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Original Article

The Effects of Transcutaneous Auricular Vagus Nerve Stimulation and Exercise on Functional Capacity of Chronic Low Back Pain

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ABSTRACT

Background: Mechanical chronic low back pain (CLBP) known as a complex problem with low resolution rate and increased disabilities. Several studies showed vagus nerve stimulation benefit to chronic pain, but no study has evaluated functional outcome of CLBP yet. This study aims to investigate the effects of adding transcutaneous auricular vagus nerve stimulation (tVNS) to exercise therapy on functional capacity (lower extremity strength and functional mobility) of CLBP patients.

Methods: A randomized controlled group study was conducted in 22 patients mechanical CLBP aged 16-55. Participants were randomized into an exercise group (control) and an exercise with tVNS group (experimental). Outcome were lower extremity muscle strength measured by Five Times Sit to Sand test (FTSST), and functional mobility using Timed up and Go test (TUG) were evaluated before and after 2 weeks intervention.

Results: The mean FTSST of control group pre-test was 12.17± 3.01 and of post-test was 12.12± 4.05 with no significant difference (p=0,945). The mean FTSST of experimental group pre-test was 18.06 ± 9.20 and of post-test was 12.33 ± 2.42, indicating a significant difference (p=0.039), but there was no significant difference on Δ FTSTS between groups (p=0.119). The mean TUG of control group pre-test was 9.23 ± 2.00 and of post-test was 8.71 ± 3.13 indicating no significant difference (p=0.553). The mean TUG of experimental group pre-test was 10.13 ± 2.68 and of post-test was 7.76 ± 1.46 indicating a significant difference (p=0.011), while there was no significant difference on ΔTUG between groups (p=0.117).

Conclusion: Our results suggest that tVNS addition to exercise therapy has beneficial effects on lower extremity muscle strength and functional mobility in CLBP patients during relatively short period in two weeks of intervention. Further research is needed to investigate the potential of tVNS therapy in CLBP.

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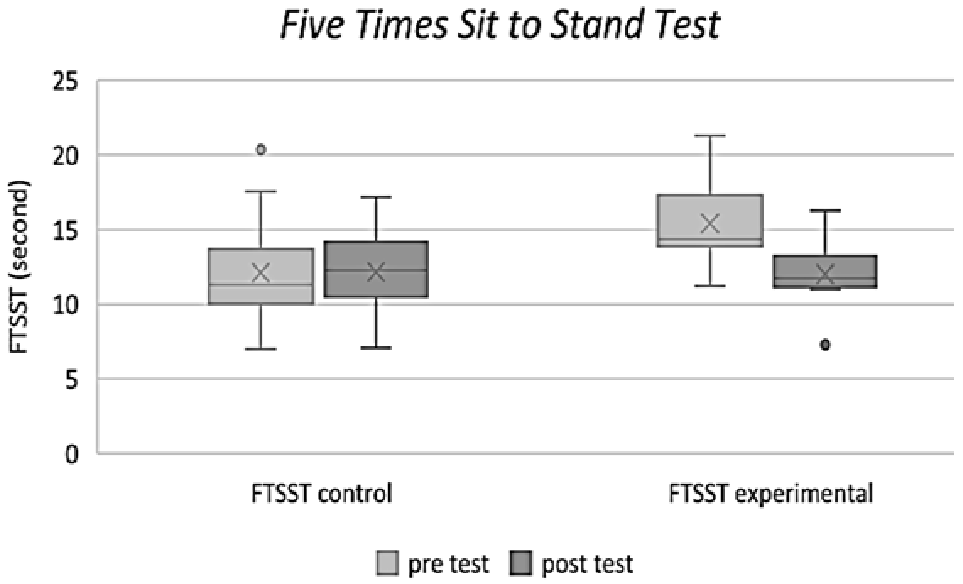
GRAPHICAL ABSTRACT



Introduction

Chronic low back pain (LBP) is one of the main causes of health problems resulting in disabilities, activity limitations, socioeconomic problems, and absenteeism from work worldwide [1]. Multiple factors including biopsychosocial condition influence transition from acute to chronic low back pain. Maladaptive movement and motor control disorders, central sensitization, fear avoidance behavior, and its effects on activity and participation are interrelated factors, forming a vicious cycle that influencing one and another [2]. This complexity results in low resolution of CLBP, counting less than 5% patient [3]. Multimodal treatment strategy by far is the most effective approach for chronic pain including pharmacology, non-pharmacology, and surgery. Strengthening exercises and core muscle stabilization are known to reduce pain and recurrence, while neuromotor training is effective in reducing the risk of injury and falls and improving several aspects of functional performance [4, 5]. Vagus nerve stimulation (VNS) is an electrical stimulation technique on the tenth cranial nerve afferents that has broad projections, can produce effects to the brainstem, sub-cortex, and cortex as well as the autonomic nervous system (ANS). Several studies have shown that VNS can be used for nociceptive modulation and pain perception [6]. Noninvasive form of VNS which is delivered by transcutaneous stimulation on auricular branch of vagus nerve (ABVN) has been shown advantages on anti-inflammatory effects and chronic pain comorbidities (depression, anxiety, and psychological factors) [7-10]. Thus, it supports therapeutic potency of tVNS in CLBP.

