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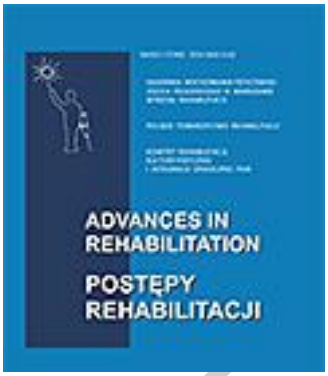

Original article

Title: Neuromuscular Exercise with Neuromuscular electrical stimulation in Knee Osteoarthritis: A Randomised Controlled Pilot Trial

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Neuromuscular Exercise with Neuromuscular electrical stimulation in Knee Osteoarthritis: A Randomised Controlled Pilot Trial

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Abstract

Introduction: The present study describes the findings of Randomized Controlled Trial that investigates the effects of Neuromuscular Exercise with Neuromuscular Electrical Stimulation on pain, physical function, balance, range of motion and gait by various measures in patients with knee osteoarthritis.

Material and methods: A 48 subjects with knee osteoarthritis were randomly allocated into four groups with primary outcomes feasibility, assessment procedure, adherence and acceptability to the intervention. The secondary outcomes were visual analog scale (VAS), knee injury osteoarthritis outcome score (KOOS),timed up & go (TUG), range of motion (ROM), community balance & mobility scale (CBM&S) and dynamic gait index (DGI). Feasibility and acceptability of the study were evaluated by number of subjects completed the pre and post-treatment data.

Results: 61 subjects were screened for the study. 48 subjects agreed to take part in study. There was significant improvement in VAS after 6 weeks of treatment in group D ($p = 0.0001$) as compared to group A. KOOS sub variables and TUG test were significant at $p = 0.0001$, ROM (R) was significant at $p = 0.01$, ROM (L) significant at $p = 0.11$ and CBM&S, DGI were significant at $p = 0.0001$ after 6 weeks of treatment in between group comparison.

Conclusions: This pilot trial suggests that it is feasible and acceptable to do fully powered "RCT" to investigate the effect of NEMEX with NMES in knee OA. The study concluded that NEMEX with NMES may significantly reduce the pain and fall risks, improves KROM, balance, and dynamic mobility in patients with KOA.

Keywords: exercise, electric stimulation, proprioception, joint diseases, quadriceps muscle

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Introduction

Knee Osteoarthritis (KOA) is the most prevalent arthropathy that causes pain and decreases the functional level leading to poor quality of life (QOL) [1–3]. KOA poses an increase in economic burden with increasing age and sedentary lifestyle [4]. Keeping this in view, the prevention and management of KOA is high priority [5]. In India the overall prevalence of knee OA was found to be 28.7% [6]. With the knee being one of the most commonly affected joints, women (31.6%) are more likely to have OA than men. Patients with KOA presents with pain, tenderness, stiffness, loss of flexibility, crepitus and impaired quadriceps functions which affects the patient's balance and gait [7,8]. The atrophy of the surrounding musculatures results in joint instability and excessive joint movement [9].

Current physical therapy intervention for KOA is Neuromuscular exercises (NEMEX) focusing on functional joint stabilization, alignment, balance and pattern of muscle activation has potential to reduce the loads on knee joint and upgrade the cartilage in OA [10].

Nowadays NEMEX is used in prevention and rehabilitation in KOA [11, 12]. Few studies have explored the effect of NEMEX on knee joint loading [13−15]. An uncontrolled pilot study discovered that the NEMEX protocol reduces the knee adduction moment up to 14% after 8 weeks [16].

Previous study suggested that exercise training along with other physiotherapy measures, decreases cartilage degeneration, inflammation, and prevent loss of the subchondral bone [17]. NEMEX is helpful in improving control of sensorimotor system, joint position sense, balance and functional movement and also reduces the risk of falls in older adults [13].

Quadriceps weakness decreases the joint stability causing joint degeneration with joint pain. Due to pain and joint stiffness, it is tough for patients to perform traditional strength training. Also, traditional resistance exercise is laborious for patients with KOA.

Therefore, light has been shown towards the Neuromuscular Electrical Stimulation (NMES) to strengthen the quadriceps muscle through the application of transcutaneous electrical current to initiate involuntary contractions in the targeted muscle. In severe KOA, there is deficiency in voluntary muscle activity contributing to quadriceps muscle weakness and therapeutic application of NMES increases the muscle strength, decrease muscle atrophy and spasticity in those patients [18].

