PAPER

Multicentre European study of thalamic stimulation in essential tremor: a six year follow up

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Background: Thalamic stimulation is an efficient treatment for disabling essential tremor, as previously shown, but follow up has mostly been short term.
Objectives: To see whether good results can be maintained in the longer term.
Methods: 37 patients with essential tremor had implantation of a thalamic stimulator, either unilaterally or bilaterally. The results at one year have been reported earlier. After six years, 19 patients were available for follow up. The main instrument for evaluation was the essential tremor rating scale. The patients were examined with pulse generators turned on and off.
Results: In the majority of patients, the very good results with stimulation seen at one year were maintained after a mean of 6.5 years. The reduction in tremor scores and improvement in activities of daily living were highly significant compared with baseline and with the stimulation turned off. There were few serious adverse events. Minor side effects related to stimulation were common. Few device related complications were observed and most could be resolved.
Conclusions: Good reduction in tremor can be maintained for more than six years in the majority of these severely disabled patients. Thalamic stimulation can be recommended in essential tremor where there is insufficient response to drug treatment. Surgical procedures and follow up should be concentrated in relatively few centres, which will thereby acquire a high degree of expertise.

In 1991 Benabid *et al* introduced deep brain stimulation (DBS) for medically untreatable tremor, because of the adverse effects of thalamotomy.[1] In short term follow up studies, thalamic stimulation was shown to cause a dramatic reduction in symptoms in essential tremor,[2–8] with less adverse effects than thalamic lesioning by coagulation.[9] Resting and postural tremor improved more than action tremor.[10] However, very few long term studies of thalamic stimulation in essential tremor have been published. One long term follow up showed a reduction in tremor suppression in some patients, and a rather high rate of surgical and device related complications, necessitating additional surgical interventions.[11]

Our main aim in this study was to investigate the long term efficacy of thalamic stimulation in essential tremor. We present the results of the six year follow up of the prospective, open label, European multicentre thalamic stimulation study.

METHODS

Patient selection

Thirty seven patients with essential tremor were included in the original study[6] between August 1992 and December 1994. The patients were enrolled in eight neurological and neurosurgical centres: one in Austria (Vienna); one in The Netherlands (Amsterdam); two in France (Grenoble and Créteil); and four in Sweden (Stockholm, Umeå, Lund, Göteborg).

Inclusion criteria were as follows:

- patients diagnosed as having essential tremor;
- tremor present during a major part of the day;
- tremor inadequately controlled under maximum tolerated doses of primidone, propranolol, and/or benzodiazepines;
- tremor disabling, with a score of between 3 and 4 on a five point tremor scale described in detail below (0, no tremor; 4, severe tremor);
- ability to abide by the protocol and to operate the pulse generator.

Exclusion criteria were:

- associated disorders that might interfere with the efficacy or evaluation of the tremor treatment, such as psychiatric illness, cognitive impairment, or concurrent neurological or other disorders;
- brain abnormalities visualised on computed tomography or magnetic resonance imaging;
- previous thalamotomy on the side of implantation, even if the thalamotomy was no longer effective.

The study was approved by the hospital ethics committees and all subjects gave informed written consent.

Demographics

Of the 37 patients included in the basic study and followed for 12 months,[6] 11 could not continue in the long term follow up for the following reasons: one was excluded for administrative reasons (only centres with more than five patients were allowed to enter the long term study); two had died before start of this study (one from pancreatic cancer and one from unknown cause); four could not participate because of concomitant disease (two strokes, one ischaemic heart disease, and one severe depression); one had moved to another country far away; and three were excluded because of protocol violations (one because his initial diagnosis of essential tremor was changed to Parkinson's disease; one because data from another patient had mistakenly been registered in his protocol; and one because he had already had DBS surgery before the study).