Chronic LBP research frequently evaluate pain and quality of life. However, pain and deconditioning have impact on functional ability that restricting patient's activities and participation, limiting work and productivity. Functional capacity is an individual's ability to perform a task or action in a standardized environment, and it indicates the highest level of subject's functional ability that can be achieved in the domain being evaluated. Tests with specific instruments that can be selected to evaluate the patient's functional capacity include the sit-to-stand test and the timed up and go test [11]. Functional mobility is important to assess because it shows the ability to carry out daily activities and plays a role in maintaining an active lifestyle, while sitting to standing is a prerequisite movement to perform functional mobility.

Five times sit to stand test (FTSST) is used to evaluate lower extremity muscle strength and balance, where LBP patients show lower performance on FTSST than healthy subjects [12, 13]. Timed Up and Go Test (TUG) is used to evaluate fall risk, balance, and functional mobility [14, 15], where LBP patients show reduced functional mobility and worse results than healthy subject [16]. Both tests are mentioned to have strong to moderate correlation with the pain scale in CLBP [17-19]. Studies on the effects of tVNS on chronic low back pain with functional capacity as a result have not been obtained. This study aims to determine the effect of adding tVNS therapy to exercise as mainstay therapy to chronic low back pain on the functional mobility and lower extremity strength of chronic low back pain patients.

Materials and Methods

Study design and procedures

This was a randomized controlled group study. Participants were consecutively selected in order of their appearance according to inclusion criteria up to number of participants were fulfilled. Based on sample calculation, 22 enrolled participants were randomly assigned to experimental group and control. The study was approved by ethic committee of Dr. Soetomo general academic hospital in Surabaya. Two physicians collected the demographic data, basic anthropometric measurement, history of mechanical CLBP, and clinical symptoms prior to randomization.

Eligibility

Inclusion criteria

Participants aged 18-55 years old with mechanical chronic low back pain (defined as LBP more than 12 weeks without organic signs and red flags), moderate pain with numerical pain rating scale between 4 and 7, and independent ambulation.

Exclusion criteria

Excluded were patients with organic LBP (trauma/fracture, tumor, infection, severe degenerative spine, and rheumatologic condition), radicular pain, analgesic consumption other than acetaminophen or NSAID, or new analgesics in 2 weeks before recruitment, underwent modalities therapy in 1 week, any injury or skin problems at auricula or face, utility of metal implant including pacemaker, pregnancy, history of seizure or epilepsy, moderate to severe depression (HDRS score ≥ 17), history of vasovagal syncope, skin allergy to metal, drugs and alcohol abuse, communication problem, obesity grade 2 according to Asia Pacific criteria, and diabetes mellitus type 2. The criteria were dropped out if participants missed stimulation schedule or exercise twice, experienced allergy, or adverse event.

Stimulation procedure

Participants in experimental group received tVNS administered by researcher. The tVNS treatment lasted 20 minutes per day and exercise session lasted 30 minutes per day. tVNS was applied to left ear at cymba choncha and choncha area using ear clip electrodes connected to Enraf-Nonius Myomed 632 device.

Conductive gel applied to metal part of electrodes to distributes conduction and prevent pain. Stimulation set to 25 Hz and pulse width 500 microseconds, in biphasic rectangular symmetric waveform. The intensity adjusted to every participant's sensory threshold by questioning the tingling sensation without pain. Stimulation was delivered 20 minutes, five times per week for 2 weeks, accompanied by monitoring of vital signs (blood pressure, heart rate, respiratory rate, and peripheral oxygen saturation) before, every 5 minutes during, and after 30 minutes stimulation ended.

Participants were asked to report any complain of increasing pain or discomfort sensation. After stimulation was finished, researcher checked area of treatment for any signs of irritation and evaluate participant's symptoms.

Exercise treatment

All participants in both groups participated in exercise therapy under the blind supervision of an experienced physiotherapist. Exercise treatment consisted of kinesthetic awareness of spinal posture, pelvic tilt exercise, diaphragmatic breathing, core strengthening exercise using abdominal drawing in cat and camel exercise, trunk flexibility training, administered twice a week, 30 minutes per session for two weeks.

