Navigated Repetitive Transcranial Magnetic Stimulation or Brunnstrom Hand Manipulation: Which Treatment is More Effective in Stroke Cases?

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Summary

Objective: We investigated the effects of navigated repetitive transcranial magnetic stimulation (rTMS) and Brunnstrom hand manipulation (BHM) on hand function in stroke cases.

Methods: This trial used a randomised, double-blinded sham-controlled design with a 3month follow-up. In total, 21 subjects who had suffered a stroke at least 1 month earlier were recruited. The cases in the treatment group received real rTMS(1 Hz rTMS at 90% resting motor threshold, 25 min) over the hand area of the motor cortex in the unaffected hemisphere, determined with navigation. The treatment group(10 cases) received real rTMS, and the control group(11 cases) received sham rTMS, for 10 days. Cases in both groups underwent BHM and upper extremity exercises. Upper extremity motor function was measured with the upper extremity Fugl-Meyer Assessment(UE-FMA) and hand skills were evaluated with the Jebsen-Taylor Hand Function Test(JTT). All outcomes were measured before treatment and 10 days, 1 month, and 3 months after treatment.

Results: No significant difference was found between the two groups in terms of their UE-FMA total, upper arm, or wrist scores at any of the four measurement times(p ≥ 0.05). There were significant differences among the cases in the treatment group in terms of their mean UE-FMA(total, upper arm, wrist, hand) scores(p ≤ 0.05). Intragroup comparisons conducted at the same times revealed significant differences among the cases in each group in terms of JTT scores for the affected hand(p ≤ 0.05).

Conclusions: These findings indicated that BHM after navigated rTMS resulted in improvements in hand function in stroke cases.

Key words: Transcranial magnetic stimulation, stroke, Brunnstrom hand manipulation

Navigasyonlu Repetetif Transkraniyal Manyetik Stimulasyon veya Brunnstrom El Manipulasyonu: Hangi Tedavi İnome Olgularında Daha Fazla Etkiliidir?

Özet

Amaç: Çalışmamızın inme olgularında navigasyonlu repetetif transkraniyal manyetik stimulasyon (rTMS), ve Brunnstrom el manipulasyonunun (BHM) el fonksiyonlarına etkilerini araştırmak için planlandi.

Yöntem: Bu çalışma randomize çift kör sham-kontrollü 3 aylık izlem çalışmasıdır. Çalışmaya en az bir ay önce inme geçirmiş 21 olgu alındı. Tedavi grubu olguları navigasyonla belirlenen etkilenmemiş hemisfer motor korteks el bölgesine gerçek rTMS (1Hz, dinlenme motor eşiğinin % 90'ı, 25dk) aldı. Tedavi grubu (10 olgu), gerçek rTMS ve kontrol grubu (11 olgu), sham rTMS 10 gün boyunca alındı. Her iki grubun olgularına BHM ve üst ekstremite

Sonuçlar: Dört ölçüm zamanında, iki grubun UE-FMA toplam, üst kol ve el bileğinin puanları arasında anlamlı fark belirlendi (p<0.05). Tedavi grubu olguları arasında, UE-FMA (toplам, üst kol, el bileği, el) skorlarında anlamlı fark vardır (p<0.05). Aynı zamanlarda grup içi karşılaştırıldığında, etkilenmiş elin JTT skorları açısından her bir grubun olguları arasında anlamlı farklılıklar saptandı (p<0.05).

Karar: Bulgular gösteriyor ki navigasyonlu rTMS sonrası BHM inme olgularında el fonksiyonlarının geliştirilmesine yol açar.

Anahtar Kelimeler: Transkraniyal manyetik stimulasyon, inme, Brunnstrom el manipulasyonu

INTRODUCTION

Stroke is a major cause of disability worldwide(27,28). Several neurological functions may be impaired by stroke; the most common impairment is motor disability contralateral to the stroke lesion side(15).

