DOI: 10.5455/bcp.20110904010344

The Neurosurgical Treatment of Depression: Can it Supersede Psychopharmacology?

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ÖZET:

Nöroşirürjikal depresyon tedavisi: Psikofarmakolojinin yerini alabilir mi?

Psikiyatrik hastalıkların tedavisinde psikocerrahi'nin tartışmalı bir geçmişi vardır. Fakat son yıllarda tedavi seçenekleri sınırlı olan dirençli depresyonun (DD) yönetiminde, bazı nöroanotomik hedeflerin kronik derin beyin uyarımı (DBU) ile uyarılma potansiyelini destekleyen deliller mevcuttur. DBU ile ideal klinik sonuca ulaşmak, depresyonun değişken klinik sürecinden sorumlu heterojen sinir döngülerini belirlemeyi ve bu döngülerin içinde uyarılacak düğümleri seçmeyi içerir. Bir dizi heyecan verici ön çalışma DBU'ını depresyonlu hastaların tedavisinde bir kaç farklı beyin bölgesinde kullanmıştır. DBU'nın terapotik etkilerinden sorumlu mekanizmaları hakkında süregiden tartışmalara rağmen, bugüne kadarki klinik sonuçlar bu tekniği DD'da uygun bir tedavi seçeneği olarak güçlü bir şekilde işaret etmektedir. DBU'nın psikiyatri'deki tam terapotik potensiyeli dikkatli etik yaklaşımlar ve uzun dönem plasebo kontrollü karşılaştırmalara odaklanmış gelecek klinik çalışmalarla açıklanacaktır.

Anahtar sözcükler: Psikocerrahi, depresyon, sinir döngüsü, derin beyin uyarımı (DBU), nöronal lokuslar

Klinik Psikofarmakoloji Bülteni 2011;21(3):175-8

ABSTRACT:

The neurosurgical treatment of depression: can it supersede psychopharmacology?

Psychosurgery has a controversial history in the treatment of psychiatric disorders, but in recent years there has been mounting evidence for the potential of chronic electrical deep brain stimulation (DBS) of several neuroanatomical targets in managing treatment-resistant depression (TRD), a debilitating mental illness with limited therapeutic options. Achieving optimal clinical outcome with DBS involves characterizing the heterogeneous neuronal circuits responsible for the variable clinical course of depression and selecting nodes within these circuits for stimulation. A number of exciting preliminary studies have used DBS in several discrete brain areas to treat patients with depression. Despite ongoing controversies about the mechanisms responsible for the therapeutic effects of DBS, the clinical results to date show strong promise for this technique as a feasible treatment choice in TRD. The full therapeutic potential of DBS in psychiatric practice will be revealed as future clinical studies focus on careful ethical approaches and the use of long-term placebo controlled comparisons.

Key words: Psychosurgery, depression, neurocircuitry, deep brain stimulation (DBS), neuronal loci

Bulletin of Clinical Psychopharmacology 2011;21(3):175-8

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Gönderme tarihi / Date of submission: 05 Ağustos 2011 / August 05, 2011

Kabul tarihi / Date of acceptance: 06 Ağustos 2011 / August 06, 2011

Bağıntı beyanı:
C.A.E., M.D., T.S., G.B.B., S.M.D.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
C.A.E., M.D., T.S., G.B.B., S.M.D.: The authors reported no conflict of interest related to this article

Modern psychosurgery began in the 1930s with ablative procedures such as prefrontal lobotomy for the treatment of a variety of psychiatric disorders. The unfortunate indiscriminate application of lobotomy, coupled with its unacceptable rate of morbidity, and the development of effective psychotropic medications supplemented by effective electroconvulsive therapy (ECT), led to the near complete demise of psychiatric surgical procedures by the 1960s. Following this period, a very few neurosurgical centers continued to perform stereotactic ablative procedures for patients with intractable psychiatric conditions. It was not until the last decade, however, with the emergence of deep brain stimulation (DBS) as an accepted therapeutic modality, that psychosurgery underwent a resurrection. Much of the renewed enthusiasm in psychosurgery has recently been focused on using DBS to manage treatment-resistant depression (TRD).

Over the past 20 years DBS has been used successfully in the treatment of movement disorders such as Parkinson's disease, dystonia and tremor, as well as psychiatric illnesses such as obsessive-compulsive disorder (OCD) and Tourette syndrome (1). Advantages of DBS include reversibility and adjustability, both of which were lacking in ablative neurosurgical procedures used to treat psychiatric conditions.

