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Effectiveness of Kinetic Oscillation Stimulation Treatment in Patients with Non-Allergic Rhinitis Refractory to Conventional Medical Therapies

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Kinetic oscillation stimulation; Non-allergic rhinitis; Idiopathic rhinitis; Quality of life; Non-surgical treatment

1. Abstract

1.1. Introduction: Kinetic Oscillation Stimulation (KOS) is a new treatment for symptoms of non-allergic rhinitis (NAR). The aim of the study was to investigate effectiveness of KOS treatment in patients affected by NAR.

1.2. Methods: From December 2018 to July 2020, 39 patients, already refractory to conventional medical therapy, were treated with KOS. As control group, we considered a group of 41 patients treated with topical mometasone furoate, observed in the same period and number of days. During the ENT visit, objective examinations were performed to assess respiratory function. In addition, all the subjects filled out quality of life (QoL) questionnaires. All patients were reevaluated after 45 days.

1.3. Results: All the instrumental assessments and QoL questionnaires showed a significant improvement 45 days after KOS treatment. Sixteen patients (43%) reported an improvement across all tests. Active anterior rhinomanometry improved for Inspiratory Resistance in 26 patients (70%) and for Expiratory Resistance for 27 patients (73%). Moreover, we found that KOS group presented a better improvement statistically significant for the QoL questionnaries, respect the control group.

1.4. Conclusion: KOS treatment is a safe and mini-invasive procedure for the treatment of NAR symptoms, well accepted from patients and with a promising improvement of QoL, better than conventional medical therapies.

2. Introduction

Recently, a new method of treatment of nasal mucosa, Kinetic Oscillation Stimulation (KOS), seems to be a possibly effective and safe short-term treatment of nasal stuffiness of idiopathic rhinitis (IR) or non-allergic rhinitis (NAR). A randomized controlled study evaluated KOS treatment in patients with non-allergic rhinitis, finding a positive effect on nasal obstruction as compared to placebo mainly in the first week after treatment [1]. Three main types of inflammatory NAR have been defined: NAR infiltrated by eosinophils (NARES), by mast cells (NARMA), and by neutrophils (NARNE). A new particular type has been characterized with current infiltration by eosinophils and mast cells (NARESMA) [2]. In a recent study, it was demonstrated that quality of life (QoL) is impaired in NAR as well as in allergic rhinitis. Furthermore, QoL impairment differs among the various forms of NAR and there is a correlation with the cellular infiltrating type, being the QoL significantly worse in NARES patients [3]. Medical treatments, such as antihistamines, topical decongestants and topical corticosteroids are commonly used to treat rhinitis, also NAR, principally to reduce nasal obstruction and restore comfortable nasal breathing. However, not all patients may respond to those medications. Therefore, there has been a variety of surgical techniques of inferior turbinates described and performed over the years to relieve the nasal obstruction. Although effective in relieving nasal block, especially non-mucosal-sparing techniques have been associated with postoperative complications such as excessive bleeding,

crusting, pain, and prolonged recovery period. These complications can be avoided with the mucosal-sparing approach, rendering it the preferred option, but also this technique can present minimal adverse reactions, such as crusting, adhesion, dryness, or nasal bleeding [4]. Furthermore, the mucosal sparing approach, without any thermal mucosal damage and in conjunction with medical therapy, also showed an improvement of the nasal flow in persistent moderate-to-severe AR no data are available in the treatment of NAR [5]. The aim of the study was to investigate the effectiveness of KOS treatment in patients affected by NAR, already refractory to conventional medical therapies, evaluating nasal function and QoL related to nasal symptoms.

