The influence of electroconvulsive therapy on pain threshold and pain tolerance in major depression patients before, during and after treatment

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Abstract

Despite the findings that pain and depression are not always directly linked, enough evidence suggest that a complex relationship between pain and depression exists. Using an electronic pressure algometer placed on the sternum, the changes in pressure pain threshold (PPThr) and pressure pain tolerance (PPTol) were evaluated in 19 patients affected by refractory major depression without psychotic features, throughout a full course of electroconvulsive therapy (ECT) treatment. Measurements were done before the first treatment, after the 6th treatment and after the last treatment. After the 6th treatment, mean (±SD) PPThr increased significantly from 11.48 (±4.81) kg/cm² at baseline, to 13.7 (±5.59) kg/cm² (p = 0.0076) while PPTol did not change significantly (from 18.46 (±6.75)kg/cm² to 17.4 (±8.1) kg/cm²). At the end of the treatment course, mean (±SD) PPThr did not increase further significantly (15.06 (±5.21) kg/cm² (p = 0.0234)) while PPTol increased significantly to 21.34 (±7.8)kg/cm² (p = 0.0047). ECT’s efficacy was measured with the 21-item Hamilton Rating Scale for Depression (21-HAM-D). Mean (±SD) 21-HAM-D scores decreased significantly from 30.9 (±4.15) at baseline, to 10.47 (±5.78) (p = 0.0001) after the 6th treatment, with no further significant change at the end of the treatment course (9.94 ± 3.07; p = 0.0254). Both pain threshold and pain tolerance increased following the alleviation of the depressive disorder and a possible usefulness of ECT may be postulated for treating severe, chronic pain syndromes. However, a more significant conclusion is that the increase of the PPThr noted early during ECT treatment may serve as an early outcome possible detector of ECT efficacy in depressed patients.

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1. Introduction

Mood has been shown to have an influence on pain perception and pain tolerance (Sternbach, 1974; Merskey, 1982; Pilowsky, 1982). Reviews of the literature indicate that depression may lead to pain, pain can be followed by depression and it is possible that both pain and depression operate through the same mechanisms, mainly serotonin and noradrenaline pathways (Pilowsky, 1988; Gamsa and Vikis-Freiberg, 1991; Craig, 1994), but opioid mechanisms may also be involved (Amiaz et al., 1999; Schreiber et al., 2002). Treatment with antidepressant medications reduce pain severity and distress in nondepressed patients (Harrison et al., 1997; Schreiber et al., 2001) thus, antidepressants demonstrate effects on pain perception independently of their antidepressant effects.

Despite the findings that pain and depression are not always directly linked, enough evidence suggest that a
complex relationship between pain and depression exists (Shacham et al., 1984). There is ample evidence that a change of pain experience occurs in conjunction with certain psychiatric disorders; however, controversy arises from several studies published regarding the nature of this change (for review, see Lautenbacher and Krieg, 1994). As concluded by Lautenbacher et al. (1994), the influence of depression on pain perception appears somewhat paradoxical because both a decrease in experimental pain sensitivity and an increase in clinical pain disorders have been observed in depressed patients. This paradox may, in part derive from a different effect of depression on acute vs. chronic pain, an issue that should be addressed separately since it is far beyond the scope of our study.

The study of the response to pressure stimulation has provided an additional means of evaluating syndromes characterized by muscle and deep tissue tenderness (Fisher, 1986; Williams, 1988; Ohrbach and Gale, 1989). Pressure pain threshold (PPThr) is the minimal pressure (force), which induces pain (Vatine et al., 1993). Pressure pain tolerance (PPTol) is the pressure (force), which induces the maximal tolerable pain. The repeated measurements of the sensitivity of depressed patients to pressure applied before, during and after a course of electroconvulsive therapy (ECT) may shed a light on the paradoxical influence of depression on pain perception and tolerance. The purpose of the present study was to assess and compare pain threshold and pain tolerance initiated by pressure stimuli applied on the sternum in nonpsychotic patients with refractory depression treated with ECT at three different points during treatment: at baseline (before the first ECT), after the sixth treatment, and at the end of the course (8–12 treatments) and to compare it with our findings in other studies, performed in normal volunteers and in women during labor and in early post-partum period. A second objective was to assess a possible differential correlation between changes of these two parameters and the gradual clinical alleviation of the depression.

