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Review

Corpus callosotomy versus vagus nerve stimulation for atonic seizures and drop attacks: A systematic review☆

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ABSTRACT

Atonic seizures are debilitating and poorly controlled with antiepileptic medications. Two surgical options are primarily used to treat medically refractory atonic seizures: corpus callosotomy (CC) and vagus nerve stimulation (VNS). However, given the uncertainty regarding relative efficacy and surgical complications, the best approach for affected patients is unclear. The PubMed database was queried for all articles describing the treatment of atonic seizures and drop attacks with either corpus callosotomy or VNS. Rates of seizure freedom, >50% reduction in seizure frequency, and complications were compared across the two patient groups. Patients were significantly more likely to achieve a >50% reduction in seizure frequency with CC versus VNS (85.6% versus 57.6%; RR: 1.5; 95% CI: 1.1–2.1). Adverse events were more common with VNS, though typically mild (e.g., 22% hoarseness and voice changes), compared with CC, where the most common complication was the disconnection syndrome (13.2%). Both CC and VNS are well tolerated for the treatment of refractory atonic seizures. Existing studies suggest that CC is potentially more effective than VNS in reducing seizure frequency, though a direct study comparing these techniques is required before a definitive conclusion can be reached.

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1. Introduction

Atonic seizures, often called "drop attacks" [1], are identified by frequent and sudden reductions in muscle tone, which can be partial (i.e., in single muscle groups, such as the head and neck or a single limb) or generalized across all muscle groups [2]. These latter generalized cases are more dangerous, in that unpredictable falls often lead to repeated and serious trauma. Patients may be required to wear helmets, and environmental modifications are regularly used to mitigate mechanical injury from ground-level falls. Atonic seizures carry a very poor prognosis, with almost all patients having seizures refractory to multiple antiepileptic medications [3]. Roughly half of patients exhibit concomitant developmental delays [3], and atonic seizures are frequently found in patients with devastating childhood syndromes like Lennox–Gastaut syndrome and myoclonic–astatic epilepsy of early childhood (Doose syndrome) [4].

Because atonic seizures are difficult to control medically and have such a severe impact on patients, surgical therapies are often proposed for their treatment. If patients have obvious focal lesions, they can undergo resective surgery, which is potentially curative. However, patients more often harbor either diffuse parenchymal changes or nonlocalizable seizure foci. For this latter group of nonlesional patients, two palliative surgical treatments are available: corpus callosotomy and vagus nerve stimulation.

Corpus callosotomy (CC) was first described by van Wagenen and Herren in 1940 as an attempt to stop epileptic discharges spreading from one cerebral hemisphere to the other, thereby preventing generalization [5]. Callosotomy has been in continuous use since, and is most often used to treat epileptic drop attacks, though CC can also be used for Lennox–Gastaut syndrome, recurrent status epilepticus, generalized tonic–clonic seizures, absence seizures, and complex partial seizures [6]. The procedure is typically done with a midline craniotomy overlying the sagittal sinus [7]. The interhemispheric fissure is carefully dissected, and the corpus callosum is divided at its midline. The extent of callosal resection has been frequently studied, with many practitioners first resecting the anterior corpus callosum and reserving further complete resection for recurrent seizures [6,8,9]. Complete callosotomy, as opposed to anterior callosotomy, confers an estimated additional 10% improvement in seizure control for all types over partial callosotomy but is believed to carry a higher morbidity, especially in regard to the disconnection syndrome [6].

Vagus nerve stimulation (VNS) is an ostensibly less invasive method of controlling seizures, with both US FDA (1997) and CE Mark (1994) approval [10]. The procedure entails wrapping a patient's vagus nerve in a spiral-shaped electrode, with a connected pulse generator implanted below the patient's clavicle in the anterior chest. The electrode

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then delivers intermittent electrical stimulation to the vagus nerve, with the ability to manually trigger additional stimulation using an external magnet. Stimulation of the vagus nerve activates fibers projecting to the nucleus tractus solitarius, which then projects widely to the brainstem and cerebral cortex. It is these widespread connections that presumably mediate the antiseizure effects of VNS, though the precise mechanisms are still unknown.

Multiple studies attest to the efficacy of VNS, including two successful randomized controlled trials, titled E03 [11] and E05 [12], both funded by Cyberonics, Inc., the manufacturer of the VNS system. E03 and E05 both showed significant reductions in seizure frequency (24.5% and 27.9%, respectively) after three months of treatment [10]. Importantly, though, both studies were limited to the study of partial seizures; neither addressed atonic seizures as a primary endpoint. Nevertheless, many patients with mixed seizure types (including atonic seizures) were subsequently implanted and treated with VNS, which has allowed us to estimate the efficacy of VNS in treating this particular seizure subtype. Moreover, because of the perceived noninvasiveness of VNS, many practitioners have gone to VNS as a first-line treatment for atonic seizures in lieu of the irreversible corpus callosotomy. Below, we examine the evidence-based outcomes for both procedures, including their documented morbidities, and try to provide guidance for the treatment of this challenging seizure subtype.

2. Materials and methods

The PubMed database was queried on May 10, 2015, for English language articles using the following Boolean terms for CC: "callosotomy" AND (seizure OR seizures OR epilepsy) AND (atonic OR "drop attack") and for VNS: (vagus OR vagal) AND (stimulation OR stimulator) AND (seizure OR seizures OR epilepsy) AND (atonic OR "drop attack"). Only those articles with outcome data specific for atonic seizures were included. That is, articles with grouped data (multiple seizure types grouped together for composite outcomes) were excluded. Although the Epilepsy Foundation defines atonic seizures and drop attacks as synonymous [1], there is a chance that some articles included drop attacks induced by seizures other than atonic seizures (e.g., tonic and generalized) that produced a drop attack phenomenon. We, therefore, also ran a separate analysis where we excluded drop attacks and only included seizures explicitly listed as atonic seizures.

