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OPTIMAL STIMULATION FREQUENCY OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION ON PEOPLE WITH KNEE OSTEOARTHRITIS

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Objective: **This is a double blind study that examined the optimal stimulation frequency of transcutaneous electrical nerve stimulation in reducing pain due to knee osteoarthritis.**
Subjects: **Thirty-four subjects were randomly allocated into 4 groups receiving transcutaneous electrical nerve stimulation at either: (i) 2 Hz; (ii) 100 Hz; (iii) an alternating frequency of 2 Hz and 100 Hz (2/100 Hz); or (iv) a placebo transcutaneous electrical nerve stimulation.**
Methods: **Treatment was administered 5 days a week for 2 weeks. The outcome measures included: (i) a visual analogue scale; (ii) a timed up-and-go test; and (iii) a range of knee motion.**
Results: **The 3 active transcutaneous electrical nerve stimulation groups (2 Hz, 100 Hz, 2/100 Hz), but not the placebo group, significantly reduced osteoarthritic knee pain across treatment sessions. However, no significant between-group difference was found. Similarly, the 3 active transcutaneous electrical nerve stimulation groups, but not the placebo group, produced significant reductions in the amount of time required to perform the timed up-and-go test, and an increase in the maximum passive knee range of motion.**
Conclusion: **Our findings suggested that 2 weeks of repeated applications of transcutaneous electrical nerve stimulation at 2 Hz, 100 Hz or 2/100 Hz produced similar treatment effects for people suffering from osteoarthritic knee.**

Key words: osteoarthritis, transcutaneous electrical nerve stimulation, TENS, pain, stimulation frequency.

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INTRODUCTION

Transcutaneous electrical nerve stimulation (TENS) is one of the most widely used physical modalities for the management of osteoarthritic (OA) knee. The benefits of TENS for relieving chronic pain are well documented (1–3). Research into TENS for OA knee pain has been carried out for more than 20 years, and various stimulation parameters have been adopted with stimulation frequencies ranging from 2 to 100 Hz. Yet the optimal stimulation frequency of TENS in the management of OA knee pain is still under study.

In 1991, Jensen et al. (4) examined the effectiveness of conventional TENS (80 Hz, 150 μsec) and acupuncture-like TENS (2 Hz pulse trains) for 20 patients with OA knees. The treatment duration was 30 minutes a day, 5 days a week for 3 weeks. There were no significant differences in pain level between the 2 groups. In 1992, Grimmer (5) compared the effects of high rate TENS (80 Hz, 30 minutes) with burst mode TENS (3 Hz trains of 7 80 Hz pulses, 30 minutes) on OA knee pain after 1 treatment session. Sixty patients were randomly allocated to receive either a high-rate TENS, burst mode TENS or a placebo TENS. No significant differences in immediate pain relief were found between the groups. Johnson et al. (6) examined the preferred waveforms and frequencies of TENS chosen by chronic pain patients, who received treatment for over 1 year. However, no specific stimulation frequencies could be concluded. In 1998, Sluka et al. (7) measured the effects of the high- (100 Hz) or low- (4 Hz) frequency TENS on hyperalgesia, spontaneous pain behaviour and joint circumference of inflamed knees of rats. They found that both the high- and low-frequency TENS reversed the hyperalgesia immediately after treatment. The effects of the high-frequency TENS group lasted for at least 24 hours while the low-frequency TENS lasted for 12 hours. There was no effect of TENS on spontaneous pain behaviours or joint swelling when compared with the controls. Early in the 1970s, Sjölund et al. (8, 9) found that using low-frequency TENS on chronic pain patients increased the cerebrospinal fluid levels of endorphins. Subsequent to their findings, several biochemical studies in humans have demonstrated that TENS with different stimulation frequencies activates different endogenous opioid systems in the central nervous system (CNS) (9–11). After the application of low-frequency stimulation (2 Hz) for 30 minutes, Han et al. (11) found a 367% increase in Met-enkephalin-Arg-Phe (MEAP). High-frequency stimulation (100 Hz) for the same stimulation period yielded only a 49% increase in dynorphin A. On the other hand, high-frequency stimulation (100 Hz) mostly accelerates the release of dynorphin, which acts on the kappa receptor (11). Low-frequency stimulation (2 Hz) releases enkephalins, β-endorphins and endomorphins (12–14), which act on the delta or mu receptors in the CNS (14, 15).