The main goal of pilot trial was to evaluate the feasibility of subject's recruitment, outcome measures and the acceptability of the intervention. The secondary goal was to acquire the data for the calculation of sample size in order to undertake full RCT.

Materials and Methods

The Consolidated Standards of Reporting Trials (CONSORT) guidelines for RCT or feasibility trials were followed in this study [19]. The study protocol was approved by the Institutional Ethical Committee (IEC) on 29.12.2020, via letter no. A.Psy/20/8487. The Clinical Trial Registry of India registered this trial (Registration no. CTRI/2021/06/034213). Research tool used in this study are scale for Visual Analogue Scale (VAS) [20], questionnaire for Knee Injury Osteoarthritis Outcome Score (KOOS) [21], Goniometer tool was used to measure the Range of Motion (ROM) [22], Timed up & Go Test (TUG) and Dynamic Gait Index (DGI) [23], Community Balance & Mobility Scale (CBM&S) [24].

Participants

Eligibility criteria

Males and females of age ≥40 years who met the American College of Rheumatology criteria for KOA and Grade II and III KOA according to the Kellgren and Lawrence grading system were included in the study. Exclusion criteria consisted of patients with history of inflammatory and infectious conditions of knee joint**,** trauma and surgery around knee joint**,** any muscular and neurological conditions affecting lower limbs**,** patients unable to walk unassisted, patients currently participating in any exercise programme for KOA, any contraindication to electrical stimulation (eg. epilepsy)**,** presence of any skin disorder around knee**,** any condition or reason restricting the participation of the patient in the study**,** unwilling and uncooperative patients and patients who have been referred for joint replacement.

Outcomes

Primary outcomes of the study were feasibility and acceptability of treatment by the participants. The feasibility of the participant's recruitment rate was assessed on the basis of number of subjects enrolled in the study. The data of total number of participants who completed the pre- and post-intervention was used to estimate the acceptability and feasibility of the outcome variables.70% subject's recruitment rate, 90% subjects completing the study, 95% subjects giving their post and follow-up data and 75% participant's attendance were considered as main parameters for the main trial [25]. The secondary outcomes were Visual

Analogue Scale (VAS), Knee Injury Osteoarthritis Outcome Score (KOOS), Community Balance & Mobility Scale (CBM&S), Dynamic Gait Index (DGI), Timed up & Go Test (TUG) and Range of Motion (ROM).

Study procedures

Firstly patient was asked to marked his /her pain on VAS scale. VAS is 0-10 point scale then patient's QOL & physical function was assessed by KOOS. It is questionnaire with 5 subscales on pain, symptom, sports/recreation, QOL and activity of daily living. After KOOS assessment patient's KROM in both right & left leg was assessed by goniometer. Patient's mobility was assessed by TUG test. CBM&S is questionnaire that assess the balance and mobility of patient and at last DGI is used to assess the dynamic balance and fall risks in patients with KOA. DGI questionnaire through which patients has to asked to perform 8 tasks. VAS was used to assess pain, KOOS was used to assess symptoms, functions in daily living, sports and recreation, and knee-related QOL, goniometer was used to measure KROM, TUG was used to measure dynamic balance, CBM&S was used to assess balance and mobility and DGI was used to assess balance and fall risk, and. All 4 groups received conventional treatment followed by the respective interventions. The intervention was 3 times a week for 6 weeks for all groups. The outcome variables were assessed at the baseline, at the end of six weeks after the intervention. Procedure and dosage for various groups are described in Table 1.

Tab.1. Procedure and dosage for various groups

Groups	Intervention
Group A	Conventional treatment that included hot pack, isometric quadriceps exercises, high sitting knee extension, and straight leg raise for once in a day with 10 repetitions for thrice a week for 6 weeks.
Group B	Forward and backward stepping, sideways exercises (3 sets of 10 repetitions), hip muscle strengthening, standing isometric abduction (2 sets of 5 repetitions), knee muscle strengthening (3 sets of 10 repetitions), step-ups & down (3 sets of 10 repetitions), balance exercise for 2 minutes for thrice a week for 6 weeks [26].
Group C	NMES with following parameters: pulsed current, asymmetrical, frequency 50 Hz, pulse duration 250 μs, contraction time 10 s, rest time 30 s every 20 minutes; current intensity maximum tolerated by each patient for thrice a week for 6 weeks [27].
Group D	Combination of NEMEX, NMES and conventional treatment for thrice a week for 6 weeks.