In patients with stroke, activity in the affected hemisphere is disrupted not only by the damage caused by the stroke itself but also by inhibition from the unaffected hemisphere, which further reduces the excitability of the affected hemisphere(18,47). Thus, various strategies have been developed that aim to enhance motor recovery(19,29,39). Motor recovery after stroke is related to neural plasticity, which refers to the ability of the brain to develop new neuronal interconnections, acquire new functions, and compensate for the impairment(3,17,27). The standard neurophysiological facilitation techniques used for hemiplegic upper limbs have not been confirmed to promote the functional recovery of hemiplegic limbs(4,31,38,46).

The idea of using rTMS to improve motor function in cases with stroke is based on interhemispheric inhibition, in which the contralesional hemisphere might inhibit surviving corticomotor systems by transcallosal inhibition. Repetitive transcranial magnetic stimulation (rTMS) is used to modulate cortical excitability(5,16,34,44). Few studies have compared the results of rTMS and exercise in stroke cases and the literature also includes no study comparing the results of rTMS and Brunnstrom hand manipulation (BHM). Therefore, the purpose of this study was to compare the effects of navigated rTMS combined with BHM in stroke cases.

MATERIAL AND METHODS

Cases

In total, 21 stroke patients aged between 18 and 90 years were enrolled in this study. The inclusion criteria were first time unilateral ischemic stroke, > 1 month after the onset of stroke, Brunnstrom stage 2–6 for the hand and fingers in the affected upper limb, no cognitive impairment, and a pretreatment Mini-Mental State Examination (MMSE) score of > 26. Exclusion criteria included haemorrhagic stroke, history of seizures, pathological conditions referred to as contraindications for rTMS in the guidelines (e.g. intracranial implant), and severe aphasia.

Of the 87 cases initially considered, 66 were excluded for reasons such as a history of epilepsy and multiple strokes (Fig. 1). Participants were randomised by means of a 1:1 allocation to the treatment or control group. Allocations were stored in sealed, numbered envelopes and opened only at the time of recruitment.
**Study Design**

The study used a randomised, double-blinded, placebo-controlled design. Treatment was performed by the first researcher and evaluation of the cases was carried out by the second researcher, who was blinded to group assignment. The subjects were not informed regarding whether the rTMS was real or sham. The treatment group (n = 10) was administered real navigated rTMS (25 min) plus BHM (45 min) by the first researcher, and the control group (n = 11) was administered sham rTMS (25 min) plus BHM (45 min).

All treatments were performed for a total of 10 days (5-day implementation, 2 days off (weekend), 5-day implementation). All subjects were instructed in “do-it-yourself” exercises and provided with a home program.

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**Figure 1: Flow chart of the study**
Measurements

Cognitive function was measured with the MMSE, upper extremity motor functions were measured with the upper extremity Fugl-Meyer Assessment (UE-FMA), and hand skills were assessed using the Jebsen-Taylor Hand Function Test (JTT). Subjects were evaluated while in a sitting position on a stool.

The MMSE is a standardised instrument for the bedside evaluation of cognitive function. It consists of a questionnaire with 11 items that assesses orientation, memory (registration and recall) and attention, as well as calculation, language, and construction functions. The maximum total score on the MSSE is 30 points, with scores below 24 indicating cognitive impairment (10, 45).

The UE-FMA is a disease-specific performance-based measure. In clinical practice, the UE-FMA is also useful for planning, and evaluating the results of, treatment. All aspects are scored on a three-point ordinal scale. The upper extremity measure is scored out of 66, with subscores for the upper arm (36), the wrist (10), and the hand (14), and up to 6 points awarded for coordination and speed of movement (7, 12-14, 36).

The JTT is a widely used instrument for assessing functional hand motor skills (20). We included six of the seven JTT subtests.

Application of Navigated Repetitive Transcranial Magnetic Stimulation (rTMS)

The subjects received rTMS over the hand area of the primary motor cortex in the unaffected hemisphere, determined with navigation by the first researcher, in the TMS laboratory after their resting motor thresholds (rMT) were detected (MagPro X100; Medtronic, Dusseldorf, Germany). In each treatment session, 1,500 pulses of 1 Hz rTMS were applied to the motor cortex in the unaffected hemisphere. Dosing parameters were based on previous studies. Sham stimulation was performed with a coil that imitated the sound of the real TMS coil. Stimulation parameters were chosen in accordance with current safety guidelines for rTMS (43, 48). Subjects in the control group underwent exactly the same that was applied to the treatment group, for 10 days, except that they were delivered sham rTMS. BHM (45 min) was administered by the first researcher to both groups immediately after the navigated rTMS.

Brunnstrom Hand Manipulation (BHM)

Brunnstrom motor training (BMT) is widely used by physical and occupational therapists in clinical practice. BHM uses synergistic muscle linkage and reflexive movements to achieve voluntary control of hand and finger movements (36, 41).

This study was approved by the local Ethics Committee (Ethical committee for Human Research, University Hospital Protocol Number 2012/15-06). Informed consent was obtained from all subjects before inclusion.

Data Analysis

The data were found to be normally distributed by the Kolmogorov-Smirnov test. Levene's test was used to check for homogeneity of variance. Demographic and clinical characteristics were assessed by frequency analysis. To assess categorical variables, Fisher's exact $\chi^2$ test and Pearson's $\chi^2$ test were used. For all four assessment time points (pre-treatment, 10 days after treatment, 1 month after treatment, and 3 months after treatment), and for both groups, the non-parametric Mann-Whitney U-test was used to evaluate the relationships between continuous independent and dependent variables. Using Friedman's variance analysis, It was determined that there was no statistically significant difference between the treatment group and the control group in terms of the four-time measurement average. To evaluate the effect of the navigated rTMS on hand function in both groups, repeated-measures ANOVA was
performed for the three UE-FMA measurements (upper arm, wrist, hand), and the F and p values for the JTT time in the affected hand were taken into consideration by applying the Greenhouse-Geisser correction.

An alpha level of $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were conducted using the SPSS software (ver. 20.0; SPSS Inc., Chicago, IL, USA).

**RESULTS**

The demographic characteristics of the cases are presented in Table 1. When the treatment and control groups were compared, no significant difference was found in the mean UE-FMA upper arm, wrist, or total scores before, 10 days after, 1 month after, or 3 months after treatment. A significantly higher pre-treatment UE-FMA hand score was observed in the control group compared to the treatment group ($p = 0.023$; Table 2).

There were significant differences among the treatment group cases in UE-FMA upper arm ($p = 0.015$), wrist ($p = 0.002$), hand ($p = 0.001$), and total score ($p = 0.004$) before, 10 days after, 1 month after, and 3 months after treatment (Friedman test).

There were also significant differences among the control group cases in UE-FMA wrist ($p = 0.007$), hand ($p = 0.004$), and total score ($p = 0.047$) before, 10 days after, 1 month after, and 3 months after treatment (Friedman test).

There was no significant difference among the control group cases in UE-FMA upper arm scores ($p = 0.296$) before, 10 days after, 1 month after, or 3 months after treatment (Friedman test).

When the affected and unaffected mean total JTT times of the treatment and control groups were compared, there was no significant difference before, 10 days after, 1 month after, or 3 months after treatment ($p \geq 0.05$; Mann-Whitney U-test; Table 3).

Analysis of the treatment group cases revealed a significant difference in mean total JTT times in the affected hand before, 10 days after, 1 month after, and 3 months after treatment (treatment group $p = 0.041$). When the mean total JTT times in the affected hand – before, 10 days after, 1 month after, and 3 months after treatment – were compared among the control group cases, a significant difference was found ($p = 0.007$; Friedman test).

To evaluate the effect of rTMS on the upper extremity in the treatment and control groups, repeated-measures ANOVA was performed including all UE-FMA scores (upper arm, wrist, hand) and time points (before, 10 days after, 1 month after, and 3 months after treatment). In the analysis, the effects of time ($F_{3.54} = 11.677$, $p = 0.001$) and group were significant ($F_{3.54} = 3.652$; Greenhouse-Geisser corrected $p = 0.041$).

To evaluate the effect of rTMS on hand skills, the treatment group and the control group were assessed by ANOVA including the JTT test results at all four time points. The effect of time was significant ($F_{1.18} = 5.120$; $p = 0.035$ with sphericity assumed) but there was no significant group effect.
<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n=10)</th>
<th>Control group (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>55.70±14.92</td>
<td>64.54±9.38</td>
<td>0.158</td>
</tr>
<tr>
<td>Gender (female:male)</td>
<td>3.7</td>
<td>5.5</td>
<td>0.659</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.72±3.54</td>
<td>25.73±2.34</td>
<td>0.159</td>
</tr>
<tr>
<td>Brain side affected by stroke</td>
<td>R: 5</td>
<td>L: 5</td>
<td>0.397</td>
</tr>
<tr>
<td>Time after stroke (month)</td>
<td>10.45±21.80</td>
<td>24.50±23.88</td>
<td>0.890</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.30±2.58</td>
<td>28.54±1.95</td>
<td>1.000</td>
</tr>
<tr>
<td>rMT</td>
<td>45.80±5.57</td>
<td>41.09±1.81</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

* p≤0.05

rMT: resting motor threshold
Table 2. The UE-FMA points of the cases (upper arm, wrist, hand, total point)

<table>
<thead>
<tr>
<th>Fugl Meyer Assessment (FMA)</th>
<th>Treatment group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UE-FMA upper arm pretreatment</td>
<td>20.70±9.96</td>
<td>26.27±8.75</td>
<td>0.191</td>
</tr>
<tr>
<td>UE-FMA upper arm posttreatment 10th day</td>
<td>25.60±9.74</td>
<td>28.36±8.52</td>
<td>0.375</td>
</tr>
<tr>
<td>UE-FMA upper arm posttreatment 1st month</td>
<td>26.00±9.54</td>
<td>28.09±8.94</td>
<td>0.502</td>
</tr>
<tr>
<td>UE-FMA upper arm posttreatment 3rd month</td>
<td>27.80±8.37</td>
<td>26.36±12.25</td>
<td>0.879</td>
</tr>
<tr>
<td>UE-FMA wrist pretreatment</td>
<td>4.60±3.27</td>
<td>5.81±3.15</td>
<td>0.414</td>
</tr>
<tr>
<td>UE-FMA wrist posttreatment 10th day</td>
<td>5.50±4.11</td>
<td>5.90±3.17</td>
<td>0.887</td>
</tr>
<tr>
<td>UE-FMA wrist posttreatment 1st month</td>
<td>6.10±3.78</td>
<td>6.45±3.29</td>
<td>0.971</td>
</tr>
<tr>
<td>UE-FMA wrist posttreatment 3rd month</td>
<td>6.00±3.68</td>
<td>5.63±3.66</td>
<td>0.969</td>
</tr>
<tr>
<td>UE-FMA hand pretreatment</td>
<td>6.10±4.12</td>
<td>9.00±3.30</td>
<td>0.023*</td>
</tr>
<tr>
<td>UE-FMA hand posttreatment 10th day</td>
<td>7.90±5.40</td>
<td>10.63±3.52</td>
<td>0.434</td>
</tr>
<tr>
<td>UE-FMA hand posttreatment 1st month</td>
<td>8.50±5.06</td>
<td>11.09±3.70</td>
<td>0.485</td>
</tr>
<tr>
<td>UE-FMA hand posttreatment 3rd month</td>
<td>10.10±4.14</td>
<td>10.09±3.70</td>
<td>0.877</td>
</tr>
<tr>
<td>UE-FMA total point pretreatment</td>
<td>33.6±17.20</td>
<td>44.90±14.98</td>
<td>0.091</td>
</tr>
<tr>
<td>UE-FMA total point posttreatment 10th day</td>
<td>41.5±19.40</td>
<td>48.09±15.32</td>
<td>0.549</td>
</tr>
<tr>
<td>UE-FMA total point posttreatment 1st month</td>
<td>42.8±19.40</td>
<td>48.54±15.73</td>
<td>0.800</td>
</tr>
<tr>
<td>UE-FMA total point posttreatment 3rd month</td>
<td>46.5±16.80</td>
<td>43.90±21.37</td>
<td>0.820</td>
</tr>
</tbody>
</table>

*p≤0.05
DISCUSSION

Stroke is a serious condition that leads to disability worldwide. In ~70–80% of stroke cases, dysfunction is seen in the upper extremities, to varying degrees (28). Fischer et al. reported that upper extremity dysfunction occurred, particularly in the hand region, in ~60% of stroke cases (8).

Post-stroke loss of function in the upper extremity, and particularly in the hand, affects the ability to perform activities of daily life and the quality of life (15). In our study, the hand functions that are sometimes neglected in stroke rehabilitation, due to the slow recovery of the hands, were the focus. Foley et al. stated that neurodevelopmental approaches, such as Bobath therapy, BHM and proprioceptive neuromuscular facilitation (PNF), which are used for the treatment of hemiparetic upper extremities, do not perform other therapeutic approaches; furthermore, evidence that the frequency of treatment improves upper extremity function in the short run is not certain (9). Pandian and colleagues compared BHM and Carr Shepherd’s motor relearning program in the hand rehabilitation of 30 chronic stroke cases with an approximate stroke duration of 35 months, and stated that, while both hand protocols were effective, BHM was more effective in the rehabilitation of hands in chronic stroke cases (36). In light of these data, BHM was used in our study.

Our evaluation of hand function, in terms of the JTT times of affected hands, showed that the mean total time in both groups decreased 10 days after treatment, 1 month after treatment, and 3 months after treatment, thus indicating some recovery. Comparison between the groups showed no statistically significant difference in affected hand JTT times. The assumed negative effects of excessive activity in the unaffected hemisphere on the affected hemisphere, and the loss of transcallosal inhibition from the affected hemisphere towards the unaffected hemisphere, are important in post-stroke dysfunction. Regulation of interhemispheric interactions, by increasing the excitability of the affected cortex or inhibiting the excitability of the unaffected cortex, could support neurorehabilitation programs (5,34,42).

### Table 3. The JTT points of the cases

<table>
<thead>
<tr>
<th>Jebsen-Taylor Test of Hand Function (JTT)</th>
<th>Treatment group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>JTT affected hand pretreatment</td>
<td>53.70±92.34</td>
<td>76.00±77.49</td>
<td>0.277</td>
</tr>
<tr>
<td>JTT affected hand posttreatment 10th day</td>
<td>45.60±69.09</td>
<td>42.00±30.61</td>
<td>0.638</td>
</tr>
<tr>
<td>JTT affected hand posttreatment 1st month</td>
<td>35.15±48.62</td>
<td>35.59±24.20</td>
<td>0.612</td>
</tr>
<tr>
<td>JTT affected hand posttreatment 3rd month</td>
<td>17.15±21.20</td>
<td>33.90±32.47</td>
<td>0.197</td>
</tr>
<tr>
<td>JTT unaffected hand pretreatment</td>
<td>11.30±110.00</td>
<td>10.73±110.00</td>
<td>0.032</td>
</tr>
<tr>
<td>JTT unaffected hand posttreatment 10th day</td>
<td>10.90±109.00</td>
<td>11.09±122.00</td>
<td>0.944</td>
</tr>
<tr>
<td>JTT unaffected hand posttreatment 1st month</td>
<td>11.50±115.00</td>
<td>10.55±116.00</td>
<td>0.724</td>
</tr>
<tr>
<td>JTT unaffected hand posttreatment 3rd month</td>
<td>10.05±100.50</td>
<td>10.95±109.50</td>
<td>0.733</td>
</tr>
</tbody>
</table>
stroke cases has been developed on the basis of this mechanism. Reports show that implementation of low-frequency rTMS in the motor cortex of the unaffected hemisphere reduces the pathologically increased transcallosal inhibition towards the affected motor cortex. It has been shown that paretic extremity function can be improved in this manner(6,11,32-35,43).

The purpose of the 1 Hz (low frequency) navigated rTMS used in our study was to produce inhibition in the unaffected hemisphere and help in hand recovery. The benefits of rTMS in motor recovery after stroke have been shown in previous studies(25,30). Seniow et al. studied 40 hemiparetic stroke cases and administered 1 Hz (1,800 beats) 30 min real rTMS to the intact hemisphere in the treatment group, and placebo rTMS in the control group; both groups were provided with 3 weeks of motor education(42). The evaluation covered the pre- and post-treatment periods, including up to the third month after treatment. Seniow et al. found no significant difference between the groups in terms of hand function when evaluated with the Wolf motor function test (WMFT), and also reported that the effect sizes in both groups were small. Given their findings, they suggested that producing inhibition in the hemisphere not affected by rTMS, during early neurorehabilitation of upper extremity hemiparetic cases, was not an evidence-based method. Although our study shows similarities in terms of the methodology, we instead targeted the unaffected hemisphere motor cortex hand region using navigated rTMS. This probably explains why we obtained an rTMS effect that differed from that of Seniow et al. Also, as shown by the repeated-measures ANOVA, there was further post-treatment recovery, as evaluated by UE-FMA, in group receiving rTMS. While both groups achieved recovery by means of BHM, a group comparison of recovery showed that the rTMS group achieved better recovery.

