggesting that over such a very long period of time patients with disabling neuropathic pain conditions such as CRPS would not experience deterioration of their condition when undergoing alternative treatment. (It should be noted that Kemler's study does not qualify for evaluation of long-term natural course and as the PT group did not remain intact and 4 patients actually received an implant). Therefore, ICERs may have been equally well over estimated. The Committee also noted that serious complications were not included in the models. In fact such serious complications, although anecdotally reported, are quite rare, and it is doubtful whether their inclusion in the economic models would change the overall conclusions. As an example, the recent systematic review and guidelines paper (Cruccu et al 2007) registered no serious complications in altogether 4724 patients (number obtained from Table 2, pp 957-960). Although anecdotal reports do appear in the literature, exploration of the literature reveals less than 10 cases, mostly from the early era of the therapy. Professor Nurmikko who is the first author of this report is aware of 3 serious and 3 moderately serious unreported complications (mainly neurological) collected over 15 years from several large practices, constituting to much less than 1% of all implanted cases.

3. Ischaemic pain (RA and CLI)

There is an unfortunate lack of high-quality studies addressing this issue. While the first studies in RA suggested comparable efficacy with CABG and PCI, the decisive Phase III efficacy study (STARTSTIM) has been suspended since 2006. In this trial the primary outcome measure was to be total exercise time on a treadmill, while secondary outcome measure included exercise time to angina onset, improvement of angina symptoms and

cardiovascular function (www.clinicaltrials.gov id: NCT00200070). There are therefore currently insufficient data available for firm conclusions, and the non-committal stance of the Appraisal Committee is appreciated. Similarly, data on pain in relation to CLI appears too limited for firm conclusions and recommendations. There is obviously a need for high quality research in sufficiently large populations to settle the matter conclusively, and the recommendation in this regard given by the Committee is to be supported.

The Committee have a difficult task in appraising the use of SCS in chronic pain despite the limited decisive evidence for its wide spread use in clinical practice. The four conditions addressed in the consultation process probably constitute no more than 50% of all indications for SCS in the clinic as practised today. Other pains for which SCS is considered are mostly those in which neuropathic pain mechanisms dominate. While it is reasonable to assume that in these conditions the response rate is not significantly different from those in FBSS and CRPS, the hard data are lacking. The evidence regarding these conditions (e.g., peripheral nerve injury, diabetic neuropathy, PHN, brachial plexus lesion, stump and phantom limb pain and spinal cord injury) is Class IV and only comes from case series. It is obvious that well-designed controlled trials must be conducted before the issue of ultimate effectiveness of SCS in neuropathic pain can be considered. However, for those patients already with a successfully implanted stimulator for any such alternative (neuropathic) pain who require revision of the system should be allowed to be assessed sympathetically and the fact that they report excellent pain relief (and as many patients do) improved quality of life and improved functional status should be taken into consideration as significant factors.

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