NEMEX- Neuromuscular Exercise, NMES- Neuromuscular Electrical Stimulation

Study design

Randomized, Parallel Group, Active Controlled Trial.

Randomization

The subjects were selected as per the eligibility criteria and randomly distributed into 4 groups by computer generated random number table; group A: Conventional treatment; group B: NEMEX; group C: NMES; group D: NEMEX in combination with NMES & Conventional with 1:1 allocation ratio.

Allocation concealment

Allocation and concealment were done using sealed envelopes and not revealed to subjects till they were assigned to respective groups. Enrollment of participants was done by investigator.

Blinding

Subjects were blinded to the intervention. And the blinding of subjects was achieved with sealed envelopes and not revealed to the subjects. Informed consent was provided that did not reveal any information related to intervention.

Sample Size

Total 48 subjects were included in the study, 12 subjects in each group as criterion for minimum sample size in pilot study [28,29].

Statistical analysis

For statistical analysis, IBM SPSS statistics software 21 was used. Descriptive (Mean ± SD) data was analyzed pre and post intervention. To evaluate the quality of randomization process, baseline characteristics of the study's participants were analyzed among the groups. One-way ANOVA test was used for between-group differences. The normality of the data was determined using Kolmogorov-Smirnov test and data was found to be normally distributed. VAS was analyzed using Kruskal-Wallis Test for between group comparison and Wilcoxon Signed Ranks Test for within group comparison. For KOOS, TUG, ROM, CBM&S, and DGI, one-way ANOVA was used for between-groups analysis; if significant, post-hoc multiple comparisons were performed using LSD Correction.

Results

Total 61 subjects were screened based on selection criteria. 51 (83.60%) were found to be eligible and 48 subjects (94.11%) were ready for participation. The Principle of Intention to Treat analysis was used. One participant dropped out of group C, and his post-intervention data was obtained. The details of the study are described in CONSORT flow diagram (Fig. 1.). The study trial included both males and females with age 40 to 70 years which are described in table 2. The baseline data of groups were found to be similar and is described in Table 2.

