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Research Article

Effect of Oropharyngeal Stimulation and Tongue PNF on Cognition, Quality of Sleep and Hba1c in Patients with Obstructive Sleep Apnea- A Randomized Clinical Trial

Vrushali Bhore*, Jeba Chitra, Jowena Parikh

Department of Neurophysiotherapy, KAHER Institute of Physiotherapy, Belagavi-590010, India

ABSTRACT

Background: OSA is related to cognitive disturbances and poor sleep quality. The lifetime prevalence of OSA is 21.7% causing collapse of Upper Airway muscles which then leads to recurrent hypoxia and wakening of the individual. When intensity worsens, patients tend to feel sluggish during tasks that usually require alertness (e.g., education, work, driving), daytime fatigue/tiredness, cognitive deficits (short-term memory, concentration), decreased attention, morning agitation, changes in temperament and mood like depression and anxiety.

Aim: The objective of the current research was to determine impact of Oropharyngeal Stimulation and Tongue Proprioceptive Neuromuscular Facilitation (PNF) on Cognition, Quality of Sleep and glycated hemoglobin in OSA patients.

Methods: 30 adults were recruited in the study and were randomized to 2 groups. A 4 week session of Oropharyngeal Stimulation was given to the subjects for 20 minutes for Group A and Tongue PNF for Group B. The outcome measures used in the study were Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Mindful Attention Awareness Scale, Addenbrooke Cognitive Examination- III, Trail Making Test, Digit Span Test and Glycated Hemoglobin.

Results: The results state that there was a statistical noteworthy change in the all the outcome measures for all the participants of Group A and B. Improvements were also seen in the parameters for within group analysis. ($p<0.05$). Daytime sleepiness reduced in terms of both the interventions along with quality of sleep. In terms of cognition, significant change was seen in the Tongue PNF group.

Conclusion: This study concluded that a 4 week intervention of Oropharyngeal Stimulation and Tongue PNF improved Cognition, Hba1c and Quality of Sleep in patients with Obstructive Sleep Apnea.

Keywords: Glycated hemoglobin; Oropharyngeal stimulation; Tongue PNF; Epworth sleepiness scale; ACE-III; MAAS; Obstructive sleep apnea

INTRODUCTION

Obstructive Sleep Apnea (OSA) is becoming a significant public health issue caused due to intermittent upper airway (UA) collapse [1]. Genioglossus, being the chief upper airway dilator, has ineffective muscle response towards the hypoxic and hypercapnic changes which occur during ventilation. This augmentation of the muscular activity causes narrowing of the pharyngeal lumen [2]. This compromised airflow often leads to repeated arousal during sleep along with blood gas abnormalities [3].

Being prevalent in approximately 2 to 5% of adult women and 3 to 7% for adult men, the patient is often unaware of the symptoms of OSA [3,4]. Poorquality of sleep, witnessed apneatic episodes by the partner, loud snoring and excessive hyper somnolence are the cardinal symptoms used to diagnose OSA. Cardiovascular diseases, Excessive Daytime Sleepiness, impaired cognitive functions remain as the consequences of OSA if not treated [5].The glucose metabolism also gets affected leady to alteration of the glycated haemoglobin levels [6].

Continuous Positive Airway Pressure (CPAP) has been shown to be the first treatment line, but patient compliance has failed to meet the expectations [7]. Electromyographic studies and various other imaging technologies have helped in narrowing down the

***Correspondence to**: Vrushali Bhore, Post Graduate, Department of Neurophysiotherapy, KAHER Institute of Physiotherapy, Belagavi-590010, India, Tel: 8097322104; E-mail: vrushalibhore@gmail.com

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root causes of OSA, including the anatomical and physiological dysfunctions [8]. Post these findings, various researches focused towards the interest of alternative therapies for ameliorating the effects of OSA [1]. Several studies experimented the effect of surface as well as intraneural stimulation on the UA patency and the associated pharyngeal muscle activity. A research investigated the influence of sublingual stimulation during sleep but was unsuccessful in opening the airway and overall patency of the airflow [9]. Stimulating Hypoglossal nerve and aimed to reduce the Apnea Hypopnea Index (AHI) in the subjects, but adverse side-effects and intolerance was reported by the subjects [10].

