Current Neurology and Neuroscience Reports (2019) 19: 66
https://doi.org/10.1007/s11910-019-0975-2

MOVEMENT DISORDERS (T. SIMUNI, SECTION EDITOR)

Focused Ultrasound and Other Lesioning Therapies in Movement Disorders

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Published online: 3 August 2019

Abstract

Purpose of Review Lesioning therapies have been some of the earliest, most effective surgical treatments in movement disorders. This review summarizes recent studies, emerging modalities, and trends in lesioning procedures for movement disorders.

Recent Findings Magnetic resonance–guided high-intensity focused ultrasound (MRgFUS) is the newest incisionless technology for lesioning procedures in movement disorders. It has recent FDA approval for thalamotomy in essential tremor and tremor-dominant Parkinson disease. There are current studies exploring subthalamotomy and pallidotomy in PD. Gamma knife is another incisionless modality that has been studied for decades and remains an effective treatment, albeit with less recent studies and more risks for adverse events, in movement disorders. Radiofrequency lesioning remains an efficacious treatment, particularly for unilateral pallidotomy in PD, but has fallen out of favor compared with other modalities, particularly MRgFUS.

Summary Lesioning therapies in movement disorders have shown efficacy in treating a variety of movement disorders. Enthusiasm for their use has waned with the advent of deep brain stimulation. The recent development of MRgFUS has recentered attention on lesioning therapy and its potential. Patient preference and access to care will remain determinants in the use of lesioning therapy as more data are being collected on the long-term benefit and safety.

Keywords Focused ultrasound · Gamma knife · Radiofrequency · Thalamotomy · Pallidotomy · Subthalamotomy

Introduction to Methods of Lesioning Therapies

Lesioning therapies (LT) have successfully been utilized for the treatment of Parkinson's disease (PD), essential tremor (ET), and other movement disorders for decades. Indeed, prior to widespread levodopa use, lesioning therapies in PD were amongst the most effective therapies for motor symptom management. While lesioning therapies in movement disorders have fallen out of favor with the advent of deep brain stimulation (DBS), there has been renewed interest of late. Some of the factors in this renewed interest include the development of high-intensity focused ultrasound (MRgFUS) and gamma knife (GK) technologies. In addition, LT offer surgical options for underserved and remote populations where resources and distance can limit ongoing treatment and monitoring with alternative treatments.

This article is part of the Topical Collection on *Movement Disorders*

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Magnetic Resonance–Guided High-Intensity Focused Ultrasound

While low-intensity ultrasonography has been used for decades for diagnostic purposes, high-intensity ultrasonic lesioning was first pioneered in the 1950s. However, at that time, its use required creation of a cranial window for precise targeting. With advances in imaging techniques and computing power, MRgFUS now has the ability to deliver precise, thermal lesions accurately to deep brain structures [1, 2•, 3]. While low-intensity focused ultrasound delivers approximate power intensity of 30–1000 mW/cm^2, MRgFUS delivers over 1000 W/cm^2. MRgFUS exerts its biological effects via two main modalities: mechanical and thermal. Mechanical effects include cavitation, microstreaming, and radiation force. The cavitation effects are most well understood and can be considered gas bubbles that oscillate under high frequency until ultimately collapsing in on themselves [4]. For use in movement disorders, it is the thermal effect of MRgFUS that is used to produce clinically relevant lesions. As ultrasound waves propagate through tissues, the amplitude of the wave diminishes due to wave absorption from surrounding tissues. This results in conversion of wave energy into heat [4]. Calculations using the bio-heat transfer equation can evaluate if energy transfer can achieve thresholds high enough to achieve tissue damage to specific targets [4]. This high frequency wave is brought into a tight focus that keeps thermal effects from damaging surrounding tissues.

The current Food and Drug Administration (FDA)–approved system for MRgFUS is the ExAblate system. Patients are prepped with head shaving to prevent heat trapping and then placed in an MRI-compatible stereotactic head frame coupled to an MRI-compatible multi-element, phased-array ultrasound transducer. This has been termed MRI-guided focused ultrasound Magnetic resonance–guided high-intensity focused ultrasound (MRgFUS). Patients are awake and able to interact for clinical examination during the procedure. A total of 1024 individually adjustable hemi-circumferentially placed ultrasound elements are focused in on the target area using standard reference planning. MRI thermometry is used to accurately monitor tissue temperature levels. Acoustic energy is first applied in a subablative temperature (< 54 °C) to verify clinical effect and anatomical accuracy before an increase to temperature ranges for tissue ablation (55–60) [5] (see Fig. 1).