Outcome

Outcome variables are lower extremity strength function measured by five times sit to stand test (FTSST) and functional mobility measured by Timed Up and Go Test (TUG). The outcomes were evaluated before and after two weeks of intervention. To measure FTSST, a hard seat chair 43 cm high is used. In the initial position, the patient is asked to sit with his arms crossed on his chest. Next, the patient is asked to stand and sit five times as quickly as possible [20, 21]. Cut off point to differentiate participant with or without objective functional impairment is 10.35 [22]. Functional mobility is the term used to denote balance and walking maneuvers used in everyday life (such as getting up from a chair, walking, and turning) [23]. The test is carried out by measuring the time needed by the participant to transfer from a sitting position to standing then walking as fast as possible, but not running as far as 3 meters, turning around and sitting back down [21]. Time needed to finish test was considered normal without the risk of fall if scored 10 [2]. Factors influencing TUG result are motor deficit, age, sex, body mass index, comorbidity (cardiorespiratory comorbidity), and psychological condition (i.e. motivation) [17].

Statistical analysis

In this study, IBM SPSS Statistics 23.0 and Microsoft Excel for Mac version 16.68 were used for statistical analysis and calculation. Paired t-test analysis was used to compare FTSST and TUG score pre-test and post-test within group, an independent t-test was used to compare scores between groups. P-value <0.05 is considered significant. Cohen's d calculation was also used to measure effect size of therapy.

Results and Discussion

Baseline characteristics of participants in variables of age, sex, body weight, body height, body mass index (BMI), pretest score for numerical pain rating scale (NPRS), Hamilton depression rating scale (HDRS), FTSST, and TUG pre-intervention are presented in Table 1. CLBP improvement was known to be affected by confounding factors, in terms of BMI and depression [24]. Thus, no significant difference was found between control group and experimental group in baseline variables.

Score presented as ^{1}percentage and ^{2}mean ± standard deviation. P-value based on ^{1}Chi-square test and ^{2}independent t-test. *Significant if p-value < 0.05. BMI: Body Mass Index; NPRS: Numerical Pain Rating Scale; and HDRS: Hamilton Depression Rating Scale. As presented in Table 2, experimental group had an average FTSST time before being given tVNS therapy of 18.06 ± 9.20 seconds, and the mean after being given tVNS therapy was 12.33 ± 2.42 seconds. Based on the parametric statistical test (paired t-test), there was significant improvement in the FTSST time in the experimental group (p-value = 0.039). In the control group, the average FTSST time at the initial assessment was 12.12 ± 4.05 seconds and the average at the final evaluation was 12.17 ± 3.01 seconds. Based on the parametric test (paired t-test), there was no significant improvement in the FTSST time in the control group (p-value = 0.945).

In TUG evaluation, average TUG of the experimental group before therapy was 10.13 ± 2.68 seconds, and after tVNS therapy was 7.76 ± 1.46 seconds. Based on the parametric statistical test (paired t-test), there was a significant improvement in TUG of experimental group (p-value = 0.011). In control group, the average TUG time at the initial assessment was 9.23 ± 2.00 seconds and the average at the final evaluation was 8.71 ± 3.13 seconds.

Based on the parametric test (Paired t-test), there was no significant improvement in TUG in the control group (p-value = 0.553). The difference (delta) of 5 times sits to stand (FTSST) and the timed up and go test (TUG) between the experimental group and the control group is indicated in Table 3.

Table 1: Patient characteristics at baseline

	Control group (n = 11)	Experimental group (n = 11)	*P*-value
Sex[1]			0.611
Male	9 (81.8%)	8 (72.7%)	
Female	2 (18.2%)	3 (27.3%)	
Age (years) [2]	44.90 ± 10.07	40.72 ± 10.68	0.356
Body weight (Kilogram)[2]	67.90 ± 14.80	67.09 ± 11.97	0.888
Body height (Centimeter)[2]	166.63 ± 9.26	164.63 ± 8.64	0.606
BMI (kg/m^2)[2]	24.84 ± 3.63	24.92 ± 3.59	0.961
NPRS[2]	5.81 ± 1.07	5.45 ± 1.12	0.449
HDRS[2]	3.36 ± 2.90	4.18 ± 4.06	0.593
FTSST Pre[2] (second)	12.12 ± 4.05	18.06 ± 9.20	0.064
TUG Pre[2] (second)	9.23 ± 2.00	10.13 ± 2.68	0.384

Table 2: Five Times Sit to Stand (FTSST) and Timed Up and Go Test (TUG) of both groups before and after intervention

	Control group (n = 11)			Experimental group (n = 11)		
	Pre-Test mean ± SD	Post-test mean ± SD	*P*-value	Pre-Test mean ± SD	Post-test mean ± SD	*P*-value
FTSST (second)	12.12 ± 4.05	12.17 ± 3.01	0.945	18.06 ± 9.20	12.33 ± 2.42	0.039*
TUG (second)	9.23 ± 2.00	8.71 ± 3.13	0.553	10.13 ± 2.68	7.76 ± 1.46	0.011*