Many of the researches had contradictory results with regard to clinical outcomes. The dynamics of genioglossus in OSA subjects and concluded that rehabilitation options for this muscle would be a promising treatment option [11]. Along with these approaches, myofunctional therapies were also introduced as a therapeutic alternative for combatting the consequences of OSA. A recent metaanalysis explained reduction of snoring post pharyngeal exercises in OSA subjects but had temporary effects as the local musculature remained untreated [12]. Though there are several treatment options, many of them have poor patient compliance and are not known to the general population. Hence, some patients are inadequately treated owing to poorly tolerated treatment options. This exposes the patients to a significantly increased risk of cardiovascular and metabolic disorder with no effective treatment. It has also been described as a risk factor for injuries, neurocognitive dysfunction and depression, declining quality of life and increased cost of health care.

In the course of UA collapse, arbitration of ventilation leads to hypopnea or apnea causing hypoxia and hypercapnia. Eventually there is increase in respiratory drive in order to reopen the Upper Airway. This process reflects dysfunction of genioglossus which is a major Upper Airway dilator muscle along with hyper tonicity of pharynx which also collapses. Hence training of UA muscle will alleviate OSA

CPAP is considered to be the gold standard treatment for management of OSA. But some patients are inadequately treated owing to poorly tolerated CPAP. This exposes the patients to a significantly increased risk of cardiovascular and metabolic disorder with no effective treatment.

Neuro-electrical stimulation of genioglossus induces acute transient improvements in airflow dynamics and strengthens the Upper Airway muscles. Along with this, training the tongue musculature with certain exercises will promote excitation of the motor units and promote the strengthening of genioglossus muscle.

The present study explains the role of genioglossus in ventilation during sleep and aims to study the effect of Oropharyngeal Stimulation and Tongue PNF on cognitive abilities, quality of sleep and the changes in the levels of Glycated haemoglobin in OSA patients.

METHODOLOGY

A randomized, non-blinded, experimental clinical study was conducted on 30 patients with OSA. Institutional Ethics committee approved the research. A written informed consent was obtained from the participants, and the two classes were randomly allocated to those who met the inclusion and exclusion requirements. All the subjects were assessed at baseline as well as after a treatment period of 4 weeks.

Subjects above 18 years of age, clinically diagnosed to have OSA and who scored more than 10 on Epworth Sleepiness Scale were considered eligible for the study. Subjects with uncontrolled T2 DM, any condition of COPD, nasal polyps and having any congenital, malignant, autoimmune, and neurological conditions were excluded based on medical history and documentation from the study.

INTERVENTION

Oropharyngeal Stimulation was given for 20 minutes with an intensity ranged between 30-100 Hz. The electrodes were placed at the suprahyoid region with the subjects in supine lying position [13].

Tongue exercises were performed with subjects in sitting position. First tongue PNF exercise included “opening of mouth” wherein subject was asked to perform opening of mouth and a resistance was provided from the jaw in an upward direction with a 10 seconds hold. Next exercise was “closing of mouth”, in which subject was asked to maintain a mouth open position and was then asked to perform closing of mouth and the therapist resisted this movement by giving a downward resistance at the chin with 10 seconds hold [14].

Tongue movements were resisted using a wooden craft stick. Subject was instructed to touch tongue to the hard palate and a resistance was provided in a downward with 10 seconds hold. Next, the subject had to move the tongue in downward direction and a resistance was given with the help of stick in upward direction. For resisting the lateral movements, subject had to perform protrusion of the tongue and had to perform lateral movements in both left and right directions. Both these directions were resisted with opposite force [15]. All these exercises were performed with 5 repetitions in each session. The same routine was carried out for 3 days in a week for 4 weeks. The treatment lasted for twenty minutes each day. At the end of the treatment session the subject’s Daytime Sleepiness, sleep quality, cognition and glycated hemoglobin levels were re-assessed.

OUTCOME MEASURES

Epworth Sleepiness Scale was used to measure the rate of Daytime Sleepiness experienced while various daily activities in the subjects. The ranking ranges from 0 to 24, with a ranking above 10 indicating extreme daytime sleepiness [16].

