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Perspective

Yoga: Part of a Treatment Plan for Uncontrolled Epilepsy

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Abstract

There is a need for adjunctive treatments for poorly controlled seizure disorders. In people with epilepsy, between 25% and 40% treated with antiepileptic drugs (AEDs) have uncontrolled seizures. In adults, the majority of uncontrolled seizures have a temporal lobe focus. The temporal lobes contain structures that mediate a person's response to stress. As stress is a contributing factor to seizure frequency, treatments that reduce stress should be considered in developing a treatment plan for individuals with epilepsy. Yoga practices have been associated with decreased stress, decreased cortisol, a biologic marker of stress, increased vagal activity, a biologic marker for parasympathetic activity, increased gamma aminobutyric acid, a neurotransmitter implicated in the actions of many AEDS, and decreased seizure frequency. While yoga is promising as an adjunctive treatment for epilepsy, the current quality of research regarding the use of yoga to reduce seizure frequency is of low quality. More research with well-designed controlled studies is needed to develop optimal yoga interventions to safely and effectively improve seizure control and quality of life for epileptic individuals.

ABBREVIATIONS

ACT: Acceptance and Commitment Therapy; ACTH: Adrenocorticotropic Hormone; AEDs: Antiepileptic Drugs; ANS: Autonomic Nervous System; CCK-4: Cholecystokinin-tetrapeptide; CAM: Complementary and Alternative Medicine; EEG: Electroencephalogram; GAD: Generalized Anxiety Disorder; GABA: Gamma Aminobutyric Acid; HF: High Frequency; HRV: Heart Rate Variability; HPA: Hypothalamic-pituitary Axis; MDD: Major Depressive Disorder; MRI: Magnetic Resonance Imaging; MRS: Magnetic Resonance Spectroscopy; PBN: Parabrachial Nucleus; PNS: Parasympathetic Nervous System; PTSD: Post Traumatic Stress Disorder; SNS: Sympathetic Nervous System; VNS: Vagal Nerve Stimulation

INTRODUCTION

There is a need for adjunctive treatments for poorly controlled seizure disorders. In people with epilepsy, between 25% and 40% treated with antiepileptic drugs (AEDs) have uncontrolled seizures, many experience adverse effects from medication, and some have a higher degree of psychiatric illness compared to people with other chronic illness [1,2]. The use of yoga as part of a treatment plain for seizure control deserves consideration. Yoga practices have been associated decreased stress (by self-report) [3,4], decreased cortisol (a biologic marker of stress) (2), increased vagal activity (a biological marker for parasympathetic activity) [5], increased brain gamma aminobutyric acid (GABA) levels [6], decreased anxiety and depressive symptoms (by self-report) [7], and decreased seizure frequency [8].

THE RELATIONSHIP BETWEEN EPILEPSY, STRESS, AND NEGATIVE EMOTIONS

Stress is a major trigger for seizures in individuals with epilepsy [9]. Up to 30% of seizures have been associated with stress [10]. Adults with poorly controlled seizures frequently have a temporal focus [11]. The limbic system is functionally involved in emotional regulation and structurally includes medial temporal lobe structures such as the hippocampus and amygdala, that are implicated in the stress circuit [11]. These same medial temporal structures are involved in depression, and anxiety [12]. Specific factors associated with increased seizures with a temporal lobe focus are the experience of negative emotions such as worry, anxiety, frustration or anger [10]. The anatomic location of a temporal lobe seizure focus could explain the co-morbid psychiatric disorders seen in some individuals with epilepsy. Yoga-based therapies by decreasing psychological stress and associated physiological stress reactions, could reducing the stress related risk of seizures [13].

ARIZONA EPILEPSY FOUNDATION STUDY

In 2003, a survey by the Arizona Epilepsy Foundation reported that 44% of the epileptic population had used a Complimentary and Alternative Medicine (CAM) treatment including yoga for

their seizures [14]. Twenty-two percent of responders used stress management for seizure control, and of that group, 68% perceived stress management as beneficial for seizures control. Yoga was used by 6% of responders for seizures control, and of that group, 57% perceived yoga as beneficial for seizure control. In the same study, only ten percent of healthcare professionals surveyed reported actively encouraging CAM therapies in the form of stress management or prayer.