**Significant if p-value < 0.05*

As provided in Table 3, the mean delta time of the FTSST experimental group was 5.73 ± 7.98 seconds, while the control group was 1.74 ± 1.47 seconds, means that there was no significant difference of FTSST time between groups (p-value = 0.119). The effect size was calculated by Cohen's d, with result of experimental group was 0.85, indicated that therapy in the experimental group had a large effect on improving the FTSST time, while the result in the control group was 0.01 indicating that therapy in the control group had a weak effect on improving the FTSST time. The mean TUG time delta for the experimental group was 2.38 ± 2.50 seconds, while the control group was 0.52 ± 2.82 seconds. Based on the independent t-test statistical test, there was no significant difference between the TUG time improvements between groups (p-value = 0.117). The effect size was calculated by Cohen's d, resulting in effect size of the experimental group was 1.09, indicated that therapy in the treatment group had a large effect on improving TUG time, while the effect size in the control group was 0.19 indicating that therapy in the control group had a weak effect on improving TUG time. In application of tVNS stimulation, there was no reported side effect. All of the patient enrolled finish the treatment. Figure 1 displays the comparative data of FTSST pre- and post-intervention in box and whisker plot between the two groups. With the pre-intervention data showed higher plot distribution of experimental group, the post- intervention data showed smaller range, skewed to the left side and larger differences between pre- and post- intervention of experimental group.

In Figure 2, comparative data of TUG before and after treatment between the two groups shown that the experimental group pre intervention has larger range value, post-intervention data showed shorter range and smaller distribution, suggest larger differences between them compared to the control group.

This is the first study to evaluate tVNS addition to exercise therapy effects on physical function of CLBP patient in Indonesia. In CLBP patients, pain is the most frequent outcome used in studies. Several studies state that the outcome of functional capacity is affected by the pain scale, as shown by the correlation between the pain scale, FTSST, and TUG [15, 19]. Concerning non-physiological factors (psychological and environmental) that impact on the result of physical performance [25], our study further evaluated depression scale of the participants with the result of HDRS showed no significant difference between groups. The results showed significant improvement of lower extremity strength in experimental group compared to baseline (p<0.05). In terms of the minimal clinically important difference (MCID) value of the FTSST range from -5 to -7 [26], there was a mean difference of 5.73 ± 7.98 in experimental group, indicating clinically significant improvement, while in the control group, with a mean difference of 1.74 ± 1.47, did not. Previous study combining tVNS and physical therapy for fibromyalgia patient did not show improvement in 30 times sit to stand test that was evaluated at the 6th and the12th weeks after intervention, although pain scale improvement was obtained [19]. This study has similarities in combination therapy and outcome. However, the different subject, stimulation dose, duration, exercise type, and additional acupuncture therapy made difficult comparison. Other analgesic study without exercise therapy for 2 weeks also fail to show improvement in function, suggest that although a significant decrease in pain scale was obtained, it did not necessarily improve the subject's functional abilities [27]. Functional abilities also being influenced by other factors namely motor control, strength and stabilization, sensory feedback, postural control, coordination, and balance that developed through physical exercise [28, 29]. The mechanism that causes significant improvement in the experimental group given additional tVNS therapy is unclear, but it is thought to be obtained from tVNS mechanism of action which provides analgesics, anti-inflammatory effects, and psychological improvements, namely depression and mood [10, 30-33].

Table 3: The difference (delta) of 5 times sit to stand (FTSST) and the timed up and go test (TUG) between the experimental group and the control group

	Control group (n = 11)		Experimental group (n = 11)		*P*-value
	mean ± SD	Effect size	mean ± SD	Effect size	
Δ FTSST (second)	1.74 ± 1.47	0.01	5.73 ± 7.98	0.85**	0.119
Δ TUG (second)	0.52 ± 2.82	0.19	2.38 ± 2.50	1.09**	0.117

*Significant if p-value < 0.05. **Large effect size if p-value > 0.8

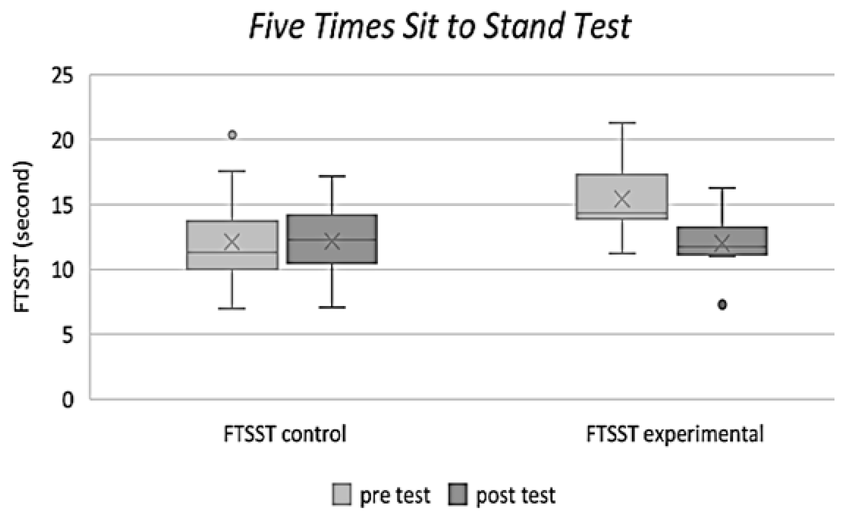


Figure 1: Box and whisker plot diagram of five times sit to stand test (FTSST) pre-and post-intervention between the two groups. Light grey box showed pre-test measurement and dark grey box showed post-intervention

