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Research progress of right unilateral electroconvulsive therapy for major depressive disorder

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Abstract: Major depressive disorder (MDD) is the most prevalent form of neuropsychiatric disorder and a leading cause of disability in many developed countries. The efficacy of ECT in the treatment of major depression has been demonstrated by numerous studies over the past decades. However, the use of right unilateral (RUL) and bilateral (BL) ECT has been controversial. Therefore, this study aimed to compare the efficacy of RUL ECT and BL ECT for the treatment of depression. We reviewed studies on major depression and found that high-dose short-pulse right unilateral ECT for depression appears to be as effective as short-pulse biphasic ECT and appears to confer some cognitive advantages.

1. Introduction

Major depression (MDD) is the most prevalent form of neuropsychiatric disorder, affecting approximately 400 million people worldwide, and is a leading cause of disability in many developed countries [1]. Epidemiological data suggest that by 2030 MDD will be in the top 3 of the global burden of disease, leading to loss of disability-adjusted life and premature death. With a 12-month prevalence of 6.6% and a lifetime prevalence of 16.2%, MDD is twice as common in women as in men and causes considerable damage. The distribution of age at onset suggests that depression is prevalent across the life span. In contrast to other chronic conditions (such as angina, arthritis, asthma, and diabetes), the condition not only leads to comparable health decline, but also to significantly greater deterioration in mean health scores when coexisting with these conditions than when the condition occurs alone.

Emerging evidence suggests that approximately 30% of patients with MDD are addicted to alcohol or nicotine, indicating a significant development of comorbid substance use disorders. MDD is also widely recognized as a risk factor for suicidal behavior. Current treatment focuses on the brain monoamine hypothesis of MDD and conventional antidepressants such as serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors that enhance synaptic levels of monoamine neurotransmitters in the brain. However, the effectiveness of these drugs is limited, and only one third of depressed

patients benefit from this treatment strategy. It takes 3-4 weeks for these drugs to take effect to produce a limited benefit on MDD symptoms.

Many patients who do not respond to standard therapies may benefit from ECT. Compared with drug therapy, ECT has a faster response and is necessary in serious situations that require emergency treatment, such as major depression at risk of suicide. The American Psychiatric Association has listed these conditions as the preferred indication for ECT. The effectiveness of ECT in the treatment of depressive symptoms has been demonstrated by numerous studies conducted over the past decades. According to Prudic [2], ECT is the most effective biological treatment currently available for the treatment of depression, as no other treatment has been shown to be superior to ECT in the treatment of depression in controlled studies to date. In fact, approximately 1.4 million people worldwide are treated with ECT each year, and treatment-resistant depression is the most common indication in Western industrialized countries. The study by Pinna et al. [3] also showed ECT as a profound treatment strategy for patients with severe and refractory neuropsychiatric disorders.

2. Electroconvulsive therapy

Electroconvulsive therapy (ECT) is a functional treatment for severe psychiatric disorders that involves the brief application of electrical stimulation to induce generalized seizures [4]. Since its development in 1938, electroconvulsive therapy (ECT) has been the most effective treatment for severe depression. Although ECT has been in practice for more than 45 years, there is still debate about which psychiatric disorders it is appropriate for, the effectiveness of treating them, the appropriate mode of administration, the potential consequences, and the amount of it. In recent decades, researchers' efforts have focused on determining the efficacy of ECT and its indications, as well as understanding its molecular mechanisms, determining the degree of side effects, and determining the optimal treatment.

ECT has and will continue to improve over the years, aiming to maintain clinical effectiveness while minimizing cognitive side effects. Variations in ECT waveforms, dosing frequency, dose, and electrode placement may in part explain the differences in patient outcomes.

3. ECT and quality of life

Studies have shown that ECT improves QOL in addition to improving patients' symptoms. One study showed that ECT was effective in improving QOL, with a significant improvement in scores on the WHOQOL-brief scale after ECT treatment. Fisher et al. used the SF-36 QOL scale when comparing hospitalized patients with depression who received ECT with those who received other treatments than ECT [5]. Both groups showed significant improvements in SF-36 scores at baseline and during discharge. McCall et al. evaluated 283 patients with depression admitted to a community hospital, also using the SF-36 scale as a measure of QOL. Improvement in QOL scores occurred in 87% of patients immediately after ECT, and 78% of patients continued to have this improvement 6 months after ECT [6]. In those patients with sustained remission of depression, improvement in QOL was maintained up to 6 months after ECT.

Other studies designed to measure QOL in patients undergoing ECT have used subscales of the BASIS-32 Psychopathology instrument. McCall et al. compared depressed patients treated with ECT with those treated with medications alone. At the 12-month follow-up, the ECT group had significantly greater improvement in scores on the Daily Living and Role Functioning (DLRF) subscale of the BASIS-32. In another study of depressed patients, significant improvements in scores on the DLRF and relating to Self and others (RSO) subscales of BASIS-32 were observed at 2 and 4 weeks after a series of ECT39 ($P<0.0001$).