Outcomes in the original studies were grouped inconsistently (e.g., >70% seizure reduction and >50% reduction). We, therefore, regrouped the atonic seizure outcomes into (1) complete seizure freedom, (2) >50% reduction in seizure frequency, and (3) <50% reduction in seizure frequency.

Statistics were computed using SPSS version 22 (IBM Corp., Armonk, NY). Risk ratios were calculated with the χ^2 statistic, with 95% confidence intervals indicated. Group means were compared using Student's *t*-statistic.

3. Results

Eighteen articles were identified for VNS and 62 for CC. Of these, 19 articles on CC [8,13–30] and 7 on VNS [23,26,31–35] met the inclusion criteria (see the Materials and methods section), corresponding to 317 patients undergoing CC and 38 patients undergoing VNS (Table 1). Median follow-up was 2 years for CC patients and 1.5 years for VNS patients. When patients were pooled across studies, significantly more patients experienced a >50% reduction in seizures after undergoing CC (281 (88.6%) patients) than after undergoing VNS (20 (52.6%) patients), with a risk ratio (RR) of 1.7 (95% CI: 1.2–2.3). When looking at complete seizure freedom from atonic seizures, again, significantly more patients were seizure-free after undergoing CC (184 (58.0%) patients) than after undergoing VNS (8 (21.1%) patients), with a RR of 2.8 (95% CI: 1.5–5.1). Documented adverse events were far more common with VNS (e.g., 20.1% hoarseness and voice changes), compared with CC, where the most common complication was the disconnection syndrome (13.2%; see Tables 2 and 3). Severe complications were infrequent, mostly reflecting differing surgical risks (cortical disconnection and craniotomy for CC and vagus nerve manipulation for VNS) or the expected residual seizures for these palliative techniques (e.g., SUDEP; Tables 2 and 3).

Because there is concern that some authors might include under the name "drop attacks" events other than atonic seizures, we ran an additional analysis where we included only those studies that specifically analyzed atonic seizures and excluded those referencing drop attacks (Table 4). This analysis had similar results to those above, though with less power since fewer patients were analyzed. Again, significantly more patients experienced a >50% reduction in seizure frequency with CC than with VNS: 73 (88.0%) patients versus 17 (50.0%), respectively, (RR: 1.8; 95% CI: 1.2–2.5). Additionally, more patients achieved seizure freedom with CC (33.7%) than with VNS (23.5%), though this difference was not significant (RR: 1.4; 95% CI: 0.7–2.8).

4. Discussion

Atonic seizures are a severe manifestation of epilepsy, frequently refractory to antiepileptic medications. There are two predominant surgical treatments available: corpus callosotomy (CC) and vagus nerve stimulation (VNS). By examining the medical literature, we were able to evaluate the evidence supporting these methods with respect to comparative efficacy and morbidity.

Corpus callosotomy has been available as a treatment for far longer than VNS (1940s versus 1990s), which is likely responsible for the greater number of available case series available for CC patients with atonic seizures (19 studies for CC versus 7 studies for VNS). Many more studies exist for both methods in regard to general seizure control, but only the above-described subset specifically comments on atonic seizures, which is likely due to the relative rarity of this seizure subtype compared with generalized tonic–clonic and focal seizures.

While both surgical methods offer a degree of seizure control, CC appears possibly more successful than VNS, with 58.0% of patients being free of atonic seizures after CC compared with 21.1% of patients being free of atonic seizures after VNS (RR: 2.8; 95% CI: 1.5–5.1). These results also hold for seizure reduction rather than for complete seizure freedom: 88.6% of CC patients experienced a reduction in seizures of >50% versus 52.6% of VNS patients (RR: 1.7; 95% CI: 1.2–2.3).

While the above analysis offers insight into relative efficacy, there has never been a study evaluating the relative cost-effectiveness of each procedure and none concerning CC specifically. One study in 2000 reported an upward CC surgical cost of $3995 [36], while the cost of the VNS device alone was roughly £5500 (in 2006 prices) [37]. Multiple cost-effectiveness studies of VNS have been undertaken and are favorable [38,39]. However, again, there is no comparable study of CC and no comparison of the two modalities.

Surgical complications were more prevalent in patients treated with VNS than with CC, although the most prevalent complication of VNS was relatively mild: hoarseness in 20.1% of patients. The most frequent complication of CC was disconnection syndrome, reported in 13.2% of patients. Patients are often able to adapt to disconnection syndromes, but the studies did not provide clear descriptions as to the duration of this complication. Focusing on severe, potentially life-changing complications, we found that VNS was associated with SUDEP, status epilepticus, and vocal cord paralysis (Tables 2 and 3). Severe complications of CC included epidural and subdural hematomas, ataxia, hemiparesis, and one surprising partial hand amputation (from an unexpected and severe arterial line complication). There were two reported deaths in the CC cohort, both from the earliest of the cited studies, Murro et al., from 1988; one due to an unrecognized bleeding diathesis; and the other due to disseminated intravascular coagulation (DIC) [13].

While these reported complication rates for VNS and CC are low, these findings should be interpreted cautiously. Primarily, these studies

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