Of the 26 remaining patients available for the study, three died during the observation period (one from pneumonia, one from extreme old age (over 90 years), and one from unknown cause). One patient could not be reached, one

Table 1 Patient characteristics

	Baseline	(Median (range))	One year	Six years
No of patients	19	–	18*	19
Unilateral/bilateral implant	15/4	–	14/4	12/7
Sex (F/M)	5/14	–	–	–
Duration of disease (years) (mean (SD))	37.7 (12.3)	(36, 17 to 58)	–	–
Age at implant (years) (mean (SD))	61.8 (11.0)	(65, 40 to 78)	–	–
Duration of follow up (years) (mean (SD))	6.53 (0.6)	(6.54, 5.54 to 7.72)	–	–

*One year data missing for one patient.

refused because he did not want his pulse generator to be turned off, one had his pulse generator turned off because of side effects, and one had reached end of battery life and lived too far away. Therefore, 19 patients remained for assessment of clinical symptoms and DBS effects at six years. The main characteristics of this cohort are summarised in table 1.

Assessment

To evaluate the severity of tremor we used the essential tremor rating scale (ETRS),[12] which includes ratings of tremor in different parts of the body at rest, during maintenance of posture, and during activity. For example, for upper extremity tremor: 0 = no tremor, 1 = slight tremor (amplitude <0.5 cm); 2 = moderate tremor (0.5–1 cm); 3 = marked tremor (1–2 cm); and 4 = severe tremor (>2 cm). In addition, subjects were asked to write a standard sentence, draw two spirals, draw two straight lines, and perform a water pouring test. During these tasks motor performance was scored as follows:

- writing a sentence: from 0 = normal to 4 = no letter recognisable;
- drawing a spiral: from 0 = normal to 4 = figure not recognisable;
- drawing a straight line between lines: from 0 = normal to 4 = figure not recognisable;
- pouring water from a one glass to another: from 0 = normal to 4 = spilling most of the water (>50%).

Finally, the effects of the tremor on activities of daily living (ADL) were assessed.

Baseline assessment was done less than one month preoperatively. Follow up assessments were done at one, three, and six years postoperatively. The evaluations were undertaken in each centre in an open fashion with the pulse generator switched on and off, by a neurologist specialising in movement disorders. Non-scheduled visits for check up of reported side effects, reprogramming, or other reasons were made as necessary.

Surgical procedures

The surgical technique and postoperative care have been reported earlier.[6]

Data analysis

The overall level of significance was set at 5%. All probability (p) values given are for two sided tests. The population analysed consists of the patients with essential tremor who achieved the six year follow up. As the numbers were few and hence the normality of the data cannot be assured, we chose the non-parametric Wilcoxon signed rank test to evaluate the outcome following implantation and to compare the results during ON and OFF stimulation periods.

Descriptive analysis consists of n, minimum value, maximum value, and mean (SD) for continuous variables. Frequency tables are used for discrete variables.

RESULTS

By the end of the study the mean period of follow up for the 19 patients analysed was 6.5 years (range 5.5 to 7.7). Compared with baseline, there was an increase in tremor score (items 1–9) from 17.6 to 19.4 points (NS) and in ADL score (items 15–21) from 13.7 to 17.4 points (p = 0.03), assessed with stimulation OFF during the 6.5 year time period.

Efficacy

Tremor

The total tremor score, as measured by the sum of items 1–9 in the ETRS, was reduced significantly with stimulation ON compared with OFF at one year (p <0.001) and at six years (p <0.001) (table 2). The same magnitude of tremor reduction as at baseline was seen with stimulation ON at six years (p <0.001). Note that these results include tremor in the non-treated side.

Focusing on the upper extremity treated side (item 5 or 6), the reduction in tremor with stimulation ON was much greater. Postural tremor was nearly eliminated at one year and reduced from marked to slight at six years compared with the OFF state (p <0.001) and with baseline (p <0.001)