2. Patients and methods

This original study was carried out in accordance with Declaration of Helsinki and approved by the hospital review board. Written informed consent was obtained from each patient. Pressure algometry was applied to 19 patients (9 males, 10 females) with a mean age of 64.1 (±13.5), (range 27–79 years) who fulfilled DSM-IV (APA, 1994) criteria for a major depressive episode without psychotic features and without dementia. In order to avoid inter-patients differences attributed to different degrees of severity of the depressive episode, only patients affected by refractory depression (Nierenberg and Amsterdam, 1990) were included in the study. Before starting the first ECT each patient underwent a routine workup, which included medical and neurological evaluation, psychiatric status evaluation and a brain computerized tomography (CT) scan. The medical evaluation included physical examination, a medical history and blood tests (serum electrolytes, serum glucose, thyroid function tests, serum vitamins B1, B12, folic acid, and differential blood counts). Assessment instrument used in the psychiatric evaluation included the 21-item Hamilton Psychiatric Rating Scale for Depression (21-Ham-D) (Hamilton, 1960). In order to exclude dementia, the Mini Mental State Examination (MMSE) (Folstein et al., 1975) was used, and only patients with a score of 30 were included. In order to enhance reliability, all psychiatric assessments were done by a single physician (first author). Bilateral ECT was administered according to the recommendations of the American Psychiatric Association (APA, 1990) using a MECTA (Lake Oswego, OR) SR-1 device that delivers a brief-pulse bi-directional current (Nilsen et al., 1986). In brief, the methods include:

1. Titration of electrical charge during the first ECT treatment using the methods of limits (Sackeim et al., 1993) – although seizure duration was assessed both by the cuff method and electroencephalographic (EEG) measurements, we used the motor response of the leg to determine seizure length.

2. Subsequent ECT treatments were performed at 2.5 times the threshold energy and charge was titrated upward every second or third treatment to maintain a seizure length of 25 s.

3. Electrode placement was bilateral in all patients.

4. All patients received 100% oxygenation during the procedure and anaesthesia with methohexital (1 mg/kg) and muscle relaxation with succinylcholine (1 mg/kg).

5. Post-ECT monitoring according to established anaesthesia procedures was performed. ECT treatments were given twice weekly.

Pressure algometry was applied at the sternal manubrium since this site is devoid of overlying muscles and covered only by skin and a thin layer of fat, thus affording near direct measurement of deep bone-periosteal pain. Each patient was first examined 24 h before the first ECT treatment, then 4 h after the 6th treatment and again 4 h after the administration of the last ECT treatment. In order to enhance reliability all tests were performed by the same examiner (D.S.) (Nussbaum and Downes, 1998) and each examination consisted of two successive pressure measurements at adjacent locations on the manubrium.

The pressure algometer used in the study has been described previously (Adler et al., 1991; Vatine et al., 1993). In brief, it consists of a modified force-displacement transducer (Grass Instruments, Model FT 10) responding to a maximal pressure of 40 kgs/cm² with a
round 0.25 cm² teflon covered pressure tip connected to a Hewlett-Packard carrier amplifier (Model 8805) and linked to a dual channel recorder Hewlett-Packard (model 7702B). The recording is at the velocity of 5 mm/s, on the first channel the pressure graph is recorded, while on the second channel the patient's manual reactions are recorded. The subject activates a marker on the recorder by means of a handheld push button to signal the onset of pain (threshold) and again when pain becomes intolerable (tolerance), thus eliminating verbal delay and minimizing errors of measurement. The force manually applied through the algometer tip was increased at a rate of 4 kg/cm²/s (Fig. 1).

Change measures (delta) were calculated on 21-HAM-D, PPThr, PPTol data: one – the difference between scores before ECT and the 6th treatment; the second – the difference between scores before ECT and post-ECT.

3. Statistics

Comparisons between each two time points was performed using the Wilcoxon-Matched-Pairs-Signed-Ranks-Test. Change measures of 21-HAM-D were correlated with the change measures of PPThr and PPTol using the Spearman rho test. We assumed that the direction of the changes of 21-Ham-D would be opposite to that of PPThr and PPTol a one-tailed hypothesis, and the corresponding p-values were applied. These statistical tests were chosen in order to minimize distortion of the final results, due to the small sample.