YOGA-BASED INTERVENTIONS

Most yoga-based interventions include a combination of yoga postures (asanas), breathing exercises (pranayama) and meditation (dhyana). Numerous meditation techniques commonly used in the West that are derived from yogic traditions, such as Mindfulness Based Stress Reduction, Transcendental Meditation, and the Relaxation Response [15]. For the purpose of this discussion, meditation, relaxation, and stress reduction techniques derived from yoga will be included under the umbrella of yoga-based practices.

YOGA IS ASSOCIATED WITH REDUCED BIOLOGIC MARKERS OF STRESS

Studies have demonstrated that yoga-based practices are associated with a reduction in cortisol levels [13]. In addition, yoga has been shown to modify other biological markers of stress. Sahaja yoga has been shown to both decrease seizure frequency and decrease stress markers in patients with epilepsy, as measured by changes in galvanic skin response, blood lactate, and urinary vinyl mantellic acid markers [16,17].

GABA AGONISTS REDUCE STRESS

GABA, the primary inhibitory neurotransmitter in humans, is involved in mood regulation [18, 19]. Benzodiazepines, $GABA_A$ agonists, are used to treat acute stress and anxiety disorders [20]. Benzodiazepines inhibit the activity of the hypothalamic-pituitary axis (HPA) by blunting increases in adrenocorticotropic hormone (ACTH) and cortisol [21]. The relationship between GABA agonists and decreased stress, as measured by decreased cortisol, is demonstrated using two GABA agonists with different mechanisms of action, alprazolam and vigabatrin. Anxiety, induced by a pharmacologic challenge with cholecystokinin-tetrapeptide (CCK-4), was reduced by self-report and decreased cortisol levels after treatment with alprazolam and vigabatrin [22,23]. Thus, the following links can be made. Two agents, alprazolam and vigabatrin, that improve seizure control, increased GABA-argic activity and decreased stress. An additional link can be made between psychological stress and abnormalities in the autonomic nervous system.

AUTONOMIC NERVOUS SYSTEM (ANS) IMBALANCE

The ANS is comprised of two components. The sympathetic nervous system (SNS) responds to stress or perceived threat with arousal, fight, or flight. The SNS is counterbalanced by the parasympathetic nervous system (PNS), which induces a state of calmness, social interaction, restoration of energy, and cellular repair [24]. ANS imbalance manifested by decreased PNS activity, as observed in depression and anxiety, is associated with negative affective states [25]. Power spectral analysis of heart rate variability (HRV) demonstrates that fluctuations in the high frequency (HF) band, ranging between 0.12 to 0.40 Hz, are almost exclusively due to parasympathetic activity [26]. Accordingly, HF HRV is used as a biologic marker of parasympathetic dominance.

YOGA BREATHING TECHNIQUES AND AUTONOMIC FUNCTION

Yoga breathing can shift the autonomic balance towards a healthier sympathovagal balance and greater stress resilience by increasing PNS activity [27]. The yoga technique of slow Ujjayi (Ocean Breath) breathing (4 – 6 breaths per minute), creating airway resistance by laryngeal contraction and partial closure of the glottis, rapidly reduces SNS activity and increases PNS activity [3,4]. The Resonance Breathing Technique combines the respiratory rate that optimizes HRV (an indicator of autonomic balance) for each person (4.6 to 6.5 breaths per minute) with increased airway resistance using pursed lips during expiration [28,29]. Coherence Breathing uses 4.5 to 6.0 breaths per minute with equal duration of inspiration and expiration to increase HRV [28]. Experienced practitioners of Qigong, a Chinese form of yoga, have higher HRV than age-matched sedentary controls, with higher HRV reflecting greater resilience [30]. In summary slow yoga breathing techniques optimize ANS balance as measured by increased parasympathetic influence on HRV [5,31-33].