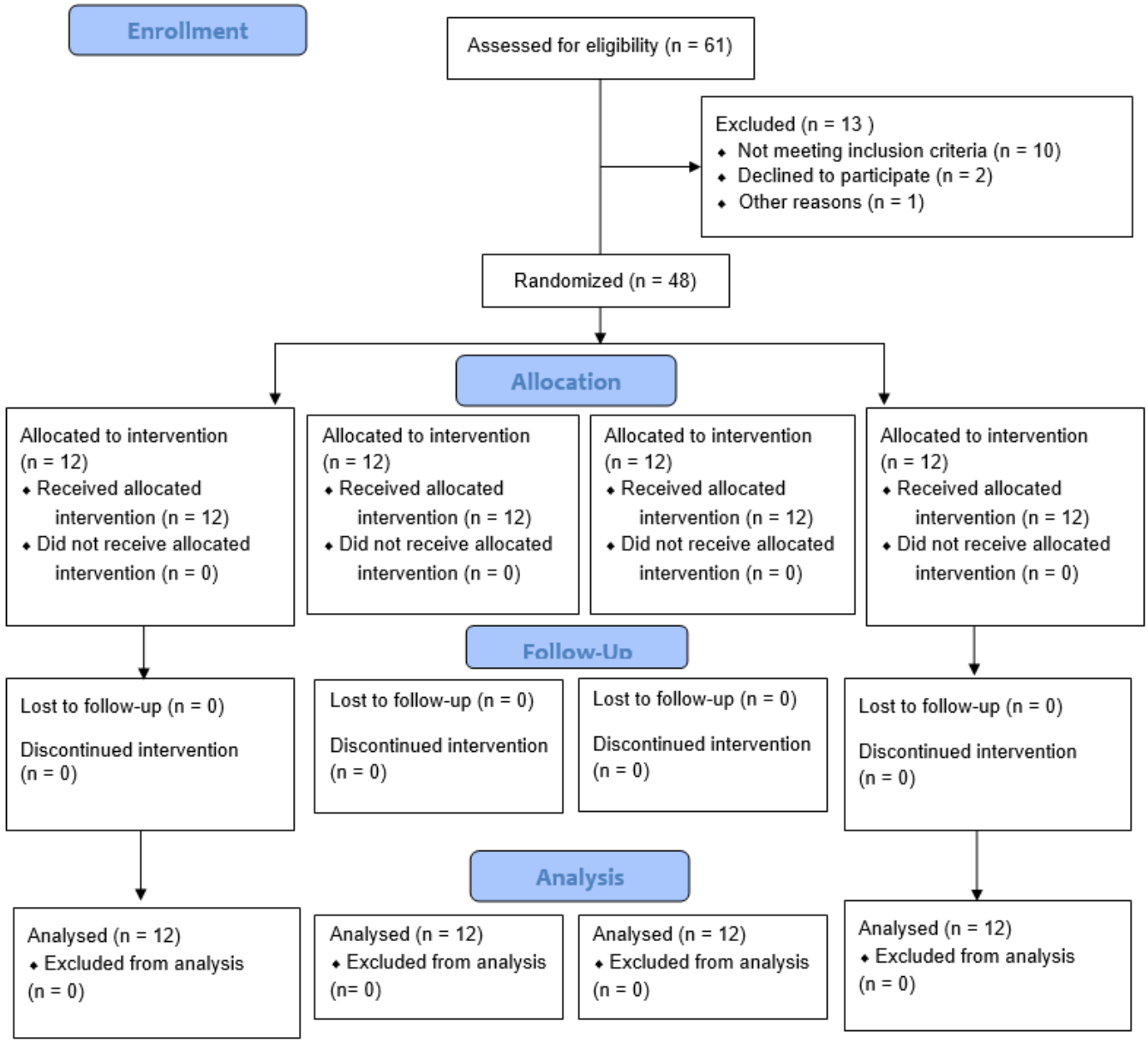

Fig. 1. Shows the CONSORT Flow Diagram

Tab. 2. Participant's baseline characteristics in various groups

		Group A (n = 12)	Group B (n = 12)	Group C (n = 12)	Group D (n = 12)
Age	Mean ± SD	52 ± 6.51	55.33 ± 7.01	53.00 ± 8.50	55.17 ± 8.83
Height		154.92 ± 7.91	154.17 ± 8.26	160.08 ± 10.57	156.92 ± 7.40
Weight		72.42 ± 6.13	72.42 ± 5.05	74.00 ± 5.06	70.00 ± 4.18
BMI		30.18 ± 1.38	30.51 ± 1.37	28.99 ± 1.97	28.47 ± 1.25

BMI- body mass index, N- number of subjects in each group, SD- standard deviation

Feasibility of outcome measures was determined by pre-and post-intervention data. Out of 48 subjects 47 completed the intervention period (6 weeks) so fully powered "RCT" is feasible. The present pilot trial demonstrated strong acceptability to the intervention. There was significant improvement in VAS after 6 weeks of treatment in group D ($p = 0.0001$) as compared to group A (Fig. 2.). Between Group analysis for VAS is described in Table 3.