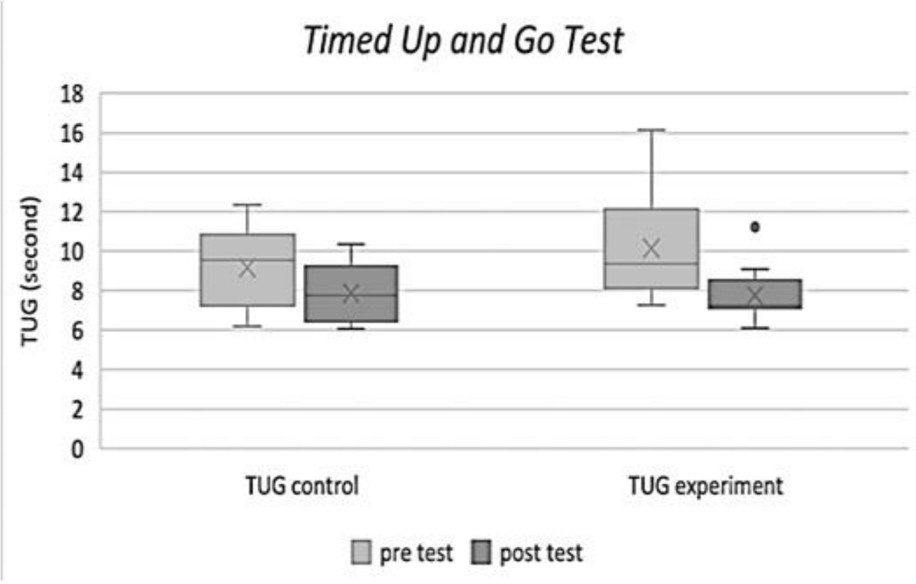


Figure 2: Box and whisker plot diagram of timed up and go test (TUG) pre- and post-intervention between the two groups. Light grey box showed pre-test measurement, and dark grey box showed post- intervention

The effect of VNS on pain scale of patients with chronic LBP supports this study result. The tVNS study in Indonesia on CLBP showed significant improvement of pain scale in both the tVNS group and exercise [34]. Similar results showed by other studies conducted by Sator-Katzenschlager [35]. The results of this study indicated that there was a significant improvement in the TUG of the experimental group who received exercise therapy plus TVNS before and after the intervention (p=0.011). In terms of the minimal clinically important difference in chronic LBP of 2.1 seconds [36], the treatment group obtained a mean difference of 2.38 ± 2.50, which means that there was clinical improvement in TUG, while control group *mean difference* was 0.52 ± 2.82 means no clinical improvement. Although no significant difference found in TUG results between groups, the effect size value in the experimental group was 1.09 indicating a large effect on improving TUG, and an effect size of 0.19 indicated a weak effect in the control group. There have been no studies regarding tVNS in chronic LBP patients with TUG outcomes, so comparisons are difficult to make. Improvement in TUG of experimental group probably because decreased pain mechanism. This is supported by several studies state that showed strong to moderate correlation between TUG and VAS [17]. Previous studies investigated tVNS on TUG and gait speed in Parkinson's disease resulting in improvement of gait speed and motor function with suspected mechanism from indirect effect on brain cholinergic system that induce neuromodulation. This interesting result could also be the mechanism contribute to improvement in TUG, considering maladaptive cortical reorganization that occur in CLBP, and tVNS ability to induce neuroplasticity shown as cortical motor reorganization [37, 38]. The non-significant difference results between the two groups probably because exercise therapy has provided a relatively small effect to improve outcomes although inadequately pass threshold of meaningful difference due to relatively short-term treatment.

Meanwhile, tVNS adjunctive therapy added the effects so that the results exceeded the threshold which could be seen statistically significant. The small effects resulted from exercise is likely because of the short period of intervention as only two weeks, that inadequately obtain positive outcome in function. Previous study showed significant improvement in FTSST in longer periods after 6 weeks and 12 weeks of aerobic and core stability exercise [12] while TUG after 8 and 12 weeks of exercise treatment [39, 40]. This is supported by a study investigated responsiveness of TUG to minimal change that could be detected in 2 weeks after multidiscipline treatment in frail patient supports the result of the current study [41-44]. Furthermore, diagram box and whisker plot skewness to the left showed us a trend of data to smaller value, which means tendency of improvement in the result test.