Table 2 Effect of stimulation on essential tremor and activities of daily living

			One year		Six years	
Score (item from ETRS)	Group	Baseline	Off stimulation	On stimulation	Off stimulation	On stimulation
Tremor ETRS (item 1–9)	All	17.6 (7.5) (n = 19)	15.1 (6.6) (n = 18)	8.2 (5.4) (n = 19)**††	19.4 (9.2) (n = 19)	10.4 (5.4) (n = 19)**††
Voice tremor (item 3)	All	0.5 (0.6) (n = 19)	0.3 (0.5) (n = 19)	0.2 (0.4) (n = 19)	0.8 (1.1) (n = 19)	0.4 (0.6) (n = 19)
	Unilateral	0.4 (0.5) (n = 14)	0.1 (0.4) (n = 14)	0.1 (0.3) (n = 14)	0.6 (1.0) (n = 12)	0.3 (0.5) (n = 12)
	Bilateral	1.0 (0.8) (n = 4)	0.8 (0.5) (n = 4)	0.5 (0.6) (n = 4)	1.3 (1.1) (n = 7)	0.4 (0.8) (n = 7)
Head tremor (item 4)	All	1.2 (1.5) (n = 19)	0.9 (1.5) (n = 19)	0.7 (1.4) (n = 19)	1.2 (2.1) (n = 19)	0.5 (1.1) (n = 19)*†
	Unilateral	1.1 (1.4) (n = 14)	0.9 (1.7) (n = 14)	0.9 (1.7) (n = 14)	0.8 (1.8) (n = 12)	0.6 (1.2) (n = 12)
	Bilateral	2.0 (1.8) (n = 4)	0.8 (1.0) (n = 4)	0.3 (0.5) (n = 4)	1.9 (2.5) (n = 7)	0.3 (0.8) (n = 7)
ADL ETRS (items 15–21)	All	13.7 (3.7) (n = 17)	13.6 (7.9) (n = 14)	2.4 (2.7) (n = 15)**††	17.4 (6.8) (n = 16)*	8.4 (6.0) (n = 18)**††
Hand function (items 10–14)	All	26.1 (6.4) (n = 19)	24.0 (6.9) (n = 19)	14.2 (5.6) (n = 19)**††	25.6 (7.7) (n = 17)	16.4 (6.4) (n = 17)**††

Values are mean (SD).
Significance *v* baseline: *p <0.05, **p <0.001.
Significance on *v* OFF state: †p <0.05, ††p <0.001. ADL, activities of daily living; ETRS, essential tremor rating scale.

Table 3 Effect of stimulation on treated and non-treated hemibody

Score (item from ETRS)	Hemibody	Baseline	One year		Six years
			Off stimulation	On stimulation	On stimulation
Upper limb action tremor	Treated	3.4 (0.5) (n = 22)	3.2 (0.9) (n = 22)	1.0 (0.8) (n = 23)**††	1.7 (1.1) (n = 26)**††
	Non-treated	2.8 (1.1) (n = 13)	3.2 (1.0) (n = 13)*	3.2 (1.2) (n = 13)	2.7 (1.3) (n = 12)
Upper limb postural tremor	Treated	3.0 (0.8) (n = 22)	2.6 (1.1) (n = 22)	0.5 (0.7) (n = 23)**††	0.9 (0.9) (n = 26)**††
	Non-treated	2.2 (1.1) (n = 13)	2.8 (1.3) (n = 13)	2.6 (1.3) (n = 13)	2.5 (1.0) (n = 12)
Lower limb action tremor	Treated	0.4 (1.0) (n = 22)	0.2 (0.5) (n = 22)	0.1 (0.3) (n = 23)	0.5 (0.9) (n = 26)*
	Non-treated	0.2 (0.6) (n = 13)	0.2 (0.6) (n = 13)	0.2 (0.4) (n = 13)	0.5 (0.7) (n = 12)
Lower limb postural tremor	Treated	0.8 (1.2) (n = 22)	0.1 (0.5) (n = 22)*	0.1 (0.3) (n = 23)*	0.2 (0.5) (n = 26)*
	Non-treated	0.5 (1.0) (n = 13)	0.3 (0.6) (n = 13)	0.2 (0.4) (n = 13)	0.4 (0.7) (n = 12)

Values are mean (SD).
Significance *v* baseline: *p <0.05, **p <0.001.
Significance on *v* OFF state: ††p <0.001.
ETRS, essential tremor rating scale.

(table 3). Furthermore, there was a highly significant reduction in action tremor at six years compared with stimulation OFF (p <0.001) and with baseline (p <0.001) (table 3, fig 1).