Pittsburgh Sleep Quality Index is being used to measure sleep quality and patterns. It explains seven areas: subjective quality of sleep, sleep latency, sleep duration, habitual efficiency of sleep, sleep disturbances, use of sleep medication, and last month's daytime dysfunctions. Scoring of the answers is based on a scale of 0 to 3, whereby 3 reflects the Likert Scale negative extreme [17].

Mindful Awareness Scale measured core features of dispositional perception, namely, responsive or receptive awareness and sensitivity to what is happening in the present. It is a Likert type scale with scoring options from 1 to 6, indicating lesser the score, lesser is the mindfulness and attention [18].

The five cognitive domains were tested using Addenbrooke Cognitive Examination-III: attention/orientation, memory, vocabulary, verbal fluency, and visuospatial abilities. It is scored from 100, with a higher score indicating better cognitive function [19]. Tail Making Test was included in order to assess visual attention and task switching abilities of the subjects.

Digit Span Test was used to assess the immediate verbal recall, attentional capacity, and working memory. Glycated Hemoglobin was considered in the study as there is poor glucose metabolism in OSA [20,21].

STATISTICAL ANALYSIS

Mathematical evaluation for the present study was performed by using Statistical Product and Service Solution 23 Version so as to authenticate the results found. The data was filled manually into an excel sheet and then tabulated which was then subjected for evaluation for the same. Various mathematical evaluations such as mean, standard deviation were employed. The test for Normality for the data set was done using Kolmogorov-Smirnov test. The Homogeneity of the data was checked using the Chi Square Test for gender distribution, age, weight, height and BMI distribution in the present study. Independent t test was administered for the pre and post between group effect and Dependent t test was used for within group effect outcome measures in terms of Epworth Sleepiness Scale, Addenbrooke Cognitive Examination-III, Pittsburgh Sleep Quality Index, Mindful Attention Awareness Scale, Trail Making Test A and B, Digit Span Test and Glycated Hemoglobin. P-values <0.05 was contemplated powerful and the p-values <0.001 was mediated highly powerful.

RESULTS

Homogeneous distribution of data was seen terms of all the outcome measures and their variables (Table 1). The total number of males in the current study were 16 that is 66.67% and the total number of females in the current study were 14 that is 33.33%.

Table 1: Normality of pretest and posttest scores of different variables in two groups (Group A and Group B) by Kolmogorov Smirnov test.

Variables	Time points	Group A		Group B	
		Z-value	P-value	Z-value	P-value
ESS	Pretest	0.672	0.758	1.219	0.102
	Posttest	1.203	0.111	1.279	0.076
	Difference	0.831	0.494	0.613	0.846
PSQI	Pretest	0.679	0.746	0.808	0.531
	Posttest	0.692	0.725	0.672	0.757
	Difference	0.718	0.682	1.002	0.268
MAAS	Pretest	0.752	0.623	0.821	0.51
	Posttest	0.542	0.93	0.737	0.649
	Difference	0.708	0.697	0.703	0.706
ACE-III	Pretest	0.747	0.631	0.453	0.986
	Posttest	0.912	0.376	0.662	0.773
	Difference	0.733	0.655	0.564	0.908
TMT-A	Pretest	0.885	0.414	0.76	0.61
	Posttest	0.863	0.446	0.718	0.681
	Difference	0.577	0.893	0.703	0.705
TMT-B	Pretest	0.643	0.803	1.204	0.11
	Posttest	0.632	0.819	0.405	0.997
	Difference	0.409	0.996	0.936	0.345
DST	Pretest	0.824	0.505	0.809	0.529
	Posttest	0.758	0.613	0.683	0.739
	Difference	0.551	0.922	1.112	0.169
HbA1C	Pretest	1.039	0.23	0.646	0.798
	Posttest	0.982	0.289	0.843	0.476
	Difference	0.831	0.494	0.88	0.42

The gender distribution was homogeneous (p-value 0.1431) in the present study which was estimated by Chi Square Test (Table 2).

The mean BMI of the Group A in the current study was 27.20 ± 2.57 and of Group B was 26.33 ± 2.74. The BMI distribution has indicated limited homogeneity (p-value 0.3794) in the present study (Table 3).