Conclusion

As growing evidence supports the beneficial effects of tVNS in chronic pain, this study supports the potency on its effects to functional capacity in terms of functional mobility and lower extremity strength of CLBP patient in relatively short term of two weeks therapy, also its safety and effectivity. Further investigation in larger study would needed to confirm this potential effect.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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References

[1]. Wu A., March L., Zheng X., Huang J., Wang X., Zhao J., Blyth F.M., Smith E., Buchbinder R., Hoy D. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017, *Annals of translational medicine*., 2020, **8**:299 [Crossref], [Google Scholar], [Publisher]

[2]. Cifu DX. Braddom's Physical Medicine and Rehabilitation. vol. 1. 6th ed. Elsevier; 2021[Crossref], [Publisher]

[3]. Almaghrabi A., Alsharif F. Prevalence of Low Back Pain and Associated Risk Factors among Nurses at King Abdulaziz University Hospital, *International Journal of Environmental Research and Public Health*., 2021, **18**:1567 [Crossref], [Google Scholar], [Publisher]

[4]. Allegri M., Montella S., Salici F., Valente A., Marchesini M., Compagnone C., Baciarello M., Manferdini M.E., Fanelli G. Mechanisms of low back pain: a guide for diagnosis and therapy, *F1000Research*., 2016, **5**:1530 [Crossref], [Google Scholar], [Publisher]

[5]. Mahyudin F., Prakoeswa C.R.S., Notobroto H.B., Tinduh D., Ausrin R., Rantam F.A., Suroto H., Utomo D.N., Rhatomy S. An update of current therapeutic approach for Intervertebral Disc Degeneration: A review article, *Annals of Medicine and Surgery*., 2022, **77**:103619 [Crossref], [Google Scholar], [Publisher]

[6]. Yap J.Y.Y., Keatch C., Lambert E., Woods W., Stoddart P.R., Kameneva T. Critical Review of Transcutaneous Vagus Nerve Stimulation: Challenges for Translation to Clinical Practice, *Frontiers in neuroscience*., 2020, **14**:284 [Crossref], [Google Scholar], [Publisher]

[7]. Johnson R.L., Wilson C.G. A review of vagus nerve stimulation as a therapeutic intervention, *Journal of inflammation research*., 2018, **11**:203 [Crossref], [Google Scholar], [Publisher]

[8]. Redgrave J., Day D., Leung H., Laud P.J., Ali A., Lindert R., Majid A. Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans; a systematic review, *Brain stimulation*., 2018, **11**:1225 [Crossref], [Google Scholar], [Publisher]

[9]. Kaniusas E., Kampusch S., Tittgemeyer M., Panetsos F., Gines R.F., Papa M., Kiss A., Podesser B., Cassara A.M., Tanghe E., Samoudi A.M. Current Directions in the Auricular Vagus Nerve Stimulation I – A Physiological Perspective, *Frontiers in neuroscience*., 2019, **13**:854 [Crossref], [Google Scholar], [Publisher]

[10]. Mastitskaya S., Thompson N., Holder D. Selective Vagus Nerve Stimulation as a Therapeutic Approach for the Treatment of ARDS: A Rationale for Neuro-Immunomodulation in COVID-19 Disease, *Frontiers in neuroscience*., 2021, **15**:667036 [Crossref], [Google Scholar], [Publisher]

[11]. Pourahmadi M.R., Takamjani I.E., Jaberzadeh S., Sarrafzadeh J., Sanjari M.A., Bagheri R., Jannati E. Test-retest reliability of sit-to-stand and stand-to-sit analysis in people with and without chronic non-specific low back pain, *Musculoskeletal Science and Practice*., 2018, **35**:95 [Crossref], [Google Scholar], [Publisher]

[12]. Turner B.J., Liang Y., Simmonds M.J., Rodriguez N., Bobadilla R., Yin Z. Randomized Trial of Chronic Pain Self-Management Program in the Community or Clinic for Low-Income Primary Care Patients, *Journal of General Internal Medicine*., 2018, **33**:668 [Crossref], [Google Scholar], [Publisher]

[13]. Vachalathiti R., Sakrulsriprasert P., Kingcha P. Decreased Functional Capacity in Individuals with Chronic Non-Specific Low Back Pain: A Cross-Sectional Comparative Study, *Journal of Pain Research*., 2020, **13**:1979 [Crossref], [Google Scholar], [Publisher]

[14]. Christopher A., Kraft E., Olenick H., Kiesling R., Doty A. The reliability and validity of the Timed Up and Go as a clinical tool in individuals with and without disabilities across a lifespan: a systematic review, *Disability and rehabilitation*., 2021, **43**:1799 [Crossref], [Google Scholar], [Publisher]

[15]. Gautschi O.P., Corniola M.V., Joswig H., Smoll N.R., Chau I., Jucker D., Stienen M.N. The timed up and go test for lumbar degenerative disc disease, *Journal of Clinical Neuroscience*., 2015, **22**:1943 [Crossref], [Google Scholar], [Publisher]