Head and voice tremor were mild at the beginning of the study (table 2). At one year, a non-significant trend for reduction in the head tremor score (item 4) with stimulation ON was noted, particularly for the patients with bilateral stimulation. At six years, head tremor was reduced from 1.2 to 0.5 (p <0.05) compared with stimulation OFF for the whole group, and from 1.9 to 0.3 (NS, n = 7) for those with bilateral stimulation. There were minimal changes in voice tremor (item 3) both at one year and at six years. However, this voice tremor reduction was slightly greater with bilateral stimulation (NS).

Activities of daily living

The action tremor is most important from a functional point of view. This is reflected in manual tasks—writing, drawing, and pouring (items 10 to 14)—which are particularly affected by action tremor. The scores for these tasks were reduced by 41% (p <0.001) with stimulation ON at one year, and by 36% (p <0.001) at six years compared with stimulation OFF. Again, the results at the one and six years follow up were significantly better than at baseline (both p <0.001) (table 2).

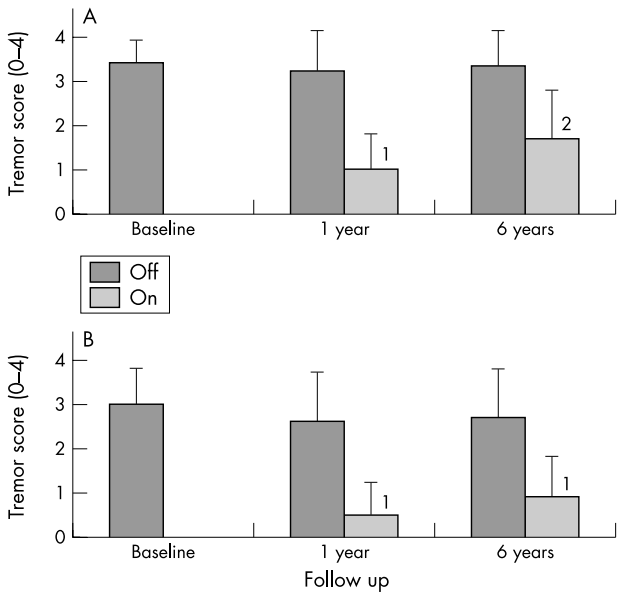

Figure 1 Essential tremor rating scale (ETRS) subscores: (A) upper limb action tremor 5+6; (B) upper limb postural tremor 5+6, for the hemibody contralateral to surgery. [1]p <0.00001; [2]p <0.00005, *v* off stimulation.

The specific ADL scores (items 15–21) were improved even more with stimulation. There was an 82% reduction compared with stimulation OFF at one year (p <0.001) and a 51% reduction at six years (p <0.001) (table 2).

Drug treatment

The overall amount of drug treatment was less at the end of the study than before it began. It had to be maintained in a few patients because of tremor on the non-operated side or because of midline tremor. One patient used primidone at the end of the study, compared with five who were using it before surgery. Five patients were using propranolol at the end of the study compared with three before it began (two switched from primidone to propranolol). Two patients were using benzodiazepines at the end compared with three at the start. The remaining patients were not using anti-tremor drugs.

Adverse events

In 16 of the 19 patients followed for six years, there were one or more adverse events or system complications (table 4). Most of these can be related to stimulation and thus disappeared when the pulse generator was turned off. The most common adverse event of this type was paraesthesiae. Dysarthria was also relatively common, particularly with bilateral stimulation. Most of the side effects were classified as mild or moderate. There was one case of severe dystonia. This problem occurred after a few years and was present only with stimulation. Because of the dystonia, the patient stopped using the pulse generator.

The perioperative and immediate postoperative complications have been reported earlier.[6] In summary, for the present subgroup of patients the following complications occurred:

- One case of mild hemiparesis during surgery but before electrode implantation; this symptom disappeared spontaneously after one day and was interpreted as a haemodynamic transient ischaemic attack.
- One case of thalamic bleeding occurred during the implantation procedure, resulting in a hemiparesis.
- An ischaemic pontine stroke occurred in one patient, some time after the implantation.
- One patient with a chronic preoperative neurosis developed a severe depression.
- Two infections occurred, both of which resolved. One of the infections started at the pulse generator and went along the extension cable. The cables were explanted and the electrode cut outside the skull. The system was later replaced. The other infection was at the electrode; the electrode was explanted and later replaced.