Gamma Knife

Lars Leksell, considered the “grandfather” of modern-day stereotactic radiosurgery, first described the idea to converge multiple beams of low-dose ionizing radiation onto one defined target point, inducing radionecrosis. This target would receive the sum total of each beam’s radiation without damage along the path of any one beam and defined the concept of stereotactic radiosurgery as we know it today [6]. Leksell and physicist Larsson developed the first GK using cobalt-60 gamma rays in 1965–1968 [6]. Today, gamma knife radiosurgery is performed by securing the patient’s head in a Leksell G frame and using computed tomography and MR imaging to set the coordinates of the radiation exposure field. As with MRgFUS treatment, there is no burr hole or incision required. During the procedure, it is not possible to confirm improvement in symptoms or determine adverse effect as therapeutic changes, and adverse events can take months to become apparent [7••, 8••]. In a baboon model using single-dose radiation of 150 Gy, imaging studies showed development of thalamic lesions after 60 days [9].

Radiofrequency

Thermocoagulation of a target by radiofrequency (RF) techniques was first reported in 1954 by Hassler and Riechart [10]. RF thermoablation is the most straightforward of the lesioning techniques to date. Patients are fitted in a stereotactic frame and targets are chosen using anatomical coordinates. Patients are traditionally awake and able to participate in examination. Once coordinates are identified, a wire is passed transcranially into the target area. The target area is confirmed using either microelectrode recording technique or macrostimulation with clinical evaluation to confirm positioning. Once target is identified, heat sufficient to result in thermocoagulation is applied from the tip of the electrode [11••]. The radiofrequency thermoablation effect spreads from the center of lesion outward, and the size and extent of that lesion are reliant on multiple factors: diameter of electrode, exposed tip length, duration, and peak temperature exposure [12].

Outcomes of Lesioning Therapies

Focused Ultrasound

Essential Tremor

Thalamotomy The US Food and Drug Administration first approved MRgFUS use for thalamotomy in essential tremor. The approval was largely based on the study published by Elias et al. [13•]. In this multi-center, randomized controlled trial, 76 patients were randomized to FUS intervention versus sham procedure. The CRST and QOL in Essential Tremor Questionnaire were administered at baseline and at 1, 3, 6, and 12 months. Primary endpoints were change in upper limb tremor at 3 months as rated by blind raters. After 3 months, sham could cross over to treatment. At 3 months, there was a drop in CRST from 18.1 to 9.6 in treated versus sham-control ($N = 20$) patients. This improvement persisted at 12 months. The most common adverse events were gait ataxia (36%) and paresthesias or numbness (38%). Of these, 9% and 14% persisted at 12 months, respectively [13•]. An open-label 24-month extension study of this cohort included 67 of the original 76 participants. In this extension study, the prior reported tremor reduction was maintained at 24 months. No new adverse events were reported at 24 months, and of the adverse events at 12 months, 2 patients had resolution of previous paresthesia and dysergia [14]. A subgroup extension study carried out at Seoul, S. Korea, followed participants in the initial controlled trial that were enrolled at this site for a 4-year follow-up period. A total of 15 patients were enrolled in the original trial at that site, of these 12 participated in the 4-year follow-up period. They again found that tremor reduction results were maintained at the 2, 3, and 4-year follow-ups.