[16]. Bhatti Z.M., Khan I., Akbar U.U. Effect of Chronic Low Back Pain on Balance and Functional Mobility in Women above 40 Years, *Journal Riphah College of Rehabilitation Sciences*., 2021, **09**:71 [Crossref], [Google Scholar], [Publisher]

[17]. Gautschi O.P., Smoll N.R., Corniola M.V., Joswig H., Chau I., Hildebrandt G., Schaller K., Stienen M.N. Validity and Reliability of a Measurement of Objective Functional Impairment in Lumbar Degenerative Disc Disease: The Timed Up and Go (TUG) Test, *Neurosurgery*., 2016, **79**:270 [Crossref], [Google Scholar], [Publisher]

[18]. Özüdoğru A., Canlı M., Ceylan İ., Kuzu Ş., Alkan H., Karaçay B.Ç. Five Times Sit-to-Stand Test in people with non-specific chronic low back pain-a cross-sectional test-retest reliability study, *Irish Journal of Medical Science (1971-)*., 2023, **192**:1903 [Crossref], [Google Scholar], [Publisher]

[19]. Staartjes V.E., Klukowska A.M., Schröder M.L. Association of maximum back and leg pain severity with objective functional impairment as assessed by five-repetition sit-to-stand testing: analysis of two prospective studies, *Neurosurgical Review*., 2020, **43**:1331 [Crossref], [Google Scholar], [Publisher]

[20] Bohannon R.W. Reference Values for the Five-Repetition Sit-to-Stand Test: A Descriptive Meta-Analysis of Data from Elders, *Perceptual and motor skills*., 2006, **103**:215 [Crossref], [Google Scholar], [Publisher]

[21]. Rodrigues C.P., da Silva R.A., Nasrala Neto E., Andraus R.A.C., Fernandes M.T.P., Fernandes K.B.P. Analysis Of Functional Capacity In Individuals With And Without Chronic Lower Back Pain, *Acta ortopedica brasileira*., 2017, **25**:143 [Crossref], [Google Scholar], [Publisher]

[22]. Staartjes V.E., Schröder M.L. The five-repetition sit-to-stand test: Evaluation of a simple and objective tool for the assessment of degenerative pathologies of the lumbar spine. *Journal of Neurosurgery: Spine*., 2018, **29**:380 [Crossref], [Google Scholar], [Publisher]

[23]. Shumway-Cook A., Brauer S., Woollacott M. Predicting the Probability for Falls in Community-Dwelling Older Adults Using the Timed Up & Go Test, *Physical therapy*., 2000, **80**:896 [Crossref], [Google Scholar], [Publisher]

[24]. Handini L. Correlation Analysis between Women's Body Mass Index and Mechanical Low

Back Pain, *Indian Journal of Forensic Medicine & Toxicology*., 2020, **14** [Crossref], [Google Scholar], [Publisher]

[25]. Huijnen I.P., Verbunt J.A., Wittink H.M., Smeets R.J. Physical performance measurement in chronic low back pain: measuring physical capacity or pain-related behaviour?, *The European Journal of Physiotherapy*., 2013, **15**:103 [Crossref], [Google Scholar], [Publisher]

[26]. Benaim C., Blaser S., Léger B., Vuistiner P., Luthi F. Minimal clinically important difference" estimates of 6 commonly-used performance tests in patients with chronic musculoskeletal pain completing a work-related multidisciplinary rehabilitation program, *BMC musculoskeletal disorders*., 2019, **20**:1 [Crossref], [Google Scholar], [Publisher]

[27]. Schiphorst Preuper H.R., Geertzen J.H., van Wijhe M., Boonstra A.M., Molmans B.H., Dijkstra P.U., Reneman M.F. Do analgesics improve functioning in patients with chronic low back pain? An explorative triple-blinded RCT, *European Spine Journal*., 2014, **23**:800 [Crossref], [Google Scholar], [Publisher]

[28]. Gordon R, Bloxham S. A Systematic Review of the Effects of Exercise and Physical Activity on Non-Specific Chronic Low Back Pain, In *Healthcare*., 2016, **4**:22 [Crossref], [Google Scholar], [Publisher]

[29]. Ambrose K.R., Golightly Y.M. Physical exercise as non-pharmacological treatment of chronic pain: Why and when, *Best practice & research Clinical rheumatology*., 2015, **29**:120 [Crossref], [Google Scholar], [Publisher]

[30]. Breit S., Kupferberg A., Rogler G., Hasler G. Vagus Nerve as Modulator of the Brain–Gut Axis in Psychiatric and Inflammatory Disorders, *Frontiers in psychiatry*., 2018, **9**:44 [Crossref], [Google Scholar], [Publisher]

[31]. Chakravarthy K., Chaudhry H., Williams K., Christo P.J. Review of the Uses of Vagal Nerve Stimulation in Chronic Pain Management, *Current pain and headache reports*., 2015, **19**:1 [Crossref], [Google Scholar], [Publisher]