Table 4 Adverse events and system complications that were reported for the 19 patients included in the analysis

	Reported (n)	Resolved (n)	Ongoing (n)
Adverse events related to stimulation			
Paraesthesiae	6	3	3
Dysarthria	4	1	3
Gait disorders	3	3	–
Dystonia	1	–	1
Local adverse symptoms			
Headaches	2	–	2
Head and chest pain	1	1	–
Pain at pocket site	2	2	–
Pain at connector site	1	1	–
Local pain over pulse generator	1	1	–
Postoperative adverse events related to surgery			
Infection	2	2	–
Erosion	2	2	–
Skin irritation	2	2	–
Subcutaneous haematoma	1	1	–
Paresis	1	1	–
Lead repositioning owing to unsatisfactory effect	1	1	
Other adverse events			
Fracture left wrist	1	1	–
Fracture right clavicle	1	1	–
Subtotal	32	23	9
Hardware related adverse events			
End of battery life	5	5	
Loss of effect for other reasons	2	2	
Intermittent stimulation	1	1	
Subtotal	8	8	–
Total	40	31	9

- There were two cases of skin erosion, one of which was cured by local revision and the other by explantation of the extension cable and its replacement in a new position two months later.

System complications

There were several cases of loss of stimulation for technical reasons. All of those were resolved (table 4). Five pulse generators were replaced because of end of battery life after a mean of 70 (18) months. As the majority of the originally implanted pulse generators were still in use and functioning at the end of the study, the real mean lifetime is longer. Two pulse generators were replaced prophylactically before the anticipated end of battery life.

Stimulation parameters and electrode connections

The mean stimulation amplitude increased somewhat over time, from 2.0 V shortly after implantation to 2.3 V at one year and 2.6 V at six years. There was a small increase in mean stimulation rate from 156 Hz at baseline to 163 Hz at one year and 173 Hz at six years. The mean pulse width was 103 μs at baseline, 86 μs at one year, and 89 μs at six years.

At the end of the study, monopolar (case positive and at least one contact negative) stimulation was used for 18 electrodes and bipolar stimulation for seven electrodes. For most electrodes with monopolar stimulation, only one negative contact was used. The electrical parameters are summarised in table 5.

DISCUSSION

Since the successful treatment of essential tremor by chronic electrical stimulation of the ventral intermediate thalamic nucleus by Benabid *et al*,[1] there have been several reports on the efficacy of this method.[2–11] However, most of these studies report only short term results of about one year or less. To our knowledge, there are only three studies with systematic long term follow up of stimulation in essential tremor. Hariz *et al* described a group of patients followed for 17 months.[7] Koller *et al* recently presented long term data for a larger group of patients.[11] In their study, the mean follow up time was almost three and a half years. In the present study and in a study by Rehncrona *et al*,[13] the patients were followed for more than six years. According to Benabid *et al*,[14] thalamic stimulation becomes less effective over time in essential tremor as opposed to parkinsonian tremor because of the development of tolerance. Our present study shows, however, that good results are maintained after six years and thus seem to persist. The increase in stimulation amplitude during the first six to 12 months might reflect the diminishing microthalamotomy effect often observed after the implantation procedure, but might also be explained by a conservative approach in initial programming of the pulse generator in order to preserve its life expectancy. In the 12 month data,[6] where patients with Parkinson's disease were also reported, there was no difference in the increase in amplitude in the essential tremor group compared with the Parkinson's group. In the present study, however, a slight further increase in stimulation amplitude during the ensuing years was noted. One explanation for this increase may be a need to compensate for disease progression. The natural course of essential tremor is slow progression. Slightly increased tremor and ADL scores with stimulation turned off during the observation period reflected this. There were also slightly increased total scores with stimulation on. This increase might be a result of disease progression and could not be explained by increase in any particular subscore. An element of tolerance development cannot be ruled out, however.