We did not observe any significant difference between the groups in the mean total JTT time in the affected hand at any of the four time points. However, the mean total JTT time in the affected hand were reduced in both groups, from the pre-treatment period up to 10th day after treatment, and then continued to decline until the third month after treatment. Accordingly, we suggest that the significant recovery of the hand in both groups, in terms of fine motor skills and speed of movement (treatment group, p = 0.041; and control group, p = 0.007) is notable given that JTT scores reflect the ability to perform activities of daily life. Moreover, the pre-treatment UE-FMA hand scores in our treatment group were lower than reported previously in the literature when rTMS was implemented.

In our study, the rTMS performed was “navigated rTMS” with MRI guidance, in contrast to previous studies. The reason for using navigated rTMS is that it allows for local stimulation of the desired region in the brain(40). In this way, we were able to stimulate the unaffected hand hemisphere region in the motor cortex during each session, such that standardisation was ensured by stimulating the same point each time(1). A 2012 study sought to detect cortical excitability changes in stroke recovery using navigated rTMS in 14 cases and reported the prognostic data(37). While studies using navigated rTMS are rare in the literature, there is no reported stroke rehabilitation study that used navigated rTMS. We believe that our study contributes to the literature in this regard. We are of the opinion that the use of navigation will be beneficial in future rTMS studies.

The BHM method that we used is preferred by physiotherapists and focuses on the motor recovery of the hand. However, when the literature is examined, it can be seen that, although the Brunnstrom method has long been used, there are few studies that used a randomised controlled design.
Kim et al. compared the effects of rTMS at 1 Hz in a 15-min session with 30-min range of motion (ROM) exercises in the hand. A comparison of our study with that of Kim et al. shows that their study included fewer cases produced only short-term (i.e. over a 6-day period) results\(^\text{26}\). Moreover, the BHM method that we implemented offered more extensive and specific rehabilitation than ROM exercises. That rTMS made an additional contribution – even after the apparently optimal rehabilitation achieved with our BHM method – leads us to think that rTMS should probably be implemented in stroke rehabilitation. Our study, and similar studies in the literature, suggest that the combination of rTMS and physiotherapy shows a synergistic effect.

A literature review showed that low-frequency rTMS in combination with occupational therapy has been used recently to improve motor function\(^\text{21-24}\). Kakuda et al. combined low frequency rTMS and occupational therapy for the treatment of chronic stroke cases (stroke that occurred at least 1 year earlier) with visible upper extremity paresis. They found that this rehabilitation combination was effective, depending on the severity of the stroke.

Various TMS implementation methods have been reported. These methods aim to produce motor cortical inhibition with low-frequency (1 Hz) rTMS, followed by motor cortical facilitation at higher frequencies (5 Hz and above), to increase neural activity\(^\text{2,34}\). Our study showed that 1 Hz rTMS in addition to BHM significantly increased recovery in stroke cases. It can be seen from the literature that, in stroke cases, differing results have been obtained with rTMS versus physiotherapy. We believe that physiotherapists who specialise in neurological rehabilitation should learn to apply navigated rTMS, and use it in clinical research – and for the treatment of patients – in conjunction with exercise programs (the efficacy of which has been demonstrated previously).

**CONCLUSION**

In our study, recovery in stroke cases in both groups was seen until 3 months following the treatment. BHM alone, and BHM after navigated rTMS, were both effective methods for stroke rehabilitation.

**Conflict of interest**

The authors confirm that there is no conflict of interest relevant to this work or to the preparation of this manuscript.

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