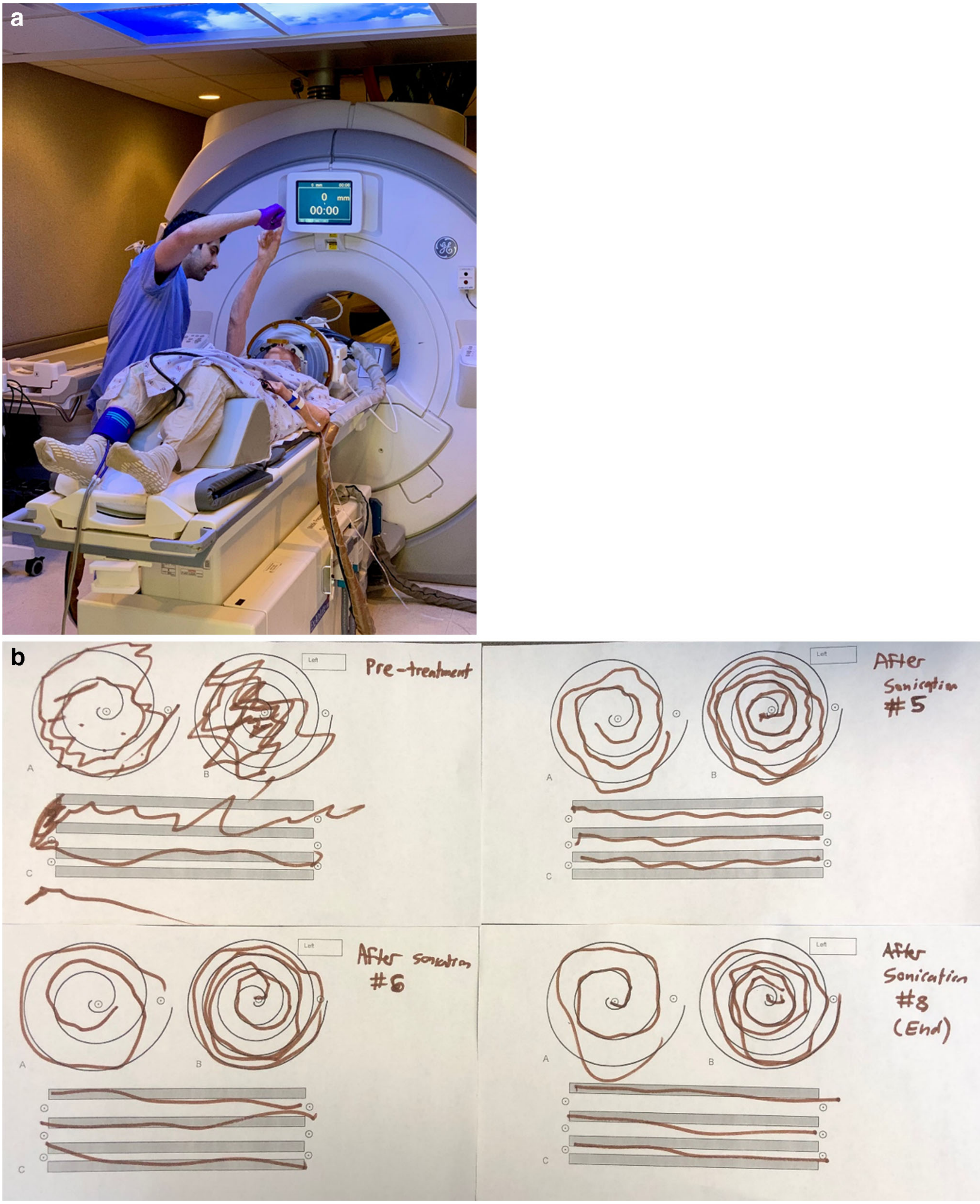

Fig. 1 **a** Intraprocedural tremor testing in an MRgFUS procedure after delivering of a sublesioning sonication. Such lower temperature sonications typically produce transient clinical effects and are used for target verification and assessment of adverse effects prior to delivery of the final lesion. **b** Comparison of Archimedes spiral and line drawings during MRgFUS thalamotomy for essential tremor. Clockwise from the top left: baseline left hand assessment; assessment after the fifth sonication (sublesional energy); assessment after final sonication; and assessment after sixth sonication (sublesional but with greater energy than sonication 5)

There was slight worsening of tremor overtime, but there continued to be statistically significant improvement compared with baseline [10]. This is not incongruent with other lesioning studies such as GK thalamotomy or RF ablation that also report slow recurrence and/or progression of tremor with time. This is also seen with DBS of the VIM [15].

Parkinson's Disease

Subthalamotomy Martínez-Fernández et al. published a pilot study of 10 asymmetric PD patients who underwent MRgFUS subthalamotomy [16]. The primary endpoint of this study was safety and improvement in motor features of PD at 6-month follow-up using the MDS-UPDRS part III [16]. Adverse events were notably transient except for one case of off-medication limb dyskinesia that persisted, though greatly reduced in severity by month 6. Eight of ten patients had greater than 30% reduction in MDS-UPDRS motor scores for the contralateral treatment side at 6 months. Rigidity and tremor seemed to have the largest improvements. In a post hoc 12-month assessment, there seemed to be sustained benefit of treatment. This pilot study suggests that MRgFUS has a similar clinical benefit as previously described radiofrequency subthalamotomy [13, 17].

There is currently an ongoing study of unilateral MRgFUS subthalamotomy with sites in Madrid and Charlottesville, USA (NCT03454425 and NCT02246374). As with the pilot study, this larger study is assessing improvement in earlier PD symptoms with tremor predominance.