The absolute stimulation amplitude in our study was 2.0 to 2.6 V during the observation time, which is lower than the amplitudes of 3.4 to 3.6 V reported by Koller *et al*.[11] A hypothetical explanation for this is that the electrodes in the present study were positioned closer to the optimal target. We also had fewer dropouts than Koller *et al*,[11] in spite of our much longer follow up time. The number of dropouts in the present study was also significant, however, and might be a confounding factor. In this group of elderly patients, significant co-morbidity during a six year follow up period

Table 5 Electrical parameters of stimulation at implant, one year, and six years follow up

	At implant	One year	Six years
Voltage (V)	2.0 (2.8) (n = 23)	2.3 (0.9) (n = 22)	2.6 (0.7) (n = 25)*
Pulse width (s)	103.0 (49.4) (n = 23)	85.9 (28.2) (n = 22)	88.8 (37.2) (n = 25)
Rate (Hz)	156.3 (24.4) (n = 23)	163.2 (24.1) (n = 22)	172.6 (19.7) (n = 25)
Monopolar	n = 17	n = 19	n = 18
No of negative contacts (1, 2, 3) per electrode	14, 3, 0	15, 3, 1	13, 5, 0
Bipolar	n = 6	n = 3	n = 7

Values are mean (SD); n = number of electrodes.
*Data for one electrode missing.

must be taken into account. The number of serious adverse events was lower in the present study than in the one reported by Koller *et al*,[11] particularly with respect to system explants. Device related complications have also been reported by Pahwa *et al* for subthalamic nucleus stimulation.[15]

The effect of thalamic stimulation is greatest for extremity tremor but there seems to be some positive effect on at least head tremor with bilateral stimulation, even if statistical significance was not achieved. Positive effects on head and voice (''midline'') tremor have also recently been reported by Obwegeser *et al*.[8] The effect of thalamic stimulation on isolated head or voice tremor remains to be demonstrated.

The traditional surgical approach to essential tremor is thalamotomy. Recently, comparative studies between thalamic stimulation and thalamotomy have been published.[9 16] The results from those studies support the use of thalamic stimulation, with respect to both efficacy and lack of side effects. Schuurman *et al* concluded that stimulation is preferable in patients who are available and willing to be followed up properly and where the cost can be afforded.[9]

The present study shows that thalamic stimulation can be an efficient and relatively safe procedure. The positive effect seems to be long lasting and maintained over more than six years at least. Compared with thalamotomy, stimulation is clearly more complicated and requires more resources, both at surgery and during follow up. A significant number of follow up visits with adjustment of the pulse generator parameters must be made. Lead fractures and erosions require surgical procedures. Eventually, the pulse generator will have to be replaced in all cases because of end of battery life. The total cost will be considerable but may be justified in these severely handicapped patients who cannot achieve adequate tremor control with the presently available drug treatments. Although to our knowledge no formal health economy studies have been done, it is likely that the cost-benefit ratio would be favourable in, for example, patients who cannot feed themselves or write.

CONCLUSIONS

Thalamic stimulation can be recommended for the treatment of essential tremor in cooperative patients with insufficient response to drug treatment. The surgery and follow up should be carried out in relatively few centres that have good knowledge of stereotactic surgery and movement disorders.

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OS, ST, and JDS evaluated the patients in their group and wrote the paper, together with FA who performed the surgical procedures in his group. Study group collaborators included a neurosurgeon and a neurologist at each centre. They evaluated and implanted the patients. They also reviewed and provided comments on the paper. Members of the group were: P Pollak, A Benabid (CHU de Grenoble, France), O Sydow , B Meyerson (Karolinska Hospital, Stockholm, Sweden), R Ekberg, S Rehncrona (University Hospital, Lund, Sweden), B Johnels, L Augustinsson (Sahlgrenska University Hospital, Göteborg, Sweden), F von Raison, J N=Guyen (Hôpital Henri Mondor, Créteil, France), F Johansson, M Hariz (University Hospital, Umeå, Sweden), M Pinter, F Alesch (AKH Wien, Vienna, Austria), J D Speelman, D A Bosch (Academic Medical Centre, Amsterdam, Netherlands).

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