Effects of flexor reflex stimulation on gait aspects in stroke patients. A pilot study

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Abstract

Background

Gait deficits are very common after stroke and therefore an important aspect in poststroke rehabilitation. A currently little used method in gait rehabilitation after stroke is the activation of the flexor reflex (FR) by electrical stimulation of the sole of foot while walking. The aim of this study was to investigate the effect of FR stimulation on gait performance and gait parameters in stroke patients within a single session of flexor reflex stimulation using Incedo™.

Methods

Twenty-five patients with subacute (n = 14) and chronic (n = 11) stroke participated in the study. Motor functions were tested with a 10-meter walk test (10mWT), a 2-minute walk test (2minWT), and a gait analysis. These tests were performed with and without Incedo™ within a single session in randomized order.

Results

This study showed that stroke patients walked significantly faster in 10mWT and a longer distance in 2minWT with Incedo™ compared to without electrostimulation (p < 0.03). The gait parameters remained unchanged except for the step length. A subgroup analysis indicated that subacute and chronic patients responded similarly to the stimulation. There was a correlation between the degree of response to electrostimulation while walking and degree of improvement in 2minWT (r = 0.50, p = 0.01).

Conclusions

This study is the first to examine FR activation effects in chronic stroke patients and suggests that stimulation effects are independent of the time since stroke. A larger controlled clinical trial is warranted that addresses issues as the necessary number of therapeutical sessions and for how long stimulation-induced improvements outlast the treatment period.

Trial registration:

The trial was retrospectively registered in German Clinical Trials Register. Clinical trial registration number: DRKS00021457. Date of registration: 29 June 2020.

Background
The most common pattern of walking impairment poststroke is hemiparetic gait (1). Hemiparesis stands out as very frequent and widely recognized impairment that had been reported in approximately 65% of patients (2). Gait recovery is an important aspect of stroke rehabilitation and a primary goal for most patients (3–5), because gait is of fundamental importance in the activities of daily living (6). Thus, for improvement of poststroke gait impairment, numerous rehabilitative training methods have been developed, such as overground walking, cycling, treadmill walking, balance and cardiorespiratory training, repetitive standing exercise, proprioceptive neuromuscular facilitation, repetitive transcranial magnetic stimulation and electrostimulation (7–16).

Eliciting the flexor reflex (FR) by electrical stimulation of the sole of foot has been described as a method of gait rehabilitation poststroke, but scientific evidence of the effects is limited (17–20). To the best of our knowledge, there are only four studies that have investigated the effect of FR stimulation during gait training in stroke patients. Three of these studies investigated the effect of electrical FR stimulation during gait training in subacute stroke patients and found positive effects of the treatment on walking speed (17–19) and gait parameters (17, 19). A recently published case report demonstrated a positive effect of FR stimulation during gait training in terms of walking speed and stride length in a severely affected chronic stroke patient (20).

Moreover, to our knowledge there are no studies testing the effect of FR stimulation on various aspects of walking in poststroke patients (subacute and chronic) in a single session. There are several studies that have investigated the effects of FR activation during walking in hemiplegic patients (21–23). However, these studies focused on technical and methodological issues, such as electrode locations (21–23), different stimulation onset times (23), stimulation frequency (Hertz) and pulse duration (milliseconds) (21).

The aim of this study was to examine the effect of FR stimulation during walking in subacute and chronic stroke patients within a single session. Two hypotheses were tested:

- The gait performance (10-meter walk test and 2-minute walk test) can be changed within a single session of flexor reflex stimulation using Incedo™.
- The gait parameters (gait analysis) are modified within a single session of flexor reflex stimulation using Incedo™.

## Methods

### Subjects

Overall 203 subacute (< 6 months after stroke) and chronic stroke (≥ 6 months after stroke) patients were identified as potential participants in this study from January 2020 to May 2022. Figure 1 shows the selection process in the study.

Fig. 1 shows the selection process in the study.
Inclusion criteria were unilateral lower extremity paresis resulting from a stroke (ischemic or hemorrhagic), an age of at least 18 years, ability to understand the instructions and to give informed consent for the participation in the study. Furthermore, patients had to be able to stand freely and walk without assistance and orthoses for at least 10 meters, basically corresponding to the Functional Ambulation Category 3. Exclusion criteria were prior history of neurological illnesses or psychiatric conditions, lack of compliance, epilepsy, patients with heart pacemakers, severe heart or lung diseases, cancer, pregnancy, and skin lesions in the area where the electrode is positioned. Both inpatients and former patients from the department of Neurorehabilitation (Kliniken Schmieder Allensbach, Germany) were recruited to participate in this study.

After screening inclusion and exclusion criteria 45 patients participated in a pre-investigation. The Incedo™ system (Nordic NeuroSTIM ApS, Aalborg, Denmark) was presented to the patient and tested on the patient. The Incedo™ system was used for eliciting the FR. The system consists of an impulse generator, electrodes, and a sensor. The electrodes are attached to the patient's sole of the foot. The sensor is placed in the patient's shoe. As soon as the sensor recognizes the initiation of a step, a signal is sent to the impulse generator, which produces an electrical stimulation through the electrode. The FR is activated to cause the movements of the hip, knee and ankle joints during the swing phase. For participation in the study it was required that (1) a visible flexor reflex is triggered in the affected leg while sitting, (2) the patient tolerated the electrostimulation well, and (3) the patient can walk safely without a foot drop orthosis. If these criteria were met, the patient had enough time to get used to the device while walking. The patients walked with Incedo™ for up to 30 minutes.

After this pre-investigation 25 stroke patients were included in the study (Table 1). The other 20 patients had to be excluded.
Table 1
Demographic and clinical data

<table>
<thead>
<tr>
<th>Category</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong> (male/female)</td>
<td>16/9</td>
</tr>
<tr>
<td><strong>Age (years)</strong>(^a)</td>
<td>62.8 ± 13.1</td>
</tr>
<tr>
<td><strong>Phase</strong> (subacute/chronic)</td>
<td>14/11</td>
</tr>
<tr>
<td><strong>Affected side</strong> (right/left)</td>
<td>9/16</td>
</tr>
<tr>
<td><strong>Ischemic stroke / hemorrhage</strong></td>
<td>21/4</td>
</tr>
<tr>
<td><strong>Time since incident in subacute patients</strong></td>
<td>(9.2 ± 4.5)</td>
</tr>
<tr>
<td><strong>Time since incident in chronic patients</strong></td>
<td>(150.6 ± 113.2)</td>
</tr>
<tr>
<td><strong>Barthel Index</strong> (points)(^a)</td>
<td>66.6 ± 19.4</td>
</tr>
<tr>
<td><strong>Foot drop orthosis in everyday living</strong></td>
<td>17/8</td>
</tr>
</tbody>
</table>

\(^a\)Values are presented as mean ± 1 standard deviation

Experimental procedure

Motor functions were tested with a 10-meter walk test (10mWT), a 2-minutes walk test (2minWT), and a gait analysis. These tests were performed with and without Incedo™ in randomized order. The randomization was done using a coin. Patients had a five-minute break between these two examinations.

The 10mWT has been shown to be reliable and valid (24). The performance is closely correlated with measures of strength, balance, and physical activity (24). For 10mWT, the individuals were asked to walk 10 meters ‘as fast as possible’. Performance time was measured in seconds.

The 2minWT is a popular and well-established walking test to obtain a detailed impression of walking ability (25). However, the gold standard of endurance testing is considered to be the 6-minute walk test (26). Since some patients participating in this study were unable to walk for longer than two minutes we selected the 2minWT. In addition, the 2minWT can be well compared to the 6-minute walk test (25, 27–29). The distance walked in two minutes correlates well with the 6-minute walking distances (28). Particularly, the 2minWT is probably best for documenting the patient’s self-selected walking speed, because it minimizes fatigue effects (28). For 2minWT, participants were requested to walk as far as possible for two minutes on a 30-meter-long course. The distance they covered was measured in meters.

In addition, the threshold value and the stimulation stimulus intensity of Incedo™ during the measurements were recorded in the study protocol. The perception of the electrical stimulus was defined as the threshold value. Furthermore, the visible reaction to the stimulation of the FR was recorded both while sitting and
walking. The assessment included four assessment levels: good response, moderate response, slight response and no response. It was also noted whether patients walked with or without devices such as a cane during the walking tests. Moreover, it was recorded whether patients were wearing an orthosis in everyday life.

All patients underwent 3D gait analysis (RehaGait system, HASOMED GmbH, Magdeburg, Germany) over a distance of 30 meters. The equipment includes two inertial sensors, which were mounted on the dorsum of the foot. The inertial sensors contain tri-axial accelerometers for measuring acceleration and tri-axial gyroscopes for measuring the angular velocity. Two sets of gait parameters were obtained for each patient: spatiotemporal (stride duration, cadence, stand phase, swing phase, single support, double support) and kinematic gait parameters (stride length, heel strike angle, toe off angle, maximum food height and maximum circumduction).

In addition, motor and sensory functions of the lower extremities were examined. A muscle function test (30) was used to test the muscle strength of the leg. The muscle strength was tested during the main movements in the hip, knee, and ankle joints of the affected side (hip flexion/extension, hip abduction/adduction, knee flexion/extension, dorsiflexion/plantar flexion). Six grades from 0 (no evidence of contractility) to 5 (normal muscle strength) are used. In the somatosensory test, patients were asked whether they felt a difference between touching the sole and the dorsum of the foot of the affected side compared to the non-affected side. The non-affected side was rated as 100%.

After the measurements, patients were asked about their impression regarding various aspects of the electrical stimulation. The questionnaire consisted of eight questions:

1. Did you have any concerns about treatment with this device?
2. Was the electrical stimulation pleasant?
3. Was wearing the device comfortable?
4. Did you feel pain during the electrical stimulation?
5. Did you feel pain after the training session?
6. Do you feel this electrical stimulation as being beneficial?
7. If possible, would you train with the device for a longer period of time?
8. Do you recommend this device for others?

A visual analogous scale ranging from 0 to 10 was used to quantify the patient's answers.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows (Version 28.0.0.0 (190)). The data was first tested for normal distribution using the Shapiro-Wilk test. Differences in normally distributed parameters between with and without Incedo™ were detected using Student's t-test for paired samples. Differences in non-normally distributed parameters between with and without Incedo™ were
analyzed using Wilcoxon signed-rank test. Correlations between numerical and ordinal data were assessed using Spearman's correlation analysis. The level of significance for all tests was set at p < 0.05.

Degree of improvement. Finally, the percentage of change that occurred between with and without electrostimulation variables was calculated. For this purpose, the following equation was applied (5):

$$|\text{Degree of improvement}| = \left( \frac{\text{Value with Incedo} - \text{Value without Incedo}}{\text{Value without Incedo}} \right) \cdot 100\%$$

Results

The descriptive data of the muscle function tests of the paretic leg and the somatosensory function tests of the foot are presented in Table 2.

<table>
<thead>
<tr>
<th>Category (affected side)</th>
<th>MV ± SD</th>
<th>Range (min. – max.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle strength in hip flexion (points: 0–5)</td>
<td>3.4 ± 0.7</td>
<td>1–4</td>
</tr>
<tr>
<td>Muscle strength in hip extension (points: 0–5)</td>
<td>3.7 ± 1.1</td>
<td>1–5</td>
</tr>
<tr>
<td>Muscle strength in hip abduction (points: 0–5)</td>
<td>3.2 ± 0.9</td>
<td>2–5</td>
</tr>
<tr>
<td>Muscle strength in hip adduction (points: 0–5)</td>
<td>3.5 ± 0.8</td>
<td>2–5</td>
</tr>
<tr>
<td>Muscle strength in knee flexion (points: 0–5)</td>
<td>3.2 ± 1.2</td>
<td>0–5</td>
</tr>
<tr>
<td>Muscle strength in knee extension (points: 0–5)</td>
<td>3.9 ± 0.9</td>
<td>2–5</td>
</tr>
<tr>
<td>Muscle strength in dorsiflexion (points: 0–5)</td>
<td>2.3 ± 1.3</td>
<td>0–4</td>
</tr>
<tr>
<td>Muscle strength in plantar flexion (points: 0–5)</td>
<td>2.5 ± 1.4</td>
<td>0–5</td>
</tr>
<tr>
<td>Sensitivity of the sole of the foot (%)</td>
<td>78.6 ± 24.3</td>
<td>20–100</td>
</tr>
<tr>
<td>Sensitivity of the dorsum of the foot (%)</td>
<td>78.6 ± 26.4</td>
<td>10–100</td>
</tr>
</tbody>
</table>

MV mean value, SD standard deviation, min. minimum, max. maximum

The muscle strength was reduced on the affected side, in particular for dorsiflexion and plantar flexion in the ankle joint followed by knee flexion, hip abduction and hip flexion. The patients showed an average sensitivity of almost 80% on both the dorsum and sole of the affected leg compared to the unaffected side.

17 patients were wearing a foot drop orthosis and 18 patients used assistive devices such as a cane or walker in everyday life. During the walk tests and the gait analysis, patients walked without an orthosis
and without support from the therapist. However, 15 patients used a cane and 3 a walker throughout the testing.

On average the threshold value for Incedo™ was 8.6 mA ± 2.7 mA and the stimulus intensity during the tests was 30.2 mA ± 8.2 mA. Overall 11 patients showed a good response to stimulation of FR in both during sitting and walking. Ten patients demonstrated a good response to stimulation of the FR while sitting but only moderate response while walking. One patient showed a good response to stimulation of the FR while sitting but only slight response while walking. One other patient presented a moderate response while sitting but only slight response while walking. Two patients showed a slight response to electrical stimulation of FR using Incedo™ while sitting and no response to the stimulation of the FR while walking.

Table 3 presents the results for the 10mWT and 2minWT with and without Incedo™.

<table>
<thead>
<tr>
<th>Functional test</th>
<th>MV ± 1SD</th>
<th>p-Value</th>
<th>Degree of improvement (%)</th>
<th>MV ± 1SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mWT without Incedo™ (s)</td>
<td>17.0 ± 11.4</td>
<td>p = 0.01a</td>
<td>7.4 ± 12.1</td>
<td></td>
</tr>
<tr>
<td>10mWT with Incedo™ (s)</td>
<td>15.0 ± 8.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2minWT without Incedo™ (m)</td>
<td>86.3 ± 36.8</td>
<td>p = 0.03b</td>
<td>6.3 ± 10.7</td>
<td></td>
</tr>
<tr>
<td>2minWT with Incedo™ (m)</td>
<td>90.0 ± 36.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10mWT 10-meter walk test, 2minWT 2-minute walk test, s seconds, m meters, MV mean value, SD standard deviation

aWilcoxon signed-rank test for non-normally distributed parameters

bPaired sample t-test for normal distributed parameters

In the 10mWT, a significant difference was found between walking with and without Incedo™. Patients walked on average 7.4% faster with electrostimulation compared to without electrostimulation. Nineteen patients improved their performance while using Incedo™. In one patient, the performance remained unchanged and five patients walked slower during electrical stimulation.

The 2minWT showed a significant change related to the Incedo™ use. Patients walked on average 6.3% longer distance within two minutes with the Incedo™ system than without. Nineteen patients improved their performance while using Incedo™. In three patients no changes in the 2minWT could be observed during electrostimulation. In three other patients, the Incedo™ stimulation led to deterioration in performance.
Overall, 15 patients improved their performance in both functional tests while using Incedo™. Three patients showed improvement in one and remained unchanged in the other test. Five patients showed improved performance in one functional test but worse performance in the other. One patient's performance remained unchanged in one and decreased in the other test. Another patient showed a decrease in performance during electrostimulation in both tests.

The analysis showed that there was no correlation between the degree of response to electrostimulation while walking and the degree of improvement in 10mWT ($r = 0.15, p = 0.5$). However, there was a correlation between the degree of response to electrostimulation while walking and degree of improvement in 2minWT ($r = 0.50, p = 0.01$).

Subacute and chronic patients behaved very similarly. In both subgroups, performance improved when using the Incedo™. Neither the two values nor the degree of improvement in the 10mWT and the 2minWT were different between both groups ($p > 0.30$).