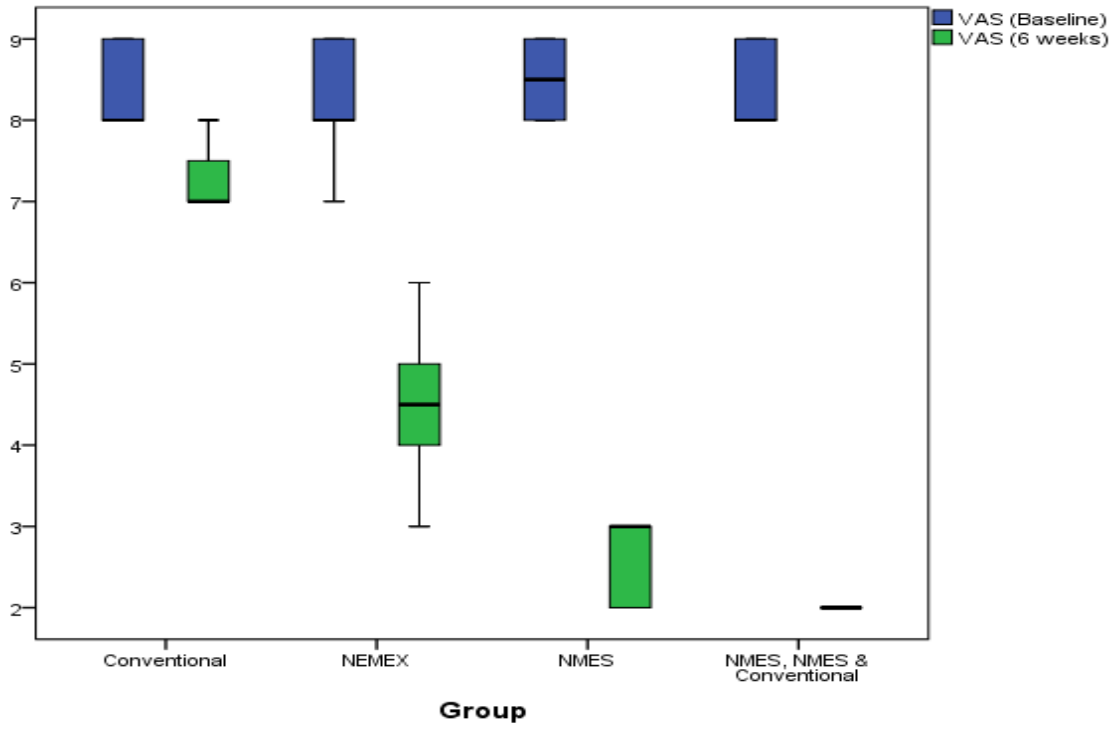

Fig. 2. Shows VAS in various intervention groups at baseline and at 6 weeks

Tab. 3. Shows between Group analysis for VAS

		Groups				Kruskal-Wallis	p- value
		Group A	**Group B**	**Group C**	**Group D**		
VAS (Baseline)	N	12	12	12	12	1.257	.739
	Median	8.00	8.00	8.50	8.00		
	Quartile-I	8.00	8.00	8.00	8.00		
	Quartile-III	9.00	9.00	9.00	9.00		
VAS (6 Weeks)	N	12	12	12	12	42.998	.0001**
	Median	7.00	4.50	3.00	2.00		
	Quartile-I	7.00	4.00	2.00	2.00		
	Quartile-III	7.50	5.00	3.00	2.00		

N- number of subjects in each group, VAS-visual analogue scale, **- statistically significant

KOOS sub variables and TUG test were significant at p = 0.0001, ROM (R) was significant at p = 0.001, ROM (L) significant at p = 0.1 and CBM&S, DGI were significant at p = 0.0001 after 6 weeks of treatment in between group comparison. Significant difference was found in group D in comparison with group A after 6 weeks of intervention period. All variables were found significant in within group comparison except KOOS ADL's in Group A after 6 weeks of intervention. Between group analysis for all variables in between groups is described in Table 4.

Tab. 4. Shows between group analysis for all variables

Variables	Group A		Group B		Group C		Group D		Between Group (Baseline)		Between Group (6 Week)	
	Baseline	At 6 week	Baseline	At 6 week	Baseline	At 6 week	Baseline	At 6 week	F-value	p-value	F-value	p-value
KOOS Pain	39.08 ± 4.10	45.17 ± 5.46	36.25 ± 7.06	58.83 ± 8.18	33.92 ± 8.31	57.42 ± 7.57	41.5 ± 10	64.9 ± 10.02	2.268	.094	12.924	.0001**
KOOS symptom	40.67 ± 5.96	34.75 ± 6.30	44.92 ± 5.84	64.25 ± 4.96	43.25 ± 5.40	66.17 ± 4.97	46.67± 6.62	66.5 ± 5.99	2.195	.102	92.096	.0001**
KOOS ADL	40.75 ± 3.33	41.67 ± 7.38	42.92 ± 6.52	64.33 ± 5.93	37.83 ± 4.32	58.42 ± 4.06	45.17± 10.24	65.92± 9.51	2.651	.060	30.054	.0001**
KOOS Sport/Rec	22.83 ± 3.59	25.83 ± 3.59	26.25 ± 10.82	48.83 ± 13.75	27.00 ± 7.69	51.25 ± 7.42	33.7 ± 13.67	56.8 ± 11.96	2.666	.059	22.364	.0001**
KOOS QOL	33.92 ± 9.10	39.17 ± 10.02	36.33 ± 8.92	61.67 ± 7.57	36.42 ± 7.17	62.08 ± 6.40	39.1 ± 8.61	63.6 ± 8.02	.768	.518	24.927	.0001**
TUG	18.27 ± 0.97	13.62 ± 1.21	19.83 ± 2.19	11.11 ± .55	18.38 ± 1.51	14.30 ± 2.08	18.8 ± 2.31	10.9 ± 0.49	1.831	.155	22.357	.0001**
ROM (R)	94.80 ± 4.13	97.03 ± 3.82	98.08 ± 7.82	102.8 ± 7.64	99.61 ± 4.86	102.9 ± 4.79	96.4 ± 6.91	107.8 ± 6.94	1.372	.264	6.480	.001**
ROM (L)	103.0 ± 2.67	105.3 ± 2.64	105.0 ± 7.94	109.6 ± 7.75	104.6 ± 5.12	107.8 ± 4.87	102.3 ± 8.62	114.1± 8.01	.462	.710	4.212	.011*
CBM&S	28.50 ± 4.72	33.58 ± 4.01	26.58 ± 2.43	50.25 ± 2.70	25.08 ± 4.19	46.17 ± 4.09	29.4 ± 6.22	58.8 ± 6.10	2.146	.108	68.52	.0001**
DGI	14.58 ± 1.56	17.67 ± 1.61	14.92 ± 3.00	22.75 ± 0.75	14.92 ± 2.57	17.42 ± 2.64	14.9 ± 1.73	22.8 ± 0.58	.063	.979	42.05	.0001**