VAGAL NERVE STIMULATION: THE LINK BETWEEN THE PARASYMPATHETIC AND GABA SYSTEMS

Vagal nerve stimulation (VNS) was first approved for the treatment of epilepsy, and then later approved for the treatment of Major Depressive Disorder (MDD) [34, 35]. Both epilepsy and MDD have low PNS activity and low GABA activity. Furthermore, both disorders respond, as measured by decreased symptoms, to pharmacological treatments that increase GABA system activity [36-38], VNS, and yoga-based interventions [1,39]. The development of VNS as a treatment for epilepsy was in part advanced by the hypothesis that "deep breathing used by the Lamaze method could be activating stretch receptors in the lungs, and, in turn, the vagus nerve" [40]. While the mechanism through which VNS works is uncertain, studies suggest that the antiepileptic action (reducing cortical excitability) is in part mediated by widespread release of GABA and glycine into the brainstem and cerebral cortex, probably via projections from the nucleus tractussolitarius to the reticular formation, hypothalamus, amygdala, thalamus, and cerebral cortex [41]. Transcutaneous VNS via the inner ear is associated with functional magnetic resonance imaging (fMRI) changes in brain regions associated with affect and improved well-being [42].

GABA AND EPILEPSY

The "GABA-hypothesis" of epilepsy implies that reduction of GABA-ergic inhibition results in increased seizure frequency, while enhancement of GABA-ergic inhibition has an antiepileptic effect [43]. Many AEDs work in part by increasing the activity of the GABA system. Higher brain GABA levels measured by magnetic resonance spectroscopy (MRS) are associated with improved seizure control [44-46]. Studies of healthy controls

and individuals with MDD, individuals with low back pain and depression, and experienced yoga practitioners all show increases in brain GABA levels immediately after a yoga intervention [6,12,18,46,47]. These increases in GABA levels can be observed four but not eight days after a yoga class, suggesting that at least one yoga class a week is needed to maintain increases in GABA levels [47].

DISORDERS OF LOW PNS ACTIVITY AND LOW GABA ACTIVITY RESPOND TO YOGA INTERVENTIONS

Epilepsy, MDD, Generalized Anxiety Disorder (GAD), and Post Traumatic Stress Disorder (PTSD) all exhibit both low GABA states and dysregulation of the ANS, with over-activity of the SNS, and under-activity of the PNS [25,48,49]. Decreased HRV, a sign of decreased cardiac parasympathetic control has been documented in epilepsy [50], MDD [51], PTSD [52], and GAD [51]. In disorders with low parasympathetic tone, the first step in the optimization of ANS balance is to increase parasympathetic activity. Yoga practices that include postures and breathing exercises and VNS both offer methods for increasing parasympathetic tone by stimulating vagal afferents [3-5,35]. Controlled treatment trials have reported that yoga-based therapies can improve the symptoms associated with MDD, GAD, Obsessive Compulsive Disorder, and PTSD [47,53-56].

ANATOMY OF THE VAGUS NERVE

The vagus nerve (the 10th cranial nerve) is the primary peripheral nerve of the PNS. Electrical stimulation of the vagal nerve, stimulation of the inner ear canal innervated by the vagus nerve, and yoga practices can stimulate afferent vagal pathways to the central nervous system. VNS and yoga are both associated with decreased symptoms in two distinct, but comorbid populations: adults with poorly controlled epilepsy and individuals with MDD.

Vagal afferents enter the brainstem and project to the nucleus tractussolitarius which projects to the parabrachial nucleus (PBN). From the PBN, information is relayed to the amygdala and hippocampus, as well as to the thalamus that projects to the frontal lobes, insular cortex, prefrontal cortex, and amygdala [57]. Pathways from the amygdala go to the nucleus ambiguous, containing the cell bodies of the ventral vagal complex, whose myelinated pathways through Special Visceral Efferents innervates the sinoatrialnode of the heart [58]. The relative influence of this vagal pathway on respiration-linked changes in heart rate is reflected in HF HRV [18]. There are GABA interneurons in the thalamus, insular cortex, amygdala and hippocampus, as well as GABA projections from the insular cortex to the amygdala, all structures that are linked to the PNS [18,57]. One of the roles of the amygdala is to ascribe significance to a stimulus (e.g., whether it constitutes a threat) and thereby influence the extent to which the stress response system is triggered [59]. The observation of increased seizures during perceived stress, and the presence of temporal lobe foci in most cases of adult refractory seizures, leads to the hypothesis that interventions that reduce perceived stress could support reduced seizure frequency.