In the RehaGait system-based gait analysis, one parameter showed a significant difference during walking with and without Incedo™. Step length was significantly shorter while walking with electrostimulation than without it (0.77 ± 0.21 m versus 0.79 ± 0.21 m, $p = 0.04$). All other gait parameters (cadence, stand phase, swing phase, single support, double support, stride length, heel strike angle, toe off angle, maximum food height and maximum circumduction) remained unchanged. Furthermore, a trend towards increasing the cadence while walking with Incedo™ was observed (83.4 versus 85.1 steps per minute, $p = 0.09$).

The subgroup gait analysis for subacute and chronic patients showed a significant difference in step length for chronic patients during walking with versus without Incedo™ (0.81 ± 0.20 m versus 0.84 ± 0.21 m, $p = 0.047$). All other parameters remained unchanged in these two groups ($p > 0.08$).

Table 4 presents the results of the patient questionnaire. All patients reported that they had no concerns about the treatment with Incedo™. They found the electrostimulation rather pleasant and definitely comfortable. Patients had no pain either during or after the treatment and if possible, they would exercise with the Incedo™ for a longer period of time. Furthermore, they considered the device to be effective and recommendable to others.
Table 4
The patient’s perspective: questionnaire answered by the patient

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you have any concerns about treatment with this device?</td>
<td>0.3 ± 1.0</td>
<td>0–4.5</td>
</tr>
<tr>
<td>Was the electrical stimulation pleasant?</td>
<td>5.9 ± 2.2</td>
<td>2.0–10</td>
</tr>
<tr>
<td>Was wearing the device comfortable?</td>
<td>9.5 ± 1.2</td>
<td>4.3–10</td>
</tr>
<tr>
<td>Did you feel pain during the electrical stimulation?</td>
<td>0.5 ± 1.6</td>
<td>0.0–6.8</td>
</tr>
<tr>
<td>Did you feel pain after the training session?</td>
<td>0.0 ± 0.0</td>
<td>0.0–0.0</td>
</tr>
<tr>
<td>Do you feel this electrical stimulation as being beneficial?</td>
<td>8.1 ± 2.5</td>
<td>0.0–10</td>
</tr>
<tr>
<td>If possible, would you train with the device for a longer period of time?</td>
<td>8.2 ± 2.6</td>
<td>0.0–10</td>
</tr>
<tr>
<td>Do you recommend this device for others?</td>
<td>8.8 ± 2.4</td>
<td>0.0–10</td>
</tr>
</tbody>
</table>

Answers were given on a visual analogous scale ranging from “0” corresponding to “not at all” to “10” corresponding to “yes, full agreement”

MV mean value, SD standard deviation, min. minimum, max. maximum

Discussion

This study showed that stroke patients walked significantly faster in 10mWT and a longer distance in 2minWT with Incedo™ compared to without electrostimulation. Thus, our first hypothesis that gait performance can be modified even within a single session of FR stimulation is supported by the results. Data analysis in greater detail showed that 23 of 25 patients improved their performance in at least one functional test. Only two patients failed to benefit from a single session of FR stimulation. In contrast to other patients, these two patients showed only a slight response to electrostimulation of FR using Incedo™ while sitting and no visible response to the stimulation of the FR while walking. Furthermore, the FR while walking could only be moderately triggered by Incedo™ in some patients. There were several reasons for this. Five patients could not tolerate a further increase of stimulation intensity which prohibited a stronger response to electrostimulation. Either they found the higher stimulation intensity uncomfortable and/or disturbing or the higher stimulation intensity triggered spasticity in the affected leg. Two other patients became accustomed very quickly to the higher stimulation intensity during walking so that the initially good response to FR stimulation had diminished within 15 minutes. There were also two patients for whom it was not clear why they showed moderate and good response while sitting and only slight response while walking despite an increase in stimulation intensity.

The positive correlation between the degree of response to electrostimulation while walking and degree of improvement in 2minWT confirms the importance of responsiveness to FR stimulation for patient
performance.