CBM&S- Community Balance & Mobility Scale, DGI- Dynamic Gait Index, KOOS- Knee Injury Osteoarthritis Outcome Score, KOOS ADL- Knee Injury Osteoarthritis Outcome Score Activity of Daily Living, KOOS sports/rec- Knee Injury Osteoarthritis Outcome Score sports and recreation, KOOS QOL- Knee Injury Osteoarthritis Outcome Score Quality of life, ROM (L, R)- Range of motion (Left & Right), TUG- Timed Up & Go test, **- statistically significant

Post-hoc multiple comparisons for all five KOOS sub variables (pain, symptoms, ADL, sports/recreation and QOL), TUG,ROM (R, L) CBM&S and DGI in Group D showed significant improvement as compared to Group A with MD = -19.75000, p = 0.0001, MD = -31.75000, p = 0.000, MD = -24.25000, p = 0.0001, MD = -31.00000, p = 0.0001, MD = -24.50000, p = 0.0001, MD = 2.68833, p = 0.0001, MD = -10.77500, p = 0.0001, MD = -8.74167, p = 0.0001, MD = -25.25000, p = 0.0001, MD = -5.16667, p = 0.0001 respectively.

Discussion

The present study in our great knowledge is the first study to compare the effect of two different interventions NEMEX and NMES with different mechanisms of action on pain, function, balance, fall risks and mobility skills in KOA. The result of study recommends that future "RCT" assessing the effect of solo NEMEX and NMES and in combination of both intervention in knee osteoarthritis is feasible. Recruitment rate of present study is 94.11% so fully powered "RCT" is feasible. 100% retention rate was achieved. 97.91% of participants completed all 18 sessions of treatment which can be a successful adherence rate.

The study reveals that NEMEX along with NMES results in improvement of KROM, dynamic balance, mobility and reduction in pain and fall risks. After 6 weeks of treatment, the outcomes variables were improved.

One- way ANOVA test was used for data comparing and analysis. Result of the study showed statistically significant improvement in VAS, KOOS, TUG, ROM (R, L), CBM&S and DGI in group D as compared to group A after 6 weeks of intervention.

Patients with KOA experience loss of proprioception which may affect postural stability and risk of fall. QFM weakness decreases joint stabilization and shock absorption leads to progression of osteoarthritic changes. There is scarcity of literature on the feasibility and advantages of NEMEX in patients with KOA. There is only one study which investigated effect of NEMEX in early stage of KOA with few patients and found that this type of exercises is beneficial in improving knee adduction moment(KAM) with 14 % during leg rising.

The exercises and hot packs given prior to intervention have modest effect on joints by reducing pain in patients with KOA and electrical stimulation can induce 10-30% more contraction than exercises in healthy and weak muscles [30]. Exercises can improves the joint proprioceptive

mechanism which leads to increased joint excursion and contributes to enhance ROM by inhibiting pain through constant firing of A-beta.

