Side Effects of rTMS Treatment

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8.1 Introduction

rTMS is generally very well tolerated. The most commonly reported side effects of rTMS treatment are the occurrence of discomfort or pain during stimulation and the development of a headache during or after treatment. Inductions of psychiatric symptoms, muscle tension or seizure are also possible.

8.2 Site or Regional Pain

Treatment-related discomfort or pain is usually experienced directly beneath the TMS coil. However, it can also be experienced in the forehead, the region of the upper eyelid or even in the upper jaw teeth. Pain is most likely to relate to trigeminal nerve stimulation and direct muscle contraction. It is also possible that head fixation during treatment sessions will produce pain through neck discomfort.

The experience of discomfort or pain is highly variable between individuals; it may be strongly influenced by coil location or orientation as well as the intensity and frequency of stimulation. When the rates of pain and discomfort in sham controlled studies were analysed, 39 % of patients receiving active treatment reported pain or discomfort compared to 15 % with sham rTMS [1]. Despite this relatively high rate, discontinuation due to discomfort is infrequent in rTMS treatment trials.

A variety of methods have been explored to reduce treatment-related discomfort. Researchers have used topical or locally injected anaesthetic agents or inserted air-filled or foam pads between the coil and the scalp surface. A substantial beneficial effect was seen with local anaesthetic injection but not with the other techniques in a pilot study [2]. The commercially available Neuronetics Ltd-manufactured rTMS device has a single-use disposable attachment designed to reduce local discomfort. However, no systematic studies have been published exploring whether this attachment has clinical benefit.

Stimulation-related discomfort may be reduced in several practical ways. First, small modifications of coil position or orientation may lessen the sensation produced with stimulation. Given the inherent inaccuracy with standard methods of

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coil localization, although it has not been systematically assessed, there is no reason to believe that small coil modifications would substantially affect treatment efficacy. Second, a decrease in stimulation intensity will reduce discomfort in most patients. Given that there seems to be a relationship between stimulation intensity and efficacy, this decrease should be limited. However, antidepressant effects of rTMS have been seen from 90 to 120 % of the RMT and may well still be produced if intensity is decreased from the higher stimulation levels.

Anxiety also appears to be a factor determining the intensity of rTMS-related discomfort. Therefore, in most patients it is sensible to begin treatment at a low stimulation intensity that is likely be tolerable to allow patients to become comfortable with the sensation. Stimulation intensity can then be progressively increased over one or several sessions. In our experience this is a more sensible approach than starting stimulation at full intensity and reducing if required. This later approach may establish a strong negative expectation and association with treatment that may be long lasting. It is important to note that discomfort may well lessen over several treatment sessions with consistently applied intensity [3, 4]. In one study, a substantial reduction in pain occurred in the first few days with a steady progressive reduction continuing throughout 3 weeks of treatment [4].

Strategies to Minimise Scalp Discomfort and Pain

- Shift coil 0.5–1.0 cm towards the midline.
- Shift coil 0.5–1.0 cm posterior.
- Rotate handle of coil ~20° towards midline.
- Reduce stimulation intensity.

8.3 Headache

Headache is the other common side effect experienced with rTMS treatment. It has been reported in about 28 % of patients provided with active treatment compared to 16 % with sham across clinical trials [1]. Headache can be reported during stimulation or afterward treatment. On occasion this does require the use of analgesic medication.

8.4 Psychiatric Complications

The major potential psychiatric complication of rTMS treatment for patients with mood disorders is the induction of mania. This has been documented across a number of case studies (e.g. [5–7]), which include treatment even in patients with bipolar disorder. Some researchers suggested that switch rates may not substantially be greater than with sham treatment left-sided rTMS, low-frequency right-sided rTMS and bilateral stimulation. Manic induction has been reported predominately in

patients with bipolar disorder but also in several patients with unipolar depression [7, 8]. Xia et al. in 2008 summarised the literature on manic induction finding only 13 cases across over 50 randomised trials [9]. The reported rates of manic switch with active treatment were only marginally greater than that seen with sham rTMS (0.84 versus 0.73 %) and low compared to what would be expected without treatment. This suggests rTMS may not elevate manic switch rates. Whatever the relationship between rTMS treatment and mania induction, it seems sensible to warn patients undergoing treatment of this possibility, particularly those with bipolar disorder. It would be reasonable to advise patients who have experienced substantial manic episodes in the past, especially episodes compromising their well-being, to take a mood stabiliser during their course of rTMS treatment.

In one case reported by George et al. [8], manic symptoms resolved when treatment scheduling was reduced from daily to every second day. We have had similar experiences with several patients who have been able to be successfully treated by reducing the intensity of treatment scheduling, despite early emerging manic symptoms.

A second, but less well-validated, concern is the potential induction of psychotic symptoms during rTMS treatment. The development of persecutory delusions was reported in a single case study of a non-psychotically depressed subject. In this instance, a causative relationship was suggested due to a close temporal relationship with treatment [10], and the possibility that it resulted from subcortical dopamine release has been raised. Regardless, if the induction of psychotic symptoms is related to rTMS treatment, it seems a highly infrequent possibility given the large number of rTMS patients who have undergone treatment in recent years without further reports.

8.5 Seizure Risk and Other Considerations

There are no other side effects consistently reported in randomised trials as occurring at greater frequency with active stimulation compared to sham. Muscle twitching was reported in 20 % of the subjects in the Neuronetics Ltd-sponsored pivotal trial, but it was not specified whether this occurred only during stimulation or whether it was a persistent effect posttreatment [11]. Muscle twitching in the contralateral arm during rTMS treatment can occur through the inadvertent placement of one wing of a figure of eight coil close enough to the motor cortex to cause neuronal depolarisation in this brain region. When muscle twitching occurs during rTMS treatment, it is important to try and differentiate whether it is arising through direct stimulation of the motor cortex or whether it could be occurring via spreading neuronal excitation from prefrontal to motor areas. The latter may be the precursor of a seizure event.

With direct motor cortex stimulation, twitching will occur during the stimulation train and cease immediately at the end of the train. Twitching should also be substantially reduced in magnitude or cease altogether with forward movement or rotation of the coil such that the posterior wing is less adjacent to the motor cortex.

Motor cortical stimulation due to spreading excitation will result in muscle twitching that persists beyond the end of the stimulation train. If this is noted to occur, treatment should cease until review. At a minimum, the review should entail remeasurement of the motor threshold to ensure that the subject is not being treated at excessively suprathreshold intensity. If spreading excitation is noted at standard stimulation doses following remeasurement of the RMT, strong consideration should be given to stopping rTMS and looking at other treatment alternatives.

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