As low- and high-frequency stimulations of TENS seem to work on the various analgesic mechanisms to a different extent, some researchers advocate that an alternating stimulation

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frequency of TENS could trigger optimal analgesic effects. Chen et al. (16) proposed that an alternating mode of TENS at low (2 Hz) and high (100 Hz) frequencies produces a synergistic interaction of dynorphin and enkephalin, which would produce a more potent analgesic effect than an application at a fixed frequency of stimulation.

Therefore, our study aimed to compare the relative effectiveness of this alternating stimulation mode of TENS (2/100 Hz), to the high-frequency (100 Hz) or low-frequency stimulation (2 Hz) TENS in the management of knee OA.

METHODS

Subjects

This is a double blind study. Randomization was carried out by drawing lots from the randomization envelope. Only therapists who administered treatment to the subjects knew the group allocation, while the subjects and the assessor were not given this information. The subjects were randomly allocated into 4 groups who received TENS at: (i) 2 Hz ($TENS_2$); (ii) 100 Hz ($TENS_{100}$); (iii) 2/100 Hz ($TENS_{2/100}$); or (iv) a placebo TENS ($TENS_{PL}$). Subjects diagnosed with OA knees were recruited from a local care home.

Inclusion criteria were that the subjects should demonstrate at least grade II OA changes in their X-rays (17), that they should be competent enough to complete the visual analogue scale (VAS), and that OA should be the only cause of their present knee pain. Exclusion criteria were subjects who had received prior knee surgery, had received intra-articular corticosteroids within 4 weeks of the study, and who had any chronic or uncontrolled co-morbid diseases. People with a cardiac pacemaker or who had received any TENS 1 month prior to the study were also excluded.

Thirty-six subjects participated in the study. Twelve of them were suffering from bilateral knee pain, and both knees were studied. Their demographic characteristics are shown in Table I. There were no significant between-group differences in any of the recorded demographic data. There were 2 withdrawals from the study. The first withdrawal was for medical reason. The second was because the subject had moved out of the elderly complex.

Procedures

A TENS machine (The Han Acupoint Nerve Stimulation, model LH204H; Beijing, China) was used for stimulation and the stimulation duration was set to 40 minutes. The stimulation parameters of the machines had been fixed by the manufacturer, as shown below:

For the frequency of 2 Hz, the pulse width was fixed at 576 μs. For the frequency of 100 Hz, the pulse width was set at 200 μs. For the alternating frequencies of 2 Hz and 100 Hz, 2 Hz was delivered for 3 seconds with the pulse width at 576 μs, followed by 100 Hz with the pulse width at 200 μs for 2.5 seconds.

Two pairs of rubber electrodes ($4.5 \times 3.8\ cm^2$) were placed over the acupuncture points of the knees. The points used were ST35, LE4, SP9 and GB34. The intensity of the current was set at a comfortable level as determined by the subjects, and ranged from 25 mA to 35 mA. During stimulation, subjects in the 3 active TENS groups experienced paraesthesia and mild twitches. The current was turned up if the subjects accommodated to the current 5 minutes into the stimulation. The placebo machine was identical in appearance to the real treatment unit, but the internal circuit had been disconnected by an electrical technician. When the placebo machine was turned on, an indicator light went on and the digital display of intensity control functioned normally; however, there was no electrical output. Subjects were told that they may or may not feel the tingling sensation during the stimulation. Therapists also pretended to step up the intensity of stimulation 5 minutes into the stimulation, as with the other treatment groups. The battery was replaced after each 10 hours of operation.

Outcome measures

Intensity of pain. In this study, a VAS was used to measure the intensity of pain. Patients were asked to rate the intensity of the pain they felt while walking by making a mark on the VAS line. The distance (in cm) from the "no pain" end to the marked point was measured. Scores of VAS was recorded before the intervention, during (after 20 minutes) and after the stimulation (at 40, 60 and 100 minutes). Subsequent recordings of VAS were done on separate sheets of paper. This prevented the subjects from comparing the present VAS with the previous one.

Range of motion of knees. In the present study, a 180° goniometer with a 1° increment was used to measure the range of knee motion in flexion and extension. The range of knee motion was measured in a supine lying position. The axis of the goniometer was placed over the lateral epicondyle of the femur, with the stationary arm pointing towards the greater trochanter. The movable arm was placed over the lateral border of the fibula and pointing towards the lateral malleolus. The pain-limited knee range of motion was recorded when the subjects actively flexed or extended their knees. The maximum knee range during passive movement was also measured.