4. Results

Nineteen patients – nine men and 10 women – were included in the study. ECT was an effective treatment for the depression evident already after the 6th treatment, as documented by the changes in the scores of the 21-HAM-D. The average 21-HAM-D score decreased significantly from 30.9 (±4.15) before ECT treatment to (10.47 ± 5.78) (p = 0.0022) after the 6th ECT treatment. Further reduction was seen at the end of treatment course to 9.94 (±3.07) but this reduction was not statistically significant (Fig. 2).

ECT induced changes in PPThr and PPTol. Average PPThr increased significantly from 11.48 kg/cm² (±7.31) (p = 0.023) before ECT to 13.7 kg/cm² (±5.59) after the 6th treatment. PPThr further increased to 15.06 kg/cm² (±5.21) at the end but this increase did not significantly differ from the 6th treatment (p along the whole ECT course = 0.0076) (Fig. 3). Average PPTol decreased from 18.46 kg/cm² (±6.75) before ECT to 17.4 kg/cm² (±8.1) after the 6th ECT treatment, and increased to 21.34 kg/cm² (±7.8) at the end of the treatment course. In this case only the change in PPTol along the whole ECT course was significant (p = 0.0047) (Fig. 4).

Both a significant affective improvement (21-HAM-D) and a significant increase of PPThr was evident at mid-treatment, and both parameters did not change further at post-treatment. PPTol changes reached statistical significance only the end of treatments.

Fig. 1. Representative tracing of gradually increasing pressure applied to the manubrium. Patient-marked pressure pain threshold (left arrow) and pressure pain tolerance (right arrow).

Fig. 2. Hamilton rating scale for depression (21-HAM-D) scores over the ECT treatment course. Differences are statistically significant (Wilcoxon-Matched-Pairs-Signed-Ranks-Test) regarding score before treatment compared to score after the 6th ECT treatment (*p = 0.002); and regarding score before treatment compared to score at the end of ECT treatment course (v*p = 0.0001).
5. Discussion

In previous studies we evaluated PPThr and PPTol in normal volunteers (Vatine et al., 1993) and in women during labor and in early post-partum period (Shapira et al., 1995). In the normal volunteers study (14 males, 10 females, mean age 38.7 ± 11.7 years), repeated PPThr values (mean ± SD) over the sternum were 20.96 ± 2.07, while PPTol values (mean ± SD) over the sternum were 33.52 ± 2.79 with no significant influence of sex or time for all measurements (sex-differences were evident at other sites, i.e. external malleoli). In the present study performed in an older population of patients (mean age 64.1 ± 13.5 years) we found baseline (pre-treatment) PPThr and PPTol values (mean ± SD) of severely (nonpsychotic) depressed patients significantly lower (11.48 ± 7.31; 18.46 ± 6.75, respectively). Moreover, even after resolution of the depression at the end of ECT treatment and a significant change in PPThr and PPTol values over the treatment period, post-treatment values of PPThr and PPTol remained significantly lower than those of normal controls (18.06 ± 5.21; 21.34 ± 7.8, respectively) (p = 0.0001). This difference may derive from the older age of the patients in this present study. However, a fourth measurement of PPThr and PPTol performed several weeks post-ECT treatment would have helped determining whether the described changes are the manifestation of age-related changes (Gibson and Helme, 2001), are due to the alleviation of depression or to a direct effect of ECT on pain mechanisms. However, since at the end of ECT treatment patients were started on antidepressant medication for prevention, we could not perform the fourth measurement since most antidepressant drugs possess analgesic properties either through combined serotonergic-noradrenergic mechanisms or through opioid mechanisms or both (Schreiber et al., 1998; Schreiber et al., 2000; Schreiber et al., 2002), thus affecting PPThr and PPTol.

Two separate issues brought us to conduct this present study in major depression affected patients. The first was a question regarding the possible use of ECT for the treatment of chronic pain. There seems to be a vast literature, mostly composed of case reports, of beneficial administration of ECT to a variety of severe and intractable pain syndromes (Mandel, 1975), among them thalamic pain (McCance et al., 1996), reflex sympathetic dystrophy (RSD) (King and Nuss, 1993) and chronic facial pain (Hampf et al., 1992). Bloomstein et al. (1996), reported on 21 patients with primary chronic

Graphs 2–4 illustrate the 21-HAM-D, PPThr and PPTol results.