3. Materials and Methods

From December 2018 to July 2020, from our medical center, we recruited 39 patients, treated with KOS (20 females and 19 males, aged between 18 and 79) and 41 patients, treated with topical mometasone furoate (19 females and 22 male, aged between 18 and 87) All the patients were affected by NAR, verified by negative RAST tests to common allergens, which ruled out a possible allergic etiology. In both the groups of study, the NAR symptoms were usually characterized by the classic tetrad of nasal stuffiness, rhinorrhea, sneezing and nasal itching. Moreover, all patients, included in the study, had not undergone any previous nasal surgery. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, in compliance with the guidelines for human studies. A written informed consent was obtained from each subject of the study before each treatment. All treated subjects were patients who presented spontaneously requiring treatment for non-allergic rhinitis. Furthermore, both the proposed treatments, conventional medical therapy and KOS treatment, have been validated and authorized for this type of pathology, as highlighted also in the bibliography. The KOS device has also been patented and it is CE-marked and authorized for use in the EU, for the treatment of non-allergic rhinitis [1]. Furthermore, patients were offered to undergo KOS treatment only in cases where conventional medical therapy had not previously been shown to be effective. Patients, included in the KOS group, presented NAR already refractory to common topical and systemic medical therapies as they did not report an improvement in their respiratory functional performance with persistence of rhinitis symptomatology. Therefore, the inclusion criteria for the patients treated with KOS were a persisting NAR for at least 12 weeks, which did not improve with conventional drug therapies such as nasal corticosteroids and histamine-1 antagonist (mometasone, budesonide, fluticasone and azelastine), corticosteroids and ebastine per o.s. and nasal washes with physiological or hypertonic solution. In this study, we considered patients treated with topical mometasone furoate as the control group.

All patients previously underwent an ENT specialist visit with fiber optic nasal endoscopy and CT scan, in order to exclude concomitant pathologies. The investigation of the effectiveness of each treatment was based on objective and subjective evaluation of symptoms and QoL of patients [6]. During the ENT visit, objective examinations were performed to assess respiratory and muco-ciliary function, including active anterior rhinomanometry (AAR), olfactometry and muco-ciliary transport time (MCTt). In addition, all the subjects treated filled out the SNOT-22 and I-NOSE questionnaires, both validated for the Italian population and self-administered to our patients in the presence of an examining doctor. Symptom scores were the main study variables as they are most relevant to the patients' subjective experiences and are commonly used to measure treatment effectiveness in clinical studies involving new investigational products for rhinitis treatment in humans [1].

The exclusion criteria were the following: significant nasal anatomic defects (i.e. deviated septum) acute and chronic infectious diseases of the upper airways, nasosinusal polyposis, allergic rhinosinusitis and medical diagnosis of asthma according to GINA guidelines [7], use of systemic corticosteroids or antihistamines and/or any nasal therapy in the past 4 weeks. The study also excluded patients who had undergone previous nasosinusal and/or turbinate surgery, such as endoscopic endonasal surgery, for the reduction of turbinate hypertrophy with an electrically powered shaver or radiofrequency. Patients with major psychiatric pathologies, craniofacial malformations, genetic diseases, recent major traumas of the nasal pyramid, important comorbidities such as primary and secondary immunodeficiency, coagulopathies, oncological pathologies and serious systemic diseases were also excluded from the study.

The two groups of patients underwent the relevant treatment at time t0 and were re-evaluated after 45 days at t1, during which respiratory function tests (AAR, olfactometry, MCTt) and evaluation QoL questionnaires (SNOT-22, I-NOSE) were repeated.

3.1. Kinetic oscillation stimulation (KOS) treatment

KOS treatment was administered using a minimally invasive system, consisting of a controller, connected to a single-use catheter (balloon) from Chordate Medical AB, Stockholm, Sweden. A headband was used to secure the position of the catheter. The balloon catheter, adequately lubricated with paraffin to facilitate its introduction, was inserted in both nasal cavities, starting on the side with the predominant NAR symptoms (if reported by the treated patient). For KOS treatment of NAR, for each nostril, the inserted catheter (balloon) was inflated and oscillated for 10 minutes at 68 Hz frequency, 65 mbar of average pressure and 100-mbar peak-peak pressure amplitude [8].

3.2. Active anterior rhinomanometry (AAR)

AAR was performed using a RINOPOCKET ED200 (EURO-

CLINIC®, ITALY) rhinomanometer, calibrated according to standard requirements of the ICSR guidelines. The same operator, using the same instrument and following the standard operation procedure, performed rhinomanometry measurements. Patients wore a face mask with a small plastic catheter inserted in one nostril and attached to flexible silicone tubing leading to the pressure port of the meter, through a pierced piece of tape. During the examination, it was asked to the patients to close their mouths and breathe. For each nostril a rhinogram was recorded which related inspiratory and expiratory nasal airflow to transnasal pressure. For each nasal resistance, the AAR parameters considered were inspiratory and expