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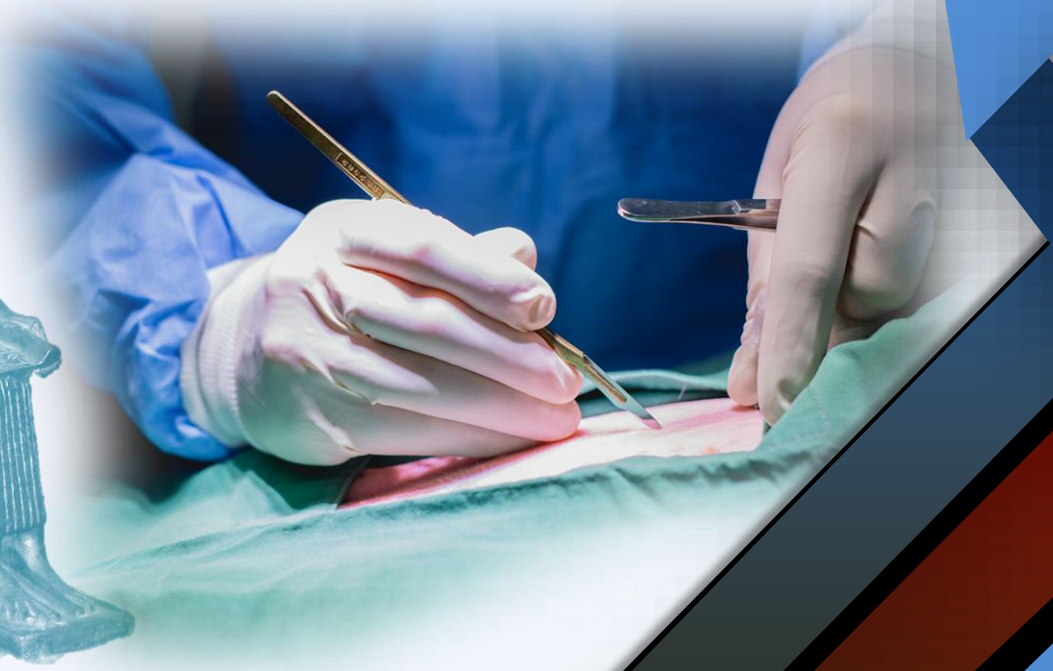

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Effect of Low Frequency Transcranial Magnetic Stimulation on Non-Motor Symptoms [Cognition, Depression and Excessive Day Time Sleepiness] in Parkinson's Disease: A Randomized, Case-Controlled, Parallel Clinical Trial

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ABSTRACT

Background: Parkinson's disease is a complex neurodegenerative disorder characterized by motor and non-motor symptoms. Non-motor issues, such as sleep disorders, depression, and autonomic dysfunction, often appear years before motor symptoms, significantly affecting daily life. However, their overall impact on the disease's burden is still debated.

The aim of the work: This study aimed to compare airway pressure release ventilation [APRV] mode and synchronized intermittent mandatory ventilation [SIMV] mode with lung protective strategy protocol.

Patients and Methods: A randomized, case-controlled trial was conducted on 40 PD patients enrolled from Al- Zahraa University Hospital. Patients were randomly assigned to receive either ten consecutive LF-TMS sessions [n=20] or sham sessions [n=20]. Cognitive function, depressive symptoms, sleep quality, and daytime sleepiness were assessed before, immediately after and after one- month of TMS sessions using the Montreal Cognitive Assessment [MOCA], Hamilton Depression Rating Scale [HDRS], Pittsburgh Sleep Quality Index [PSQI], and Epsworth Sleepiness Scale [ESS], respectively. In addition, the motor threshold was determined for the right first dorsal interosseous muscle, and patients received ten consecutive days of LF-TMS over the right dorsolateral prefrontal cortex [DLPFC].

Results: Compared to the sham group, the patient group showed significantly higher MOCA scores improvement [$p<0.001$] and significantly improvement in depressive symptoms evaluated by the HDRS. In addition, a statistically significant higher improvement percentage of PSQI and ESS in the patients group than in the sham group, with a p-value [$p<0.001$], and this improvement present immediately after LF-TMS sessions and remained for one month later. The improvement in MOCA showed a negative correlation with age in years with a p-value [$p<0.05$].

Conclusions: LF-TMS improved cognition, depression, and EDS in PD patients, supporting its potential as a non-invasive treatment for non-motor symptoms.

Keywords: Parkinson`s Disease; Transcranial Magnetic Stimulation; Cognition; Depression; Excessive Day time Sleepiness.

INTRODUCTION

Parkinson's disease [PD], a progressive neurodegenerative disorder, is predominantly characterized by motor symptoms, such as tremor, rigidity, bradykinesia, and postural instability [1]. However, the clinical picture of PD extends far beyond these motor impairments, encompassing a wide spectrum of non-motor symptoms [NMSs] that significantly impact patients' quality of life and overall well-being [2]. The pathological hallmark of PD is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta [SNpc], a region of the midbrain responsible for regulating movement. This neuronal loss leads to a reduction in dopamine, a neurotransmitter crucial for coordinating motor function [3].

The diverse array of NMSs in PD encompasses a multitude of domains, including sleep disturbances, cognitive impairments, mood disorders, autonomic dysfunction, and sensory deficits. These NMSs often emerge early in the disease course and can significantly worsen as Parkinson disease progresses [4]. In this case, NMSs includes cognition, depression and excessive day time sleepiness [EDS]. The precise mechanisms underlying NMSs in PD are still being elucidated, but several factors are implicated. Dopaminergic deficits, particularly in the non-motor regions of the brain, are thought to play a significant role. Additionally, Lewy body pathology, abnormal iron metabolism, and neuro-inflammation may contribute to the development of NMSs [5].

The management of NMSs in PD is challenging due to their complex nature and heterogeneity. While there is no single treatment approach that effectively addresses all NMSs, a combination of pharmacological and non-pharmacological interventions can be tailored to individual patient needs [6].

The Low Frequency Transcranial Magnetic Stimulation [LF-TMS], a non-invasive neuro- modulatory technique, has emerged as a promising therapeutic approach for NMSs in PD. LF- TMS involves the application of magnetic fields to specific brain regions to modulate neuronal activity [7]. However, Dorsolateral Prefrontal Cortex [DLPFC], a region implicated in cognitive function, emotion regulation, and sleep control, has been identified as a potential target for LF- TMS in PD. LF-TMS over the right DLPFC has shown promising results in improving EDS, cognitive decline, and depression [8].

In this study, we aim to determine the efficacy of LF-TMS in alleviating NMSs associated with PD, with a particular focus on cognitive impairment, depressive episodes, and excessive daytime sleepiness.

PATIENTS AND METHODS

Study Design

The study employed a randomized, case-controlled, parallel clinical trial design to evaluate the efficacy of LF-TMS in alleviating NMSs in PD patients. The trial recruited participants from both the Neurology Department and the outpatient clinic at Al-Zahraa University Hospital, with patient enrollment spanning from December 1, 2022, to July 1, 2023.

Study Participants

A total of 40 patients with a diagnosis of PD confirmed according to the Movement Disorder Society [MDS] diagnostic criteria were enrolled in this randomized, controlled clinical trial. Patients were randomly allocated to either the LF-TMS patients' group [n=20] and sham group [n=20] using a computerized randomization algorithm.

Inclusion and exclusion criteria

Participants were required to meet the MDS diagnostic criteria for clinically established PD and be at least 45 years old. On the other hand, individuals with a history of deep brain stimulation, LF-TMS treatment within the past 12 months, contraindications to LF-TMS, cerebrovascular diseases, or severe cognitive impairment were excluded from the study.

Data collection

All participants underwent a comprehensive assessment protocol that included full history taking—covering demographic data, risk factors, family history, and a complete neurological examination—as well as a general and neurological assessment to evaluate overall health and neurological function.

Cognitive function assessment: The Montreal Cognitive Assessment [MOCA] was used to assess cognitive function. The MOCA is a brief [approximately 10 minutes] screening tool designed to detect cognitive impairment. Assessing visuospatial abilities, naming, attention, language, abstraction, delayed recall, and orientation, the MOCA yields a total score of 30. **Pinto *et al*.** reported sensitivity and specificity of 90% and 87%, respectively, for detecting mild cognitive impairment [MCI] [9]. A total score of 26 or greater is considered normal, 18-25 indicates mild cognitive impairment, 10-17 moderate cognitive impairment, and less than 10 indicates severe cognitive impairment [10].

Depression assessment: The Hamilton Rating Scale for Depression [HAM-D] is a clinician- administered questionnaire [used by health care professional] designed to assess depression severity in diagnosed patients. The 17-item version, employed in this study, yields scores ranging from 0 to 52. Scores of 0-7 indicate no depression, 8-16 mild depression, 17-23 moderate depression, and greater than 24 [severe depression] [11].

Sleep quality assessment: The Pittsburgh Sleep Quality Index [PSQI] is a self-report measure developed by Buysse et al. to assess sleep quality [12]. The PSQI comprises 19 self- rated items evaluating sleep duration, latency, disturbances, and efficiency, among other factors. Although the PSQI includes five partner-rated items for clinical reference, this study focused solely on the 19 self-rated items [13]. These items are standardized representations of sleep-related clinical assessment components, including subjective sleep quality, sleep latency, duration, efficiency, disturbances, medication use, and daytime dysfunction.

Daytime sleepiness assessment: The Epworth Sleepiness Scale [ESS] is a brief, self- administered questionnaire assessing daytime sleepiness. Respondents rate the likelihood of dozing off during eight common activities on a four-point scale [0-3]. The total score ranges from 0 to 24, with higher scores indicating greater daytime sleepiness. Scores of 0-7 suggest normal sleepiness, 8-9 average sleepiness, 10-15 excessive sleepiness, and 16-24 extreme sleepiness warranting medical evaluation [14].

LF-TMS: Participants were seated upright and underwent visual

assessment of motor threshold for the right first dorsal interosseous muscle to establish cortical excitability. Single-pulse transcranial magnetic stimulation [TMS] was applied to the corresponding motor cortex region, with stimulus intensity gradually increased until a minimal muscle contraction was observed in at least five of ten trials. Stimulation parameters adhered to safety guidelines. The lowest intensity eliciting a motor evoked potential in 50% of trials or visible thumb, wrist, or finger movement in at least half of ten stimulations within a relaxed muscle defined the motor threshold. To identify the right dorsolateral prefrontal cortex [DLPFC], the TMS coil was positioned 5 cm anterior to the right motor cortex [M1], and a marker was placed at the DLPFC for subsequent stimulation [15].

Active rTMS involved daily 20-minute sessions of 1 Hz stimulation at 1200 pulses using a double-coil TMS device positioned tangentially to the scalp with the handle backward, for ten consecutive days. Sham rTMS employed an inverted coil to mimic stimulation without neural effects, identifiable only by treating physicians. In addition, the PD received the anti-parkinsonism medications including [Sinemet, Cogintol and Inderal] in combination with LF-TMS treatment.

Statistical Analysis:

Data were analyzed using SPSS version 23.0. Descriptive statistics included mean, standard deviation, and range for parametric data, and median with interquartile range for non-parametric data. Frequencies and percentages summarized categorical variables. Kolmogorov- Smirnov and Shapiro-Wilk tests assessed data normality. Independent-samples t-tests compared two parametric means, while Mann-Whitney U tests compared non-parametric groups. Chi- square or Fisher's exact tests compared categorical groups, depending on cell counts. Spearman's rank correlation coefficient evaluated associations between skewed variables. Positive correlations indicated direct relationships, while negative correlations indicated inverse relationships. Scatter plots visualized correlations. A 95% confidence interval and 5% margin of error were established. P-values less than 0.05 indicated significance, and values less than 0.001 indicated high significance.

Ethical Considerations: The ethical approval was obtained from the research ethics committee of Faculty of Medicine for girls, Cairo, Al-Azhar University [FMG-IRB], ID number 1575. In addition, an informed consent was obtained from each patient.

RESULTS

Demographic data: Forty PD patients were randomly assigned to either the Patients Group [n=20] or the Sham Group [n=20]. The two groups were well-matched in terms of demographic characteristics, including age, sex, and education [p>0.05]. However, there was a significant difference between the two groups in disease duration [p<0.001] **[Table 1]**.

Risk factors: There is no significant difference between patients group and sham group according to risk factors, with p-value [p>0.05] **[Table 2]**.

MOCA assessment before, immediately after and after one month TMS: The MOCA scores showed a statistically significant difference between the patients and sham groups, with the sham group exhibiting a higher total score both immediately after and one month after TMS. The p-value for this difference was less than 0.05. Additionally, the percentage of improvement in MOCA scores immediately after and after one month was significantly higher in the patients group than in the sham group, with a p-value less than 0.001 **[Table 3]**.

HDRS assessment before, immediately after and after one month TMS: There was a statistically significant higher severity of depression degree evaluated by HDRS before, immediately after and after one month TMS in patients group than sham group, with p-value [p=0.003], [p=0.046] and [p=0.043] **[Table 4]**. However, the percentage of improvement immediately after and after one month were significantly higher in the LF-TMS group than in sham group.

PSQI assessment before, immediately after and after one-month TMS: There was a statistically significant higher improvement percentage of PSQI in patients' group than sham group, with p-value [p<0.001] **[Table 5]**.

Table [1]: Comparison between patients' group and sham group according to demographic data

		Patients Group [n=20]	Sham Group [n=20]	Test	P-value
Age [years]	Mean±SD	64.45±5.94	61.05±5.08	1.944	0.059
	Range	50-71	51-70		
Sex [n,%]	Male	12 [60.0%]	11 [55.0%]	0.102	0.749
	Female	8 [40.0%]	9 [45.0%]		
Education	Primary	15 [75.0%]	17 [85.0%]	0.625	FE0.429
	Educated	5 [25.0%]	3 [15.0%]		
Disease duration "years"	Mean±SD	8.20±1.40	3.55±0.94	5.740	<0.001*
	Range	4-10	2-5		

Table [2]: Comparison between patients' group and sham group according to risk factors

Risk factors	Patients Group [n=20]	Sham Group [n=20]	Test	P-value
DM	9 [45.0%]	10 [50.0%]	0.100	0.752
HTN	6 [30.0%]	9 [45.0%]	0.960	0.327
IHD	1 [5.0%]	2 [10.0%]	0.360	FE0.548
Family history	2 [10.0%]	0 [0.0%]	2.105	FE0.147

Table [3]: Comparison between patients' group and sham group according to improvement percentage of cognition evaluated by MOCA scale before, immediately after and after one-month TMS

MOCA scale		Patients Group [n=20]	Sham Group [n=20]		
MoCA scale Before TMS	Median [IQR]	21 [19-23.8]	26.5 [24.3_30]		
	Range	17-25	20-30		
MoCA scale immediately after TMS	Median [IQR]	25.5 [21-27]	26.5 [24.3-30]		
	Range	17-30	20-30		
MoCA scale After one month TMS	Median [IQR]	25 [21-27]	26.5 [24.3-30]		
	Range	17-30	20-30		
		Patients Group [n=20]	**Sham Group [n=20]**	**Test value**	**p-value**
Improvement percentage immediately After TMS from Before	Median [IQR]	14.2 [6.1-23.5]	0 [0-0]	-5.109	<0.001*
	Range	0-50	0-0		
Improvement percentage After one month TMS from Before	Median [IQR]	14.2 [1.3-23.5]	0 [0-0]	-4.667	<0.001*
	Range	0-38.9	0-0		
Patients improved regarding MoCA immediately After TMS [n,%]	Improved	17 [85.0%]	0 [0.0%]	29.565	<0.001*
	Not improved	3 [15.0%]	20 [100.0%]		
Patients improved regarding MoCA After one month TMS [n,%]	Improved	15 [75.0%]	0 [0.0%]	24.000	<0.001*
	Not improved	5 [25.0%]	20 [100.0%]		