Thalamotomy The approval of the US Food and Drug Administration (FDA) of MRgFUS thalamotomy for treatment of essential tremor in summer 2016 raised the question if FUS thalamotomy may likewise offer safe and efficacious treatment of tremor in tremor-predominant PD. A number of studies have been reported. A pilot clinical trial enrolled 27 patients who were randomized to sham ($N = 7$) or treatment ($N = 20$) and assessed at 1 and 3 months by a blinded investigator and at 12 months unblinded. The primary outcome measure was changed in on-medication-treated upper limb tremor score as measured by Clinical Rating Scale for Tremor A+B (CRST A+B) at 3 months. The sham treatment group had a 22% improvement in CRST A+B scores compared with 62% in the treated group. Most adverse effects were transient and included finger paresthesia, ataxia, and orofacial paresthesia though paresthesia persisted at 1 year in 19% of patients and ataxia in 4% [18••].

Similarly, Zaaroor et al. in Israel reported their experience in unilateral MRgFUS thalamotomy in 9 tremor-predominant PD patients. They found the UPDRS III mean scores decreased from 24.9 to 13.4 ($p = 0.009$) at 6-month follow-up [19••]. Again the most common adverse events were paresthesias and ataxia, none of which persisted past 3 months in this group. The US FDA added PD tremor as an indication to the aforementioned approval of MRgFUS thalamotomy procedure in late 2018.

Other Targets One of the earliest experiences in PD with MRgFUS started in 2011 targeting the pallidothalamic tract. That study recruited 13 medically refractory PD patients. They divided patients into a group that received a single sonication application during procedure ($N = 4$) and a group that received multiple (4–5) sonications during procedure ($N = 9$). The latter group had an average 60.9% reduction in UPDRS versus 7.6% in the former [15].

A multi-center pilot safety and feasibility study looking at unilateral MRgFUS pallidotomy is currently underway and projected to complete later this year (NCT02263885). This is recruiting patients with markedly asymmetrical symptoms with severe ON dyskinesia +/− OFF dystonia. The primary outcome measure is incidence and severity of adverse events. The secondary outcome measure is change in UPDRS and UDysRS at 3 and 12 months.

Others Movement Disorders

Studies for other neurologic disorders such as epilepsy, obsessive-compulsive disorder, Alzheimer's disease, Huntington's disease, focal dystonia, and neuropathic pain are also underway in various early stages of development [20, 21].

Gamma Knife Stereotactic Radiosurgery

Parkinson's Disease

GK has limited published efficacy data in PD aside from tremor control. There have been reports of successful unilateral radiosurgical pallidotomy in PD. Young et al. published a report in the 1990s randomizing patients to traditional radiofrequency or GK pallidotomy. They found similar efficacy in terms of rigidity and bradykinesia improvement and similar AE profile [22]. There have been sporadic reports and small series of unilateral and bilateral GK subthalamotomy and pallidotomy in PD, but we have not been able to identify recent, high-quality studies using GK in PD [23, 24].

Tremor Control—PD and ET

GK Thalamotomy In one of the first multi-center prospective studies of GK thalamotomy which analyzed 59 tremor-predominant PD patients, they found a significant tremor reduction in 81% of patients using UPDRS as an outcome. The median time to symptom improvement was 6 months, and at 24 months, 58% of those treated rated a 0 on the tremor component of UPDRS III [8••, 25]. This result was reproduced in a later study of 27 tremor-predominant PD patients which showed a 50% improvement in tremor at 23 months [26]. One of the largest studies assessed 161 ET patients using the Fahn-Tolosa-Marin scale and found improvements were highly significant at follow-up as long as 60 months [8••, 27]. In the recently published International Stereotactic Radiosociety practice guidelines review looking at all published studies of SRS treatment for tremor of all cause, they found that tremor response in PD and ET was similar between groups [8••, 23]. The time to clinical response varied from weeks to months, and the total mean complication rate was 17.4% with high variability in the severity of adverse events. It is important to emphasize that complications may present months or years after treatment. The factors that were associated with a higher risk of complications included a larger volume of brains treated and higher treatment doses. Thus, the recommendation for a maximum dose of 130–150 Gy was made [8••].

Radiofrequency Thermal Ablation

Parkinson's Disease

Pallidotomy Pallidotomy was first explored as early as the 1940s and 1950s as lesioning therapies in PD moved from cortical targets to pallidal and thalamic ones [28]. With further experience and study, unilateral pallidotomy is one of the most efficacious procedural therapies in all of neurosurgery. Based on the work of Latinen and colleagues, multiple trials have supported the benefit and relative safety of unilateral pallidotomy [29]. However, with the advent of deep brain stimulation, this procedure has fallen out of favor and there have been no recent additions to the literature regarding unilateral radiofrequency pallidotomy.

Subthalamotomy While STN DBS is a standard surgical approach, subthalamotomy may be an option where DBS infrastructure is not accessible to patients, including limited availability of ongoing programming of the DBS system. One of the largest case series to highlight the effectiveness of unilateral STN lesioning was carried out by Alvarez et al. between 1995 and 2004 [17]. This study treated 89 PD patients with unilateral lesions and followed them for a period up to 36 months ($N = 25$). They found levodopa daily doses were significantly reduced post-surgery 45%, 36%, and 28% at 12, 24, and 36 months, respectively. UPDRS III "OFF" scores were significantly reduced at 12 (50%), 24 (30%), and 36 months (18%); 14 patients developed post-operative hemichorea-ballism of which 8 required pallidotomy. Other adverse effects included mild dysarthria (4.4%), scalp infection (3.3%), seizure (2.2%), and asymptomatic bleeding along the track (3.3%) [14].

Bilateral subthalamotomy has been less well studied. In 2008, Morello et al. reported a series of sixteen patients randomly split between bilateral STN DBS and bilateral subthalamotomy [30]. Benefit as defined by UPDRS scores was similar between the groups at 1 year. Neuropsychiatric outcomes were likewise similar between the groups. One DBS subject had significant hemorrhage and died, and one lesioning subject had disabling left hemiballism necessitating rescue pallidotomy at 3 months post-treatment. At a year, overall dyskinesia scores were similar between the groups. While this was a well-conducted study, the number of subjects was small and so larger conclusions of comparative efficacy and safety between bilateral STN DBS and bilateral subthalamotomy cannot be made based solely on this study.

Conclusion

The three main lesioning modalities in movement disorders are MRgFUS, GK, and RF thermoablation. Although there are limited head-to-head comparisons between these modalities and, perhaps more importantly, with deep brain stimulation, each has demonstrated efficacy in ET and PD when applied unilaterally.

The incisionless therapies, MRgFUS and GK, both have the advantage of not requiring a cranial incision and anesthesia, thus offering a potentially attractive alternative for patients who are not comfortable with the need for burr hole. Additionally, risk of hemorrhage appears to be lower with the non-incisional therapies.

In terms of clinical monitoring intraprocedurally, MRgFUS and RF thermoablation involve real-time assessments of benefit and AE prior to delivery of a final lesion. This allows for more precise clinically based targeting that may maximize benefit and reduce adverse effects. MRgFUS also augments this clinical assessment with near-real-time MR thermography, which further enhances target accuracy. At experienced centers, outcomes with GK lesioning can be as good as with MRgFUS and RF, but there is limitation with GK in that this is an imaging-only-based treatment and the effects of the treatment, as well as adverse effects, develop over days to weeks. There is rationale to the argument that AEs with GK may be less pronounced due this slower lesion development, which may allow time for compensatory neuroplasticity changes to occur. However, this has not been demonstrated in head-to-head reports.

The role of each of these modalities for delivering bilateral lesions in ET and PD is unclear. The risk of bulbar, coordination, and cognitive adverse effects is significant and has led to bilateral deep brain stimulation remaining far and away the preferred procedure in patients who need bilateral treatment. With advances in imaging and real-time clinical assessments intraprocedurally, there is a new interest in exploring the safety and efficacy of bilateral lesioning procedures, particularly with MRgFUS.

In terms of safety, these procedures are generally well tolerated. It is important to note that in MRgFUS unilateral thalamotomy in essential tremor and PD, gait ataxia and limb incoordination were seen transiently in a large proportion of subjects and remained persistent in a small but notable percent more persistently. As such, patients who have prior balance dysfunction may not be the optimal candidates for MRgFUS.

In summary, each of these lesioning treatments can safely provide benefit in ET and PD in carefully selected patients. Owing to its adjustability, deep brain stimulation remains the preferred procedural treatment in both diseases, and this is unlikely to change in the foreseeable future. That said, lesioning therapies provide alternative treatments for patients who are reluctant to have deep brain stimulation, those where general anesthesia may not be tolerable, and for patients who do not have reliable access to DBS infrastructure for follow-up visits.

Compliance with Ethical Standards

Conflict of Interest Hannah Walters and Binit B. Shah each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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