Dependent t Test was used to perform the within group analysis. For the pre and post score of ESS, PSQI and TMT-A, both Groups A and B had significant changes with p value- 0.0001*. For the MAAS score, Group A had significant changes (p-value 0.0296*), whereas there was no significant change seen in Group B. In ACE-III, Group B scores improved with a significant change (p-value 0.0090*). In TMT-B scores, both Group A and B had changes after intervention with significant p value of 0.0001* and 0.0006* respectively. In DST score, Group A had more significant changes (p-value 0.0002*) compared to Group B. In HbA1c values, both the groups had evident changes p value of 0.0002 and 0.0022* significantly (Table 4). Independent t Test was used for between group analyses. Significant change was observed in Group B score of PSQI and ACE-III with a p value of 0.0299* and 0.0063* (Table 5).

DISCUSSION AND COCLUSION

Majority of the population based studies have shown that OSA is more common in males than in females. Lin et al. examined the gender differences in OSA and analyzed the differences in pathogenic mechanisms. Differences in Upper Airway (UA) anatomy, neurochemical mechanism, the response to arousal, fat distribution and sex hormones were found to be the contributing factor for OSA to be more common in males [22]. Gallego et al. stated that the rate of female obesity was less compared to males which indicated towards prevalence of OSA higher in males [23]. The present study also had more number of males signifying the dominance of OSA in male gender.

In male patients, BMI and lifestyle habits are the prominent risk factors for OSA. Deng et al. stated that 45-53 years age group presented with OSA and its severity increased with age [24]. Ayalon et al. highlighted the increase of Apnoea-Hypopnea Index (AHI) along with age. In the present study, majority of patients were above 51 years of age [25]. This suggests that the increase in age overwhelms the brain's capacity to compensate.

Shaw etal. stated that there was significant interaction between BMI and OSA. Patients having higher BMI were prone to severe OSA [26]. Similarly, Jehan et al. mentioned that patients with BMI>25 kg/m^2 were highly recumbent to OSA [27]. In our study, all the

Table 2: Comparison of two groups (Group A and Group B) by gender.

Sex	Group A	%	Group B	%	Total
Male	6	40	10	66.67	16
Female	9	60	5	33.33	14
Total	15	100	15	100	30
Chi-square=2.1432 P=0.1431					

Table 3: Comparison of two groups (Group A and Group B) with mean age and BMI scores by independent t test.

Variables	Group A		Group B		t-value	p-value
	Mean	SD	Mean	SD		
Age in yrs	49.53	8.98	48.93	8.84	0.1843	0.8551
BMI	27.2	2.57	26.33	2.74	0.8931	0.3794

Table 4: Comparison of pretest and posttest scores in Group A and Group B by dependent t test.

Outcome measures	Groups	Time points	Mean	SD	Mean Diff.	SD Diff.	% of effect	t-value	p-value
ESS	Group A	Pretest	19	5.94	9.73	6.09	51.23	6.1918	0.0001*
		Posttest	9.27	2.34					
	Group B	Pretest	20.13	3.6	9.87	3.89	49.01	9.8262	0.0001*
		Posttest	10.27	3.51					
PSQI	Group A	Pretest	29	11.43	11.93	7.09	41.15	6.5225	0.0001*
		Posttest	17.07	5.55					
	Group B	Pretest	32.93	6.75	11.87	8.35	36.03	5.5052	0.0001*
		Posttest	21.07	3.88					
MAAS	Group A	Pretest	42.87	9.69	10.2	16.31	23.79	2.4227	0.0296*
		Posttest	32.67	13.47					
	Group B	Pretest	38.67	12.88	5.33	14.9	13.79	1.386	0.1874
		Posttest	33.33	7.86					
ACE-III	Group A	Pretest	59.07	9.22	6.93	18	11.74	1.4917	0.158
		Posttest	52.13	13.79					
	Group B	Pretest	53.4	4.73	-12.93	16.54	-24.22	3.0289	0.0090*
		Posttest	66.33	12.52					
	Group A	Pretest	2.23	1.18	0.86	0.64	38.74	5.2256	0.0001*
TMT-A		Posttest	1.37	0.78					
	Group B	Pretest	2.09	0.79	0.96	0.68	45.88	5.4883	0.0001*
		Posttest	1.13	0.6					
TMT-B	Group A	Pretest	4.23	1.44					
		Posttest	2.53	0.66	1.71	0.95	40.32	6.9848	0.0001*
	Group B	Pretest	4.03	1.49					
		Posttest	1.99	0.85	2.04	1.78	50.61	4.4448	0.0006*
DST	Group A	Pretest	2.22	0.98					
		Posttest	1.41	0.82	0.81	0.62	36.45	5.0286	0.0002*
	Group B	Pretest	2.34	0.85					
		Posttest	1.92	0.61	0.42	1.25	18	1.3038	0.2133
HbA1c	Group A	Pretest	7.41	0.65					
		Posttest	5.86	1.27	1.55	1.22	20.88	4.9219	0.0002*
	Group B	Pretest	7.29	0.56					
					2.02	2.1	27.7	3.7308	0.0022*

Table 5: Comparison of pretest and posttest scores in Group A and Group B by Independent t test.

Outcome measures	Time points	Group A		Group B		t-value	P-value
		Mean	SD	Mean	SD		
ESS	Pretest	19	5.94	20.13	3.6	-0.6318	0.5326
	Posttest	9.27	2.34	10.27	3.51	-0.9168	0.3671
PSQI	Pretest	29	11.43	32.93	6.75	-1.1481	0.2607
	Posttest	17.07	5.55	21.07	3.88	-2.288	0.0299*
MAAS	Pretest	42.87	9.69	38.67	12.88	1.0092	0.3215
	Posttest	32.67	13.47	33.33	7.86	-0.1656	0.8697
ACE-III	Pretest	59.07	9.22	53.4	4.73	2.1185	0.0431
	Posttest	65.13	20.79	79.33	12.52	-2.9526	0.0063*
TMT-A	Pretest	2.23	1.18	2.09	0.79	0.3909	0.6989
	Posttest	1.37	0.78	1.13	0.6	0.9307	0.36
TMT-B	Pretest	4.23	1.44	4.03	1.49	0.3785	0.7079
	Posttest	2.53	0.66	1.99	0.85	1.921	0.065
DST	Pretest	2.22	0.98	2.34	0.85	-0.3815	0.7057
	Posttest	1.41	0.82	1.92	0.61	-1.9481	0.0615
HbA1C	Pretest	7.41	0.65	7.29	0.56	0.5133	0.6118
	Posttest	5.86	1.27	5.27	1.87	1.0067	0.3227

patients had BMI above 25 kg/m^2 which falls under the category of Class I obese stating that obesity is a contributing factor for OSA.

The effect of Oropharyngeal stimulation and tongue PNF in obstructive sleep apnea patients was investigated in the current study. The participants were given oropharyngeal stimulation and tongue PNF for 3 days per week for 4 weeks.

In OSA, the increase in UA resistance and decreased transient ventilation occurs due to lowering of the phasic inspiratory activity of genioglossus. Hence, there is increase in frequency and intensity of snoring giving rise to increased Apnoea Hypopnoea Index (AHI) in these patients.

Two of the research trials studied the effect of electrical muscle stimulation in OSA, in which reduction of Daytime Sleepiness and snoring reduced significantly post intervention. Genioglossus muscle phasic activity increased post intervention which reduced the snoring and AHI. Since the AHI reduced, the hypoxic and hypercapnic effect is also minimized which activates the neural networks of Slow Wave Sleep (SWS) phase. This phase is known to be the deepest phase of Non Rapid Eye Movement (NREM) sleep [28]. The activation of neural networks of SWS phase will promote sound sleep. Also the mechanical effects of muscular

contraction of genioglossus during tongue exercises decrease the critical pressure and the pharyngeal restriction which reduce the rate of AHI. These findings support the outcome of our study with respect to the Epworth Sleepiness Scale (ESS), wherein there was significant decrement in the daytime sleepiness of all the subjects. The pre-post change of ESS scores within group was significant relatively to the between group scores.

Sleep has a fundamental role in optimal health as it plays a vital role in growth and cognitive functions. Patients with OSA don't have adequate sleep due to apneas which cause nocturnal wakefulness causing fragmentation of sleep. This leads to impoverished quality of sleep since the brain arouses in order to resume to normal ventilation [29].

Randerath et al. determined that intraoral electrical stimulation reduced these episodes of apneas and sleep fragmentation promoting good quality of sleep. After neuro-stimulation of the Hypoglossal nerve, there was enhancement of neural modulation and motor output of genioglossus muscle [30]. These findings directed towards improvement of quality of sleep. The effect of tongue on Upper Airway was significant causing expansion of the retropalatal distance maintaining airway patency.

Brown et al. mentioned short retro-palatal distance as the cause for high AHI and severe OSA. Thus, the airway obstruction was mitigated by tongue exercises by increasing pharyngeal muscle tension during sleep at night [31]. These findings are constant with the outcomes of our study on Pittsburgh Sleep Quality Index. All the subjects of both the groups had significant improvement in their quality of sleep. The between groups change was more compelling in Group B (p value-0.0299*) which explains crucial effect of tongue exercises on the pharyngeal patency.

Several authors have stated that awareness and attention are proportionately consistent features of optimal cognitive functioning but mindfulness is considered to be reinforcement of attention and awareness with respect to the present situation and events. Mulgrew et al. investigated the effect of OSA on attention, awareness and vigilance of the subjects. Recurrent asphyxia and fragmentation of sleep lead to decreased awareness and attention of the subjects in their professional performances. Subjects had episodes of micro sleeps and neurocognitive symptoms in their daily activities [32].

Studies have explained intermittent hypoxia with reduced cerebral blood flow as the leading cause for neurocognitive dysfunction. Treating these hypoxic events, sleep fragmentation along with loss of neuromuscular tone of genioglossus would be a promising factor for combatting the neurological deficits in OSA.

Recently, a study published encouraging the use of electrical stimulation at sub mental region and intraoral sublingual region with the use of apnoea sensors and percutaneous electrodes. These subjects were later assessed on Tests of Variables of Attention (TOVA) and there were significant changes post intervention in the scores of TOVA [33].

The present study includes Mindful Attention Awareness Scale (MAAS) as the outcome for assessing attention and awareness. The findings of the previous study valuates the results of our study wherein all the subjects have improvement in the MAAS scores post intervention. Also there is significant change in Group A (Oropharyngeal stimulation and Tongue PNF) compared to Group B.

Hypoxemic changes at the time of sleep as well as wakefulness contribute in biochemical disruption and hemodynamic changes of Central Nervous System. The function of neurotransmitters and brain adenosine is notably affected in hypoxemia. Inclining this correlations, previous investigators have stated hypoxemia to have association with cognitive impairment [15].

Joo et al. suggested that there was alterations in cortical excitability when awake and performing daily functions [34]. Several reviewers have assessed the impaired cognitive functions have revealed poor executive functions in these OSA patients. Hypoglossal nerve stimulation has been used widely in mitigation of cognitive decline since past few years but it has its own risks since it's an invasive intervention. Our study used non-invasive superficial neuromuscular stimulation for genioglossus muscle. In the present study, Addenbrooke Cognitive Examination-III scores improved post intervention in all the subjects. Group B had significant changes compared to Group A.

Similarly, the visual attention and task switching ability alters and affects the cognitive ability of OSA patients. Conclusions of the studies in treatment of OSA patients are in line with the results of our study on Trail Making Test with significant changes in post time durations of the subjects of both the groups. The post-intervention time duration of the subjects within groups decreased as to the pre-intervention time.

Research states that intermittent hypoxia is a primary contributing factor for impaired working memory and immediate verbal call. A study protocol including neural stimulation affirmed that there was neural activation of channels at the prefrontal cortex on investigation [35]. In the present study, Digit Span Test was used to assess the working memory and attention. The post-intervention duration of the subjects was reduced compared to the pre-intervention duration.

A consistent association is present between OSA and impaired glucose metabolism. The intermittent hypoxia causes increase in systemic inflammation along with oxidative stress. The increase in systemic inflammation activates the sympathetic nervous system in order to provide nourishment at the systemic level [36]. Since it is a chronic state there will be aversion of the sympathetic fibers along with disorganization of the local adrenoreceptors causing "permanent local inflammation", which furthera study focusing on Hypoglossal nerve stimulation in OSA patients assessed the oxidative stress using Reactive Oxygen Species (ROS) as a biomarker along with pre-post glycated hemoglobin levels [37]. At the end of intervention there was uniformity in the oxidative stress levels and normal regulation of glycated hemoglobin. In the present study, the Glycated hemoglobin levels of all the subjects improved post intervention with normal values.

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