The current results do not support the second hypothesis that the gait parameters can be changed within a single session of FR stimulation using Incedo™. Only one parameter showed a significant difference during walking with and without Incedo™. Step length was reduced by two centimeters while walking with electrostimulation. A trend to increase cadence when walking with Incedo™ was also observed. The lack of changes in gait parameters seems to indicate that the pattern of the gait cycle remained basically unchanged and that FR stimulation merely accelerated the same type of gait cycle. However, the changes in gait pattern during walking with Incedo™ could be visually observed in most patients. In particular, increased dorsiflexion and hip flexion could be observed in patients while walking with electrostimulation. This led to safer (reduced risk of tripping) and faster walking without an orthosis. In addition, a more symmetrical gait pattern could be also observed in some patients while walking with Incedo™. It remains speculative and unclear why the gait analysis system RehaGait had not been able to capture these changes. Perhaps the use of a motion analysis with multiple sensors placed on different body segments might be more appropriate to capture the changes in gait patterns that were seen visually.

For the first time, this study demonstrates the effects of FR stimulation in chronic stroke patients. Our results indicate that chronic stroke patients benefit from the stimulation to a similar degree as subacute stroke patients do. Thus, time after a stroke does not affect the efficacy of Incedo™ on gait performance and gait parameters.

The patients rated the device as effective and recommendable to others. Most patients would exercise with Incedo™ for a longer period of time, thus suggesting an overall good acceptance of the device. The electrical stimulation was not found pleasant in all patients. Nevertheless, the patients rated the FR stimulation as being positive.

A major question is whether the improvement of gait performance observed in this study is not only statistically significant but also clinically relevant. In literature, improvements of 0.13 m/s (31), 0.16 m/s (32) or 0.175 m/s (33) are considered to be clinically meaningful. In our patient group, gait velocity as measured during the 10mWT improved by 0.08 m/s during FR stimulation. This value is clearly below the one proposed in the literature. A further analysis indicated that seven patients improved their gait velocity by 0.13 m/s, thus meeting the criterion of a clinically relevant change.

However, it should be kept in mind that FR stimulation with the Incedo™ is meant as a tool for exercising for a longer period of time. This study was designed to examine the effect of FR stimulation during walking within a single session. Thus, over time, gait improvements might become larger. This needs to be examined in a controlled therapeutical trial, because there is still limited evidence for subacute patients and no evidence for chronic patients. Furthermore, it should be investigated who benefits most from this type of therapy e.g., depending on the Functional Ambulation Category since Spaich et al. (2014) reported the largest therapeutical gains of FR activation in patients with the most impaired mobility(19). The question of the optimal therapeutic dose should also be addressed in future studies.
Limitations/Lessons learnt from this study

These study results provide some evidence that the inclusion criteria should additionally include the requirement of a visible response to FR stimulation during walking. We observed that patients need less stimulation intensity to trigger the FR while sitting than while walking. Furthermore, some patients need more than one 30 minutes session to get used to the higher stimulation intensity during walking. In addition, the exclusion criteria should also be adjusted. Patients who adjust to the electrical stimulus within 30 minutes or patients in whom a higher stimulation intensity triggers spasticity in the affected leg should be excluded from the study.

Conclusions

This study was conducted to investigate the immediate effect of FR stimulation during walking on gait performance and gait parameters in subacute and chronic stroke patients. We suggest using this technique to conduct a randomized controlled clinical trial in subacute and chronic stroke patients to verify the effect of combined gait training with activation from FR.

Abbreviations

*FR* Flexor reflex

*max.* Maximum

*MV* Mean value

*m* Meters

mA Milliampere

*min.* Minimum

*n* Number of patients

*s* Seconds

*SD* Standard deviation

*10mWT* 10-meter walk test

*2minWT* 2-minute walk test

Declarations

Ethics approval and consent to participate
The study protocol and informed consent form were approved by the ethics committee of the University of Konstanz, Germany. The study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation.

**Consent for publication**

Not applicable

**Availability of data and materials**

All relevant data are within the paper.

**Competing interests**

The authors declare that they have no competing interests.

**Fundig**

The study was funded by the Lurija Institute, Allensbach, Germany.

**Author contributions**

All authors conceived and designed the experiments. AS and CS performed the experiments. AS and JL analyzed the data. AS and JL wrote the main manuscript text. AS prepared the figure 1 and tables 1-4. All authors read and approved the final manuscript.

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**Conflicts of interest**

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

**References**


**Figures**

**Figure 1**

Flow diagram of the study