Table [4]: Comparison between patients' group and sham group according to improvement percentage of depression evaluated by HDRS scale immediately after and after one-month TMS session

		Patients Group [n=20]	Sham Group [n=20]		
HDRS Before TMS	**Median [IQR]**	22 [16.3-27]	14.5 [9.5-19]		
	Range	10-36	4-24		
HDRS immediately after TMS	**Median [IQR]**	19.5 [14.5-22]	14.5 [9.5-19]		
	Range	6-35	4-24		
HDRS After one month TMS	**Median [IQR]**	18.5 [14.5-22]	14.5 [9.5-19]		
	Range	6-35	4-24		
		Patients Group [n=20]	**Sham Group [n=20]**	**Test value**	**P-value**
Improvement percentage immediately After TMS from before	**Median [IQR]**	-21.5 [-26.8_-6.5]	0 [0-0]	-4.888	<0.001**
	Range	-46.67_0	0-0		
Improvement percentage After one month TMS from before	**Median [IQR]**	-18.9 [-26.0_-5.1]	0.0 [0.0-0.0]	-4.888	<0.001**
	Range	-46.67_0	0-0		
Patients improved regarding to HDRS immediately After TMS [n,%]	**Improved**	16 [80.0%]	0 [0.0%]	26.667	<0.001**
	Not improved	4 [20.0%]	20 [100.0%]		
Number of patients improved regarding to HDRS After one month TMS [n,%]	**Improved**	16 [80.0%]	0 [0.0%]	26.667	<0.001**
	Not improved	4 [20.0%]	20 [100.0%]		

Table [5]: Comparison between patients group and sham group according to improvement percentage of excessive day time sleepiness evaluated by ESS scale immediately after and after one month TMS session.

Epsworth Sleepiness Scale		Patients Group [n=20]	Sham Group [n=20]		
Before TMS	Mean±SD	12.00±2.27	9.65±1.66		
	Range	8-15	7-13		
Immediately after TMS	Mean±SD	9.85±1.18	9.65±1.66		
	Range	8-12	7-13		
After one month TMS	Mean±SD	9.90±1.17	9.65±1.66		
	Range	8-12	7-13		
		Patients Group [n=20]	**Sham Group [n=20]**	**Test value**	**P-value**
Improvement percentage of ESS immediately After TMS from Before	Median [IQR]	-18.4 [-26.3_-2.3]	0 [0-0]	-4.667	<0.001**
	Range	-40_0	0-0		
Improvement percentage of ESS After one month TMS from Before	Median [IQR]	-18.4 [-26.3_-2.3]	0 [0-0]	-4.667	<0.001**
	Range	-33.3_0	0-0		

DISCUSSION

Our study included 40 PD patients who were randomly assigned to either the Patients Group [n=20] or the Sham Group [n=20]. The patients' ages ranged from 50 to 71 years old, with no statistically significant difference between the two groups. This indicates that the age distribution was similar in both groups and therefore unlikely to have influenced the study results. The demographic characteristics of the study participants were consistent with previous research findings on PD. The age distribution in our study was similar to that reported by **Park *et al.*** [16] with PD being relatively uncommon in individuals below age 50. Additionally, the mean age of our participants [61.0±10.9 years] was comparable to that reported by **Zhuang *et al.*** [17].

The sex distribution in our study, with a male-to-female ratio of 3:2 in the Patients Group and 3.3:3 in the Sham Group, was consistent with the findings of **Zhuang *et al.*** [17] who reported that a majority of their patients were males [54.5%]. However, our results differed from those of Park et al., [16] who found a higher standardized prevalence of PD in women than in men in Asia, specifically South Korea, from 2010 to 2015. This discrepancy may be attributed to geographical variations and differences in sample size.

Disease duration in our study ranged from 4 to 10 years in the Patients Group and from 2 to 5 years in the Sham Group, with a statistically significant difference between the two groups. This difference was likely due to random classification of the study subjects. **Guo *et al.*** [18] reported that NMS are common in all disease duration stages of PD patients and tend to become more severe with disease progression.

Regarding educational level, the majority of patients in both the Patients Group [75%] and the Sham Group [85%] had primary education up to primary grade 6. The remaining patients in both groups had 11 years of education. These findings align with the meta-analysis conducted by **Baiano *et al.*** [19] which revealed that PD occurs more frequently in older age and lower educational level. This suggests that a higher level of education may offer protective benefits against cognitive decline in PD patients and is strongly associated with cognitive efficiency in the later stages of the disease.

Our study investigated the efficacy of repetitive transcranial magnetic stimulation [rTMS] in improving cognitive function in PD patients. The findings demonstrate that LF-TMS significantly enhances cognitive performance, as assessed by the MOCA scale, both immediately and one month following LF-TMS. This improvement aligns with previous studies that have reported beneficial effects of LF-TMS on cognitive function in PD patients [17].

Our results partially align with **Alzahrani and Venneri** [20], who observed significant improvements in neuropsychological tests assessing executive function following rTMS. This pattern of findings is consistent with the cognitive profile of patients with frontal lobe dysfunction, a common manifestation of PD. Similarly, our findings are in line with **Furukawa *et al.*** [21] who reported significant improvements in cognition following longer stimulation durations [20-30 minutes] of low-frequency rTMS. This suggests that the length and frequency of stimulation may influence its effects on synaptic connections and associated cognitive functions. Partially consistent with our findings, **Boggio *et al.*** [22] demonstrated that active LF-TMS improved performance on the Stroop test, which assesses executive function, by 9.5% compared to the sham stimulation group.

Additionally, accuracy improved by 16% in the active treatment group, further supporting the cognitive benefits of LFTMS. In contrast, **Khedr *et al.*** [15] found no significant differences in the effects of TMS on cognitive function between groups in their pilot study on PD patients with dementia. This discrepancy may be attributed to differences in the TMS protocol, including the type, site of stimulation, and PD patient characteristics. **Khedr *et al.*** applied high-frequency TMS to both cortical and frontal regions in 33 PD patients with pre-existing dementia. Similarly, **Goodwill *et al.*** [23] conducted a meta-analysis of 33 studies examining the effects of LF-TMS and transcranial electric stimulation [TES] on motor and cognitive symptoms in PD individuals.

Broeder *et al.* [24] conducted a systematic review and concluded that LF-TMS had a greater effect on motor function than cognitive function in PD patients. This difference may be explained by variations in the TMS protocol, including the site of stimulation and neuropsychological tests. **Broeder *et al.*** [24] applied LF-TMS to the primary motor area and utilized different neuropsychological tests, such as TMT and reaction time tests.

In our study, we investigated the effect of LF-TMS on depression in PD patients. Our findings demonstrate that LF-TMS significantly improves depression severity, as assessed by the HDRS, both immediately and one month following treatment. Additionally, our findings align with previous studies that have reported beneficial effects of rTMS on depression in PD patients [17, 25]. In contrast, two studies **Brys *et al.*** [26] and **Lomarev *et al.*** [27] found no significant effects of LF-TMS on depression in PD patients. The discrepancy between these findings and our own may be attributed to differences in the TMS protocol, including the frequency and site of stimulation. **Brys *et al.*** [26] applied high-frequency TMS to bilateral M1 and left DLPFC in 50 PD patients, while Lomarev et al. applied LF-TMS to bilateral motor and DLPFC areas in 18 PD patients.

Our study investigated the effect of rTMS on sleep quality and EDS in PD patients. We found that rTMS significantly improves both sleep quality, as assessed by the PSQI, and EDS, as assessed by the ESS, both immediately and one month following treatment. These improvements align with previous studies that have reported beneficial effects of rTMS on sleep quality and EDS in PD patients [17]. In contrast, one study conducted by **Arias *et al.*** [28] found no significant effect of rTMS on sleep quality in PD patients. This discrepancy may be attributed to the small sample size of Arias et al.'s study, which included only 9 patients in each group.

Limitations: The study has several limitations, including a small sample size, a short treatment duration, a lack of long-term follow-up and a single-center design. These limitations suggest that the results of the study should be interpreted with caution. Further research with larger, longer-term, and double-blinded studies is needed to confirm these findings and to determine whether LF-TMS is an effective treatment for NMSs in PD patients.

Conclusion: In this study, LF-TMS applied to the DLPFC resulted in significant improvements in cognition, depression symptoms, and excessive daytime sleepiness in PD patients compared to a sham stimulation group. These findings align with previous research suggesting that LF-TMS may offer a valuable therapeutic approach for managing NMS in PD.

Recommendations: Low-frequency rTMS shows promise in treating NMS in PD, particularly cognition, depression, and excessive daytime sleepiness [EDS]. Larger studies with longer follow-up are needed to fully understand its benefits and mechanisms. To investigate sleep disorders improvement, we recommend collecting saliva samples and analyzing melatonin levels. Additionally, quantitative assessment tools, such as polysomnography, can provide objective measures of EDS and other sleep disturbances in PD, aiding in treatment evaluation.

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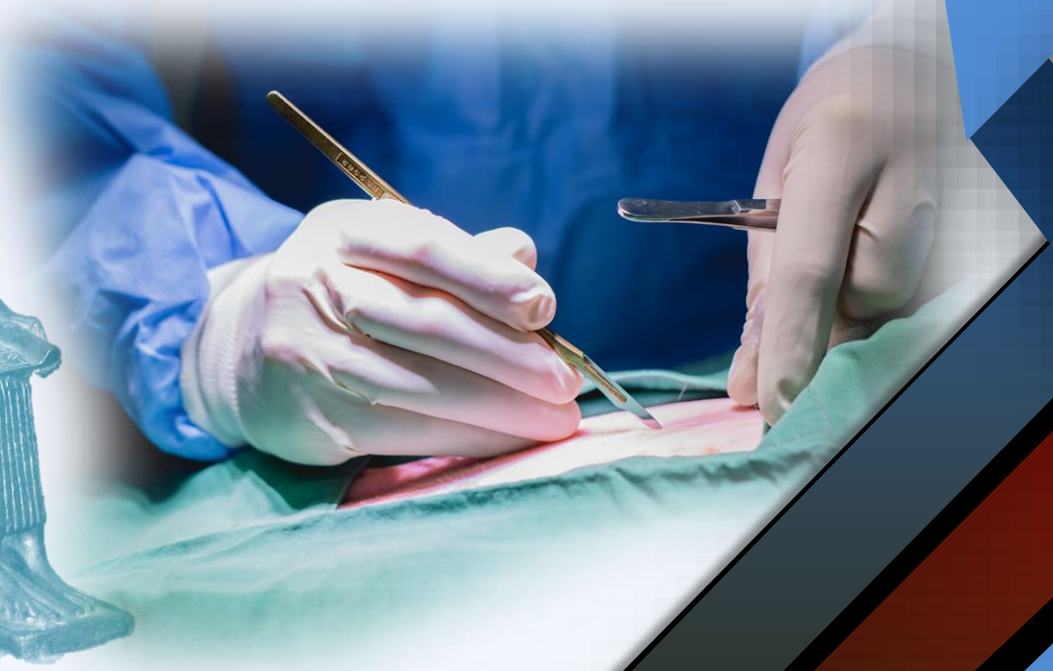

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