"Timed Up-and-Go" test. This is a simple test of basic physical functional mobility for frail elderly persons with high reliability (18). The subjects were required to walk a distance of 3 metres. The whole procedure was demonstrated first before the actual test. The test was recorded in terms of seconds.

Statistical analysis

SPSS version 11 was used for the above analysis and the significance level was set at 0.05. Repeated measures ANOVA was used to analyse the effects of the group and treatment sessions on the VAS scores, knee ROM and on the "Timed Up-and-Go" test. Linear regression was used to analyse the relationship of the VAS scores and treatment sessions. When there was interaction between sessions and groups, analysis was performed separately by groups and sessions by using one-way ANOVA.

Table I. *Demographic data of the subjects (*n *= 36). Values are given as mean with SD within parentheses*

	$TENS_2$	$TENS_{100}$	$TENS_{2/100}$	$TENS_{Pl}$	*p*-value
Age (years)	82.7 (6.1)	84.3 (6.9)	80.00 (5.8)	83.2 (5.4)	0.371
Gender	13F	12F	12F 1M	10F	0.430
Body weight (kg)	54.4 (6.6)	53.0 (7.1)	58.5 (16.6)	63.0 (16.6)	0.287
Height (cm)	147.6 (5.5)	146.3 (5.5)	148.2 (8.6)	146.8 (8.6)	0.856
Body mass index	25.0 (2.8)	24.8 (3.5)	26.4 (6.1)	29.2 (6.7)	0.162
History of knee pain (years)	5.9 (6.5)	8.1 (12.5)	9.3 (8.9)	12.5 (8.9)	0.466
X-ray grading	3.1 (0.5)	3.0 (0.6)	3.3 (0.5)	3.20 (0.4)	0.656
Baseline VAS score (cm)	6.6 (2.0)	5.2 (1.8)	5.4 (2.2)	5.8 (3.0)	0.327
Mini-mental state examination score	23.8 (3.9)	23.4 (3.9)	23.5 (6.4)	25.0 (2.3)	0.757

p-value indicates the comparisons among different groups.
F = female; M = male; VAS = visual analogue scale.

Table II. *Changes in the VAS scores of the 4 groups recorded on day 1. Values are given as mean with SD within parentheses*

Group	Time (0 minutes) Pre-treatment	(20 minutes) During-treatment	(40 minutes) 0 minutes post-treatment	(60 minutes) 20 minutes post-treatment	(100 minutes) 60 minutes post-treatment
$TENS_2$	6.6 (2.0)	5.0 (2.7)	4.6 (2.9)	3.9 (2.7)	4.5 (2.4)
NVAS	100 (0)	79.0 (37.1)	73.8 (40.2)	64.2 (43.6)	72.1 (35.3)
$TENS_{100}$	5.2 (1.8)	3.7 (2.2)	2.6 (2.2)	2.2 (1.8)	2.1 (2.3)
NVAS	100 (0)	70.2 (36.5)	52.0 (41.8)	42.4 (35.6)	40.2 (36.2)
$TENS_{2/100}$	5.4 (2.2)	3.9 (3.0)	2.3 (2.3)	2.0 (2.5)	2.7 (2.4)
NVAS	100 (0)	69.6 (39.7)	41.1 (33.9)	34.9 (34.1)	46.6 (36.9)
$TENS_{Pl}$	5.8 (3.0)	4.9 (3.3)	4.6 (3.3)	4.9 (3.5)	4.6 (3.4)
NVAS	100 (0)	88.1 (30.4)	79.8 (31.0)	86.6 (32.9)	80.8 (32.0)

NVAS = normalized visual analogue scale scores calculated with respect to the baseline values, as expressed in percentages; TENS = transcutaneous electrical nerve stimulation.
Within-group difference of the 4 groups ($p = 0.000$); Overall between-group difference ($p = 0.117$).