STATE OF EVIDENCE SUPPORTING YOGA AS A TREATMENT FOR EPILEPSY

A literature search between 1994 and 2009 using PubMed for papers with the words yoga in combination with epilepsy identified five epilepsy treatment studies that included yoga as an intervention with a control condition; randomization was not required [17,60-63]. All studies were of adults who continued to have seizures despite treatment with AEDs. The control conditions included: (1) the subject's own baseline [63]; (2) a study with three randomly assigned interventions (i.e., Sahaja yoga group that used a combination of breathing exercises and meditation; a sitting exercises group and an epileptic control condition [17]; (3) an epileptic control condition [62]; (4) an exercise control condition [61]; (5) and Acceptance and Commitment Therapy (ACT), a therapy group with meditation [60]. All five studies showed significant decreases in seizure frequency in the groups treated with yoga. The exercise control intervention and the therapy group control intervention with meditation also showed significant decreases in seizure frequency [60, 61]. A systematic review of meditation as a treatment for medical illness found strong evidence for the use of meditation in the treatment of epilepsy [15].

COCHRANE REVIEW

The 2017 Yoga for Epilepsy Review published by the Cochrane Collaboration using CONSORT criteria [64], to assess internal bias identified only two studies meeting the review criteria that included randomization; these studies were identified in the search previously discussed. The first study by Lundgren (2008) used yoga and ACT [60]. The second study by Panjwani (1996) used Sahaja Yoga, an exercise condition and an epileptic control group without an intervention [65]. Both studies reported a decrease in seizure frequency and improved quality of life. Both were deemed to have a high risk of bias regarding blinding (performance bias and detection bias). Because it is not possible to blind participants as to whether they are receiving a yoga intervention versus a non-yoga control, the criteria for blinding bias used in pharmacologic interventions should not be applied to behavioral interventions such as yoga. However, the individuals who collect and analyze the dependent variables can and should, if possible, be blinded. The lack of any new studies treating epilepsy with yoga that meet Cochrane Review Criteria since 2008 highlights the need for more studies, and for modification of requirements for blinding being used in reviews.

DISCUSSION & CONCLUSION

Use of Yoga as Adjunctive Therapy

The usual route of determining if an AED improves seizure control is to first test the agent as an adjunctive treatment to an approved AED to determine if seizure control is improved. Only after the benefit of the treatment as an adjunct has been established would it be tried as a monotherapy. The same procedures should be applied to the use of yoga as a treatment for epilepsy. Accordingly, the use of yoga as monotherapy should not be considered until the efficacy of yoga as an adjunct to an approved AED has been established.

Safety, Risks, and Contraindications

Individuals should be assessed by healthcare providers for any contraindication to the addition of yoga to their treatment regime. Although yoga-based practices are usually well-tolerated, adverse events have been reported [66]. The use of hyperventilation to induce abnormal epileptiform discharges during electroencephalogram (EEG) monitoring suggests that rapid breath practices, such as Kapalabati, should not be part of a yoga practice for individuals with epilepsy. Teaching by certified yoga instructors decreases the risk of injury [66]. The available evidence suggests that yoga is usually well tolerated and the studies specific to epilepsy do not include any reports of serious adverse events related to treatment. Although more evidence regarding safety and efficacy is needed, currently yoga-based practices could be considered as part of a comprehensive treatment plan for individuals with poorly controlled epilepsy.

LIMITATIONS

Limitations of the literature review include the small number of controlled studies, the small size of the studies, the heterogeneity of interventions, the mixed quality of the studies, and concerns about internal bias. The 2017 Cochrane Review found the two studies that met inclusion criteria to be of low quality. No new studies of yoga for epilepsy have been published since 2008. Therefore, further high quality RCT-level research is likely to have an important impact on confidence estimates of the effect of yoga on epilepsy.

CONCLUSION

The current lack of high quality studies to document the efficacy of yoga as an adjunctive treatment for seizures inadequately controlled on AEDs, or when the AED side effects are not tolerated, points to the need for larger, multi-site studies. More research with well-designed controlled studies is needed to develop optimal yoga interventions to safely and effectively improve seizure control and quality of life for epileptic individuals. Nevertheless, for practitioners interested in offering a wider range of treatment options, there is enough clinical data and neurophysiological evidence to support the use of yoga-based practices as adjunctive treatments, particularly when seizures with a temporal lobe focus are not adequately controlled by AEDs.

CONFLICT OF INTEREST

Dr. Brown and Dr. Gerbarg teach and have published Breath-Body-Mind©, a multi-component program that includes coherent breathing. Dr. Streeter is certified to teach Breath-Body-Mind©. No competing financial interests exist for the remaining authors.

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