[32]. Farmer A.D., Strzelczyk A., Finisguerra A., Gourine A.V., Gharabaghi A., Hasan A., Burger A.M., Jaramillo A.M., Mertens A., Majid A., Verkuil B. International Consensus Based Review and Recommendations for Minimum Reporting Standards in Research on Transcutaneous Vagus Nerve Stimulation (Version 2020), *Frontiers in human neuroscience*., 2021, **14**:568051 [Crossref], [Google Scholar], [Publisher]

[33]. Marano M., Anzini G., Musumeci G., Magliozzi A., Pozzilli V., Capone F., Di Lazzaro V. Transcutaneous Auricular Vagus Stimulation Improves Gait and Reaction Time in Parkinson's Disease, *Movement disorders*., 2022, **37**:2163 [Crossref], [Google Scholar], [Publisher]

[34]. Halim M.J.E., Arfianti L., Pawana I.P.A., Melaniani S. Does transcutaneous Vagus Nerve Stimulation (tVNS) reduce pain intensity in chronic low back pain patients? A randomized controlled pilot study, *Bali Medical Journal*., 2023, **12**:423 [Google Scholar], [Publisher]

[35]. Sator-Katzenschlager S.M., Scharbert G., Kozek-Langenecker S.A., Szeles J.C., Finster G., Schiesser A.W., Heinze G., Kress H.G. The Short- and Long-Term Benefit in Chronic Low Back Pain Through Adjuvant Electrical Versus Manual Auricular Acupuncture, *Anesthesia & Analgesia*., 2004, **98**:1359 [Crossref], [Google Scholar], [Publisher]

[36]. Maldaner N., Sosnova M., Ziga M., Zeitlberger A.M., Bozinov O., Gautschi O.P., Weyerbrock A., Regli L., Stienen M.N. External Validation of the Minimum Clinically Important Difference in the Timed-up-and-go Test After Surgery for Lumbar Degenerative Disc Disease, *Spine*., 2022, **47**:337 [Crossref], [Google Scholar], [Publisher]

[37]. Meier M.L., Vrana A., Schweinhardt P. Low Back Pain: The Potential Contribution of Supraspinal Motor Control and Proprioception, *The Neuroscientist*., 2019, **25**:583 [Crossref], [Google Scholar], [Publisher]

[38]. Porter B.A., Khodaparast N., Fayyaz T., Cheung R.J., Ahmed S.S., Vrana W.A., Rennaker R.L., Kilgard M.P. Repeatedly Pairing Vagus Nerve Stimulation with a Movement Reorganizes Primary Motor Cortex, *Cerebral Cortex*., 2012, **22**:2365 [Crossref], [Google Scholar], [Publisher]

[39]. Kitagawa R., Kato S., Demura S., Kurokawa Y., Shinmura K., Yokogawa N., Yonezawa N., Shimizu T., Oku N., Handa M., Annen R. Efficacy of abdominal trunk muscles-strengthening exercise using an innovative device in treating chronic low back pain: a controlled clinical trial, *Scientific*

Reports., 2020, **10**:21883 [Crossref], [Google Scholar], [Publisher]

[40]. Mahendra I., Wardhani I., Sulastri N., Melaniani S. Effect of the otago exercise program on the lower extremity muscle strength in older women, *International Journal of Health Sciences (Qassim)*., 2022, **6**:303 [Crossref], [Publisher]

[41]. van Iersel M.B., Munneke M., Esselink R.A., Benraad C.E., Rikkert M.G.O. Gait velocity and the Timed-Up-and-Go test were sensitive to changes in mobility in frail elderly patients, *Journal of clinical epidemiology*., 2008, **61**:186 [Crossref], [Google Scholar], [Publisher]

[42]. Mousavi S.T., Esfahlani M.Z. Are Water Therapy Pr-rehabilitation (Non-Chemical Drug) exercises effective on the electrical activity of the central muscles of patients with chronic back pain who are candidates for laminectomy surgery? A systematic review, *Advanced Journal of Chemistry-Section B: Natural Products and Medical Chemistry*., 2022, **4**:271 [Crossref], [Google Scholar], [Publisher]

[43]. Ghaedi M., Javidmehr E., Kalani N., Zabetian H. Comparison of Two drugs, Ephedrine and Dexamethasone, on Pain Caused by Propofol Injection in Patients Undergoing Elective Surgery, *Eurasian Journal of Science and Technology*., 2023, **3**:147 [Google Scholar], [Publisher]

[44]. van Iersel M.B., Munneke M., Esselink R.A.J., Benraad C.E. M., Olde Rikkert M G.M. Gait velocity and the Timed-Up-and-Go test were sensitive to changes in mobility in frail elderly patients. *J. Clin. Epidemiol.* 2008, **61**:186 [Crossref], [Google Scholar], [Publisher]

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