RESULTS

Analgesic effects of TENS on OA knee pain

In the first treatment session, the VAS scores reduced significantly within each of the 4 groups across treatment sessions ($p = 0.000$) (Table II). *Post-hoc* tests showed that the VAS scores recorded at 20 minutes after stimulation were significantly lower than that of the baseline ($p = 0.000$). By 1 hour after the simulation, the greatest decrease in knee pain was 59.8%, as found in the $TENS_{100}$ group (the VAS score decreased by 3.1, $p = 0.003$), followed by a 53.4% reduction in the $TENS_{2/100}$ group (the VAS score decreased by 2.7, $p = 0.005$), and then a 27.9% reduction in the $TENS_2$ group (the VAS score decreased by 2.1, $p = 0.042$). By contrast, there was a 19.2% reduction in the VAS scores of the placebo group but it did not reach a significance level (the VAS score decreased by 1.2, $p = 0.926$). Overall, the $TENS_{100}$ and $TENS_{2/100}$ groups tended to show lower VAS scores than the $TENS_2$ and $TENS_{PL}$ groups on day 1, but there were no significant between-group differences ($p = 0.117$).

When investigating the cumulative analgesic effects of TENS on OA knee pain over 2 weeks, significant interaction between the "session" and "group" ($p = 0.014$) was observed, indicating that the changes in the VAS scores from day 1 to the follow-up session varied in the 4 groups. The analysis of the VAS scores of the 4 sessions was conducted separately for each group.

For within-group comparisons, the average pre-treatment VAS scores of all of the active groups decreased significantly across sessions. From day 1 to day 10, there was a 69.6% cumulative decrease in VAS scores in the $TENS_2$ group, 84.4% in the $TENS_{100}$ group, and 81.9% in the $TENS_{2/100}$ (Table III). For the placebo group, there was a 10.6% cumulative decrease over 10 days but it was not significant ($p = 0.366$). Several subjects reported a complete pain relief at the end of the course of treatment ($n = 1$ for $TENS_2$, $n = 2$ for $TENS_{100}$, $n = 1$ for $TENS_{2/100}$, $n = 0$ for $TENS_{PL}$).

The between-group differences in VAS scores reached a significant level by day 10 ($p = 0.000$) and the follow-up session ($p = 0.002$). These p-values were still significant even after a Sharpened Bonferroni correction that was used to adjust the α level (the adjusted significance level was 0.05/4 = 0.0125). *Post-hoc* tests indicated that the VAS scores of the $TENS_2$, $TENS_{100}$ and $TENS_{2/100}$ groups were significantly lower than that of the placebo group by day 10 and the follow-up session. However, the VAS scores were not significantly different among the 3 active TENS groups in any of the treatment sessions.

Table III. *Mean VAS scores of the 4 groups across sessions. Values are given as mean with SD in parentheses*

	Day 1	Day 5	Day 10	Follow-up	Within-group p-value
$TENS_2$	6.6 (2.0)	2.1 (2.2)	1.4 (1.5)	1.6 (1.8)	0.000
NVAS	100 (0)	40.6 (40.7)	30.4 (32.2)	13.4 (13.8)	
$TENS_{100}$	5.2 (1.8)	1.5 (1.4)	0.7 (0.7)	0.9 (1.0)	0.000
NVAS	100 (0)	30.7 (33.1)	15.6 (17.5)	28.9 (27.3)	
$TENS_{2/100}$	5.4 (2.2)	1.6 (1.4)	1.1 (1.7)	1.6 (2.2)	0.000
NVAS	100 (0)	6.7 (17.1)	18.1 (21.4)	23.5 (27.3)	
$TENS_{PL}$	5.8 (3.0)	3.6 (2.8)	4.1 (2.6)	4.4 (3.0)	0.366
NVAS	100 (0)	77.4 (59.4)	89.4 (70.7)	95.6 (99.9)	
Between-group p-value	0.428	0.057	0.000	0.002	

NVAS = normalized visual analogue scale scores with respect to baseline values are expressed in percentages; TENS = transcutaneous electrical nerve stimulation.
Significant interaction between the sessions and group was noted ($p = 0.014$). Hence, the analysis of the session and the group was carried out separately.
A significant between-group difference was found on day 10 ($p = 0.000$) and the follow-up session ($p = 0.002$).
p-value denotes comparisons across sessions for each group.

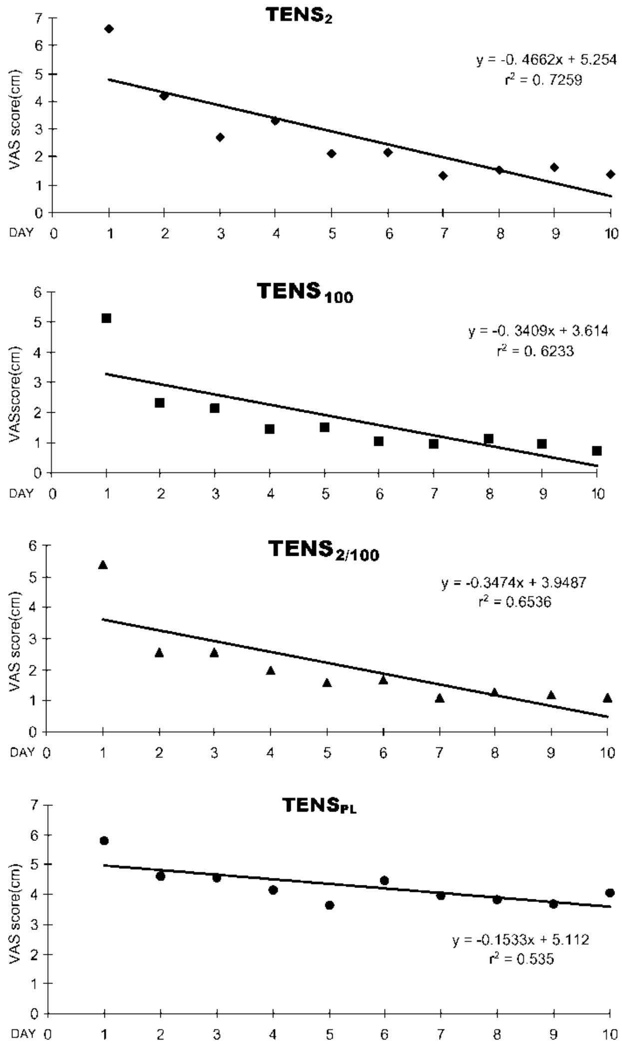

Fig. 1. Linear regression lines of visual analogue scale (VAS) scores for the 4 groups over 10 sessions.

Figure 1 illustrates the linear regression lines of the 4 groups over 10 sessions. The 3 active TENS groups demonstrated a good linear relationship, with r^2 greater than 0.6. The placebo group showed a medium linear relationship, with r^2 equal to 0.535. The negative slope indicated a reduction in VAS scores across the 10 sessions. The $TENS_2$ group possessed the steepest slope (–0.466), followed by the $TENS_{2/100}$ group (–0.347), then the $TENS_{100}$ group (–0.341). The placebo group (–0.153) had the flattest slope among the 4 groups. However, the slopes of all 4 groups did not differ significantly from each other ($p = 0.100$).

The influence of different stimulation frequencies of TENS on physical parameters

By day 10, the maximum passive knee range increased by 7.1% in the $TENS_2$ group, 10.3% in the $TENS_{100}$ group and 7.9% in the $TENS_{2/100}$ group. A negligible amount of change in knee range was found in the placebo group. The between-group difference was significant ($p = 0.047$), and this difference was maintained at least up to the follow-up session ($p = 0.032$). *Post-hoc* tests showed that the between-group difference came mainly from the greater maximum passive knee range of the 3 active TENS groups than from that of the placebo group.

For the measurements of pain-limited range of knee motion, all of the 3 active TENS groups showed a significant increase in pain limited range over the 10-day treatment period. By day 10, the pain-limited knee range increased by 7.2% in the $TENS_2$ group, 12.0% in the $TENS_{100}$ group and 9.6% in the $TENS_{2/100}$ group (all within-group $p = 0.000$). By contrast, a negligible change in the knee range was found in the placebo group. However, no significant between-group differences were detected in the pain-limited knee range in any of the treatment sessions ($p = 0.119$).

For the measurements of the timed up-and-go test, the average amount of time the active TENS groups took to complete the timed up-and-go test significantly decreased across sessions ($p = 0.000$). By day 10, the required time was reduced by 26.3% for the $TENS_2$ group, 15.5% for the $TENS_{100}$ group and 19.5% for the $TENS_{2/100}$ group. For the placebo group, there was little change in completion time across the 4 sessions. However, the between-group differences were not significant in any of the treatment sessions (all $p > 0.05$).