A negative correlation between the changes in 21-Ham-D and PPTol at post-treatment was observed \( (r = -0.40, p < 0.05) \), indicating that the reduction of depression tended to be accompanied with an increase of the tolerance to pain. The correlation with PPTol-change at mid-treatment, as well as the correlations with PPThr were not significant (all p’s > 0.2).
pain who received ECT for concurrent affective symptoms. Twenty of the 21 patients experienced improvement in the level of pain. They conclude that ECT can be an effective treatment modality for patients who have chronic pain complicated with affective symptoms. On the other hand, Salmon et al. (1988) reported of four nondepressed patients with thalamic pain who did not benefit of unilateral ECT. However, contrary to common practice in psychiatry, they did not proceed to bilateral treatment when unilateral treatment failed, leaving conclusions difficult to interpretation. In our present study we examined depressed patients without comorbid pain syndromes, treated with ECT. Our findings suggest that during the course of ECT, pain threshold and pain tolerance increase significantly. It is unclear however, whether this is due to a relief in the depression, a direct effect of ECT on pain mechanisms, or normalization of pain threshold. At any rate, it raises the possibility that ECT could be effective in some pain syndromes.

The second reason for our study was the intriguing findings published regarding pain perception in depressed patients. Some studies found that depression is associated with decreased pain threshold and pain tolerance. Some others claimed the opposite (for review see Lautenbacher and Krieg, 1994). Moreover, the debate when an antidepressant treatment initiates significant clinical action in depressed patients or in pain patients is still unsettled. While some studies found a lag in the onset of therapeutic actions, others found all symptoms to subside at about the same time.

Discussion of the various possible mechanisms of action of ECT on the pain system is extensive, and far beyond the scope of this paper. However, it may involve effects on deep brain structures (basal ganglia, thalamus), alterations of cerebral blood flow and permeability of the blood–brain barrier, modulation of the neurotransmitter receptors (β-adrenergic receptor, and a controversial effect on serotonergic neurones) or changes in the muscarinic, cholinergic and dopaminergic neuronal systems. It may affect the coupling of G proteins to receptors, the activity of adenylyl cyclase and phospholipase C, and the regulation of calcium entry into neurones, all mechanisms involved with the opioid system.

The most striking finding of this study is the dissociation between the response of the PPThr and that of the PPTol. While pain threshold improvement followed closely the pattern of improvement of the affective state (both improving significantly after the 6th treatment, with a nonsignificant further improvement at the end of treatment course) – pain tolerance manifested a “delayed pattern” of improvement, reaching statistical significance only at the end of treatments. These findings may derive from, and be directly linked to, the componential structure of severe depressive disorder and the sequence of change in the major behavioral components of the disorder associated with ECT treatment. The clinical significance and visibility of the early behavioral change of PPThr early in the ECT treatment may indicate its possible use to predict outcome in major depression syndrome after only few ECT treatments, avoiding thus unwanted side effects of prolonged ECT treatment in nonresponders depressed patients.

Our study has several flaws: We did not use any experimental control group (which would have widen the understanding of the results and add strength to the findings), since ECT is approved in Israel only for treatment of severe forms of depression; We didn’t strengthen the experimental control (e.g., by a design using multiple baselines) since most patients were reluctant to participate in a different design of study (initially approved by the hospital review board) which would have cause more pain and last longer. We attributed the difficulty to recruit patients for the study to the severity of the depressive disorder and the difficulty of depressed patients both to accept further pain and to have patience for the assessment procedure.

Another flaw is the sample size (which is rather small) and sample age, which is of a relatively high age. This would let assume a sample of nonrepresentative “pain patients” and suffering from age-related changes in pain perception. However, our study looked at the influence of ECT on PPThr and PPTol in depressed- (and not pain-) patients, and as such the question of age has little relevance. Moreover, we did not compare the absolute values of PPThr and PPTol found in the present study with those values found in our previous study with normal (younger) controls, but just the trend of results. One last issue is the discrepancy between our findings in the present study and the robust findings in literature regarding sex differences in experimental pressure pain: sex differences were evident in our previous study in normal (younger) controls, but just the trend of results. The findings), since ECT is approved in Israel only for normal controls as well, when pain was measured with the same device and technique over the mastoid processes and external malleoli. However, when measured at the sternum, comparison between mean values of repeated examination showed no statistical difference (Vatine et al., 1993). In the present study we performed measurements at the sternum only, finding no sex-differences. More study is needed in order to validate our findings and a future study should include not only a larger group of patients and a more robust design, but it should perform pain measurements at different body sites as well.

References