A study in 2021 found that strength training along with NEMEX has an additional effect of on pain in patients with KOA [30]. NEMEX increases the proteoglycan content of the cartilage immediately after an exercise intervention which increases the ability to withstand load [31].Previous study result showed that NEMEX with educational package showed significantly greater pain-relieving effects on VAS mean knee pain (-8.4mm (-16.2 to -0. 5, p = 0.0364)) and during function (-16.0 mm (-24.8 to -7.3, p = 0.0004)) after 12 weeks of exercise [32].

The mechanism for the pain relief by exercise can be the central gating mechanisms, neuroimmune mechanisms and peripheral mechanisms through increased cell density locally at sites with tissue [33]. Exercise is considered as first-line treatment of KOA along with pain modulating effects following acute bouts of exercise as well as long term [34].

The present study's result showed statistically significant improvement in group C for all variables KOOS sub variables with TUG, ROM (R, L), CBM&S and DGI in comparison with group A. The results of present study are in line with previous studies and suggest that exercise is beneficial in patients with knee OA [35, 36].

In young and middle-aged people with knee injuries and people who are at high risk of knee OA, NEMEX training programs was effective in improving function and reducing symptoms [37].

In patients waiting for total joint replacement also showed improvement in physical function with the help of NEMEX. Neuromuscular Exercises are performed in closed kinetic manner which increases compressive forces, muscular co activation which ultimately leads to joint congruency by unloading the ligaments of knee joint that is helpful in maintaining knee joint stability [38].

NEMEX seemed helpful in improving function and reducing pain in patients with KOA. A preoperative neuromuscular exercise programme improves the activities of daily living and reduces pain in patients of total joint replacement (TJR) at 6 weeks postoperatively [39].

NMES is the one of the emerging and new method for muscle strengthening with the electrical impulses that causes involuntary contractions in the muscles. Previous studies have showed the beneficial effects of NMES in the management of knee OA, and in the both pre rehabilitation and rehabilitation of knee arthroplasties [40].

The previous research suggested that NMES treatment increase the quadriceps femoris strength in patients with KOA. Combining the NMES to the Quadriceps muscle can increase the

modulation of pain and self-reported functional ability in patients with knee OA [41]. The Previous study with 63 patients suggest that NMES plays an important role in improving quadricps muscle strength and reducing pain in patients with KOA [42].

NMES targets and increasing the recruiting of the type II muscle fibres selectively which helps in increasing the strength and oxidative capacity of thigh muscles in patients with knee osteoarthritis. Alternative biphasic waves were used with frequency of 75–85 Hz of NMES on the 16 healthy women with age between 21 to 45 years on the QFM for 20 days and found an increase in the muscle strength[43].

The present trial has significant clinical and practical implications. Worldwide, around 10% of males and 18% of female's ≥60 years are living with OA and 80% are experiencing limited movements and 25% are unable to do household works and NEMEX helps in improving self reported activities of daily living ,pain and physical function in old age population NEMEX decreases the drug dependency which in turn, prevents the associated complications. Previous study concluded that NEMEX is much better in comparison to drugs (analgesics and anti-inflammatory) in terms of reducing pain ,knee joint loading and improving function in patients with mild or moderate KOA [44]. Therapeutic exercises (strengthening, neuromuscular) are feasible at varying doses to improve pain and function in patients with KOA [45].

This suggests that neuromuscular exercises are feasible in terms of reducing pain, improving function by specifically targeting the sensorimotor deficits in patients with knee osteoarthritis.

The greater retention and few drop–outs of the subjects suggest that the intervention is satisfactory and well accepted approach in managing KOA.

The strength of present study is the novelty of combining two different interventions with diverse mechanism of action for treating KOA. Combination of NEMEX and NMES can have cumulative effects in terms of reducing pain and improving strength and physical functions in patients with knee osteoarthritis. The intake of medications was supervised to avoid any biasness that could change the results of the study. Secondly, we attained 100% of retention rate and 97.91% of adherence rate.

Sample size was small and long-term follow-up of subjects were missing.

Conclusion

The findings of the pilot trial suggest that it is feasible and acceptable to conduct a fully powered "RCT" to evaluate the effects of NEMEX and NMES in the treatment of KOA. The study concluded that NEMEX with NMES may significantly reduce the pain and fall risks, improves KROM, balance, and dynamic mobility in patients with KOA. In addition, administering any of the two interventions randomly in any groups of the study resulted in improvements of outcome measures.

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Conflicts of Interest

The authors have no conflict of interest to declare.

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