DISCUSSION

Analgesic effects produced by TENS

On day 1, TENS analgesia developed with a gradual onset, during which the VAS scores of the 3 active TENS groups were significantly lower than in the placebo group. During the recording period, we found that the analgesic effects produced by $TENS_{100}$ and $TENS_{2/100}$ peaked at 20 and 40 minutes post-stimulation, respectively. The analgesic effects produced by the $TENS_2$ group also reached a peak at 20 minutes after the stimulation, but the percentage of the pain reduction tended to be lower than in the other 2 active TENS groups. This could be explained by the previous findings that TENS at 2 Hz releases predominantly enkephalin, which produces analgesic effect with a slow onset but longer lasting (19, 20).

The repeated applications of active TENS ($TENS_2$, $TENS_{100}$ or $TENS_{2/100}$) over 10 sessions led to a significant reduction in subjective pain sensation. Despite the cessation of TENS stimulation, the reduction of pain in all of the groups was maintained from day 10, at least up to the 2-week follow-up session. The cumulative effect of stimulation in this study was consistent with what our previous studies had reported earlier (21, 22). The 3 active TENS groups experienced a significantly greater reduction in pain than the placebo group. However, no significant difference was found between these 3 active TENS groups. The use of the alternating stimulation frequency mode did not demonstrate any greater analgesic effects than that of the fixed stimulation frequencies (either $TENS_2$ or $TENS_{100}$).

Analgesic mechanisms of TENS

Different stimulation frequencies of TENS seem to rely on slightly different analgesic mechanisms, the endogeneous opioid system is only one of them. Supposedly, 100 Hz TENS increases the release of dynorphin (an extraordinarily potent opioid peptide) (23); whereas low-frequency TENS increases the release of enkephalin and endorphin (11, 15) (a long-lasting analgesic effect) (19, 20). Theoretically, the alternating frequency of 2 Hz and 100 Hz frequencies ($TENS_{2/100}$) would produce synergistic mechanisms for the release of various endogeneous opioids (25), which would produce a more potent anti-nociceptive effect than a fixed stimulation frequency. However, our findings suggested that the extent of the pain relief in the $TENS_{2/100}$ group was just similar to that in the $TENS_{100}$ group and the $TENS_2$ group. This further illustrated that the opioid mechanism is only partially accountable for the analgesic mechanisms triggered by TENS. This is supported by the findings of a previous study which demonstrated that the anti-nociceptive effect induced by a 2/100 Hz stimulation was only 50% blocked by naloxone, even with a large dose (10 mg) (16). Mechanisms such as the serotonin and noradrenaline (24, 25), local segmental effect may also contribute to TENS analgesia.

Studies have revealed that the central serotonergic system does play an important role in the mechanism of electroacupuncture analgesia (25, 26). Serotonin mediates part of the descending pain inhibitory system and the meso-limbic loop of analgesia. During electroacupuncture, the rates of synthesis and utilization of 5-HT (serotonin) in the CNS are accelerated. In addition, the rate of unit discharge of serotonergic neurones in raphe dorsalis is significantly accelerated during stimulation (25).

Influence of TENS on physical parameters

After repeated TENS stimulations, all of the 3 active groups, but not the placebo group, showed a significant increase in maximum range of knee motion. As observed earlier, all of the 3 active stimulations reduced pain significantly. Pain is one of the major factors hindering movement. As the pain subsides, patients may become more willing to move their knees. Therefore, a significantly shorter amount of time was required to complete the timed up-and-go test after the repeated applications of TENS. The improvement was maintained at least up to the follow-up session. However, the between-group difference was insignificant. Sluka and Westlund (27, 28) demonstrated that a reduction in knee pain and limb guarding would encourage the limbs to bear more weight. It could also encourage more functional performance (29, 30) in people with OA knees.

In conclusion, our findings demonstrated that 2 weeks of repeated applications of TENS at 2 Hz, 100 Hz or 2/100 Hz significantly reduced OA knee pain, whereas the placebo group experienced no such reduction. Pain reduction occurred in a cumulative manner from day 1 to day 10. The analgesic effects produced by the 10-day repeated applications of TENS were able to carry over at least up to the 2-week follow-up. However, no significant between-group differences were noted among the 3 active TENS groups ($TENS_2$, $TENS_{100}$, or $TENS_{2/100)}$ in all treatment sessions. Our findings therefore do not support the claim that the application of TENS at an alternating frequency of 2 Hz and 100 Hz produces a greater analgesic effect than does a fixed stimulation frequency at 2 Hz or 100 Hz for the management of OA knee pain.

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