An increased understanding of the functional neurocircuitry of depression has revealed to clinicians and researchers alike the existence of several specific neuroanatomical targets which, as demonstrated by neuroimaging data, may be linked to particular clusters of depressive symptoms (2). The view that major depressive disorder (MDD) is the result of imbalances in a complex limbic-cortical circuit charged with the maintenance of emotional control, and that there are specific regions of the brain that display hyperactivity in MDD, set the stage for targeted DBS in the setting of TRD (3,4). The seminal example of this circuit-based approach is found in the work of Mayberg et al. (5,6), which reports functional neuroimaging data showing hyperactivity of the subgenual cingulate gyrus (SCG, aka Brodmann area 25) in depression which resolves after successful response to antidepressant medication.

The neurobiological mechanisms underlying the observed efficacy of DBS against depression in human case series remain unclear. Initial hypotheses on the mechanism of DBS centered on target inhibition, akin to a reversible lesion (7). More recently, a model of target activation resulting in local and global neuromodulation through synaptic inhibition/excitation and antidromic activation has been gaining strength with evidence from both human and basic science work (8). Moreover, animal studies support possible neurostructural dendritic modification and mechanisms of neuroplasticity as key factors responsible for behavioral changes following DBS of the nucleus accumbens (9,10). Some preliminary evidence in humans comes from a small cohort of patients treated with DBS in the ventral capsule and ventral striatum in whom specific axonal trajectories were studied in relation to post-DBS clinical outcomes (11); interestingly, all patients who achieved remission shared a common identified activated neuronal circuitry stimulated by DBS electrodes.

To date seven potential neuronal targets have been identified for TRD: SCG, nucleus accumbens, ventral caudate/ventral striatum, inferior thalamic peduncle, lateral habenula, globus pallidus internus and cerebellum (12,13). The major published case series of DBS for TRD have involved targeting the SCG6 (14,15), ventral caudate/ventral striatum (11,16) and the nucleus accumbens (17,18).

Most current studies of DBS for TRD are in good agreement regarding patient selection, technical procedures and criteria for stimulator settings. Patients considered for DBS are selected on the basis of the intractable and prolonged nature of their illness refractory to adequate trials of antidepressant medications (from at least two different pharmacological classes), psychotherapy and electroconvulsive therapy (14). A routine DBS procedure is conducted in two steps. Initially, quadripolar electrodes are implanted using a stereotactic frame under magnetic resonance imaging (MRI) guidance and then connected to a pulse generator which is implanted subcutaneously on the anterior chest wall (19,20). Most of the patients have weekly follow-ups for the adjustment of stimulation parameters in the first few months after DBS. Average settings at 3.0 - 6.0V of amplitude, 60 - 90μs of pulse width and a frequency of 130Hz appear to produce maximum clinical improvement of depressive symptoms irrespective of target (6,14,18,19). Further follow-up visits, which incorporate extensive objective evaluations of affective and cognitive functioning, are conducted on a bi-weekly or monthly basis depending on the length of the study.

Clinical reports so far on the use of DBS for TRD have shown that DBS at several neuroanatomical targets can produce a substantial and prolonged antidepressant effect (21). The largest published report of DBS for TRD to date is an open-label study of 20 patients with TRD who received bilateral DBS implantation in the SCG (14). The patients in this study were suffering from a major depressive episode at least 1 year in duration with a severity score of at least 20 on the 17 item Hamilton Depression Rating Scale (HDRS-17). In this study 60% of the patients were responders—defined as a decrease in HDRS-17 score by 50% or greater—and 35% achieved remission (defined by HDRS-17 score $\leq$ 7) at one year following surgery. Interestingly, core depressive symptoms were noted to improve more rapidly following DBS implantation compared to the neurovegetative symptoms of depression. By comparing pre- and post-operative data on cerebral blood flow attained via positron emission tomography (PET) scans, it was shown that hyperactivity of the SCG normalized over time. The same cohort of patients was followed up for periods of up to 6 years post-DBS15. The results obtained demonstrated sustained and steady benefits, with 64% of the patients being responsive to treatment and 42.9% in sustained remission at the last follow-up visit. DBS targeting the ventral caudate/ventral

striatum by Malone and colleagues (16) has revealed similar response rates, with over 50% of 15 patients experiencing a significant antidepressant effect.

DBS clearly represents a novel and exciting prospect for management of TRD, with preliminary data suggesting good efficacy. Although the optimal target of stimulation is still a matter of debate, several neuroanatomical candidate regions continue to be researched. Neuroanatomical targeting based on clinical symptomatology also remains a distinct and encouraging possibility given the complexity of the neurocircuitry involved (21). The justifiable enthusiasm in the use of DBS to help patients with treatment-resistant cases of psychiatric conditions must be tempered by the inherent risk of rare but devastating complications, such as intracranial hemorrhage, associated with an invasive neurosurgical procedure. For the time being, DBS remains a "last option" and brings with it significant ethical dilemmas in clinical psychiatric practice and research (22). Future directions will likely involve surveillance of the antidepressant effect over the long-term, placebo-controlled as well as double-blind conditions involving larger numbers of patients, and direct comparisons of the antidepressant effect of DBS at different targets (21).

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