4. Mechanisms of action of electroconvulsive therapy

ECT is known to affect multiple domains of the central nervous system (CNS), including neurotransmitters, hormones, neuropeptides, and neurotrophic factors. Neurotrophic factors are proteins that protect cells in the central nervous system, promote cell growth, growth of dendritic buds in the cell body, and the expression of monoaminergic receptors and stimulate monoamine production.

A specific neurotrophin, known as brain-derived neurotrophic factor (BDNF), has been measured in several regions of the central nervous system, particularly in the hippocampus. BDNF is a neurotrophin that is widely expressed in the central nervous system and plays an important role in brain development, maintenance and survival of neuronal function, and neuroplasticity.

A growing body of evidence suggests that BDNF plays a key role in psychiatric disorders, including depression. One study showed that BDNF levels were significantly lower in depressed patients compared with controls, and that serum BDNF was inversely related to the severity of depression. This reduction in BDNF appears to normalize with antidepressant treatment.

One study showed that serum BDNF levels were lower in depressed patients than in controls and increased to control levels after 12 weeks of treatment with antidepressants. Few studies have evaluated changes in BDNF in patients undergoing ECT. Marano et al. reported in a trial study that BDNF levels in plasma increased markedly from pre-ECT (mean 84.9pg/ml) to post-ECT (mean 141.2pg/ml), and this change was accompanied by marked clinical improvement (decrease in HRSD scores) [7]. This study showed an association between psychosis and percentage changes in BDNF, with higher percentage increases in BDNF in psychotic patients.

Another study assessing plasma BDNF behavior in patients with treatment-resistant major depression treated with ECT reported a marked increase in BDNF levels in patients who responded to ECT. There was a change from a mean of 8ng/ml before ECT to a mean of 15.1ng/ml in the five weeks after the start of ECT, which was not seen in patients who did not respond to ECT (mean 11.5ng/ml before ECT to 9.4ng/ml at week 5 after ECT). Bocchio-Chiaveto et al. demonstrated that BDNF plasma levels were significantly increased in patients with depression refractory to antidepressants one month after the end of the ECT course [8].

5. Advantages of right unilateral ECT

Electroconvulsive therapy (ECT) has been shown to be the most effective and rapid treatment for severe depression, but it is still not widely accepted by the general population due to its side effects such as nausea, headache, jaw pain or muscle pain and various cognitive deficits [9]. However, newer techniques, such as ultra-short right unilateral ECT, have been shown to have fewer cognitive side effects.

Other factors, such as anesthetic agents, treatment frequency (twice or three times per week) and electrode placement, etc., may be associated with different outcomes of ECT. Electrode placement is one of the most important factors affecting the therapeutic efficacy and side effects of ECT [10]. Bifrontal, bitemporal, and unilateral are the three most commonly used electrode placement modalities, and the UK ECT review panel reported that bilateral electrode placement provided somewhat better results than right unilateral placement. However, a later meta-analysis reported similar efficacy for bilateral, orthotemporal, and unilateral placement. Several other studies have reported no difference in efficacy between high-dose right unilateral and bilateral ECT, and some have shown that unilateral electrode placement on the right side is associated with a lower incidence of cognitive side effects.

Although bitotemporal electrode placement remains the most commonly used worldwide, right unilateral placement is preferred in some countries [11]. The first controlled trial of right unilateral

versus bitemporal ECT found significantly faster directional recovery and recall with right unilateral ECT, but no significant difference in depression scores. In the time that followed, many studies using different techniques and procedures produced conflicting results and failed to resolve the unilateral versus dual temporal "controversy".

To date, there has been a meta-analysis comparing the cognitive effects of short-pulse right unilateral versus bitemporal ECT, but this did not examine clinical efficacy and was not limited to randomized controlled trials. According to a systematic review and meta-analysis of seven RCTS by E Kolshus et al. [12], high-dose short-pulse right unilateral ECT appears to be as effective as short-pulse bitemporal ECT for depression and appears to have some cognitive advantages. Although short-pulsed bitemporal ECT remains the most common form of ECT worldwide, findings suggest that high-dose right unilateral ECT may be a better alternative for many patients.

6. Conclusion

The efficacy of ECT for major depression has been demonstrated by a large body of literature. Studies have shown that high-dose short-pulse right unilateral ECT for depression appears to be as effective as short-pulse biphasic ECT and appears to confer some cognitive advantages. Although short-pulsed biphasic ECT remains the most common form of ECT worldwide, high-dose right unilateral ECT may be a better option for many patients. Evidence-based options for electrode placement and pulse width substitution are now available for clinicians to prescribe ECT. There may not be a "gold standard" ECT that is currently appropriate for each patient's needs, but we suggest that right unilateral ECT could be an acceptable first-line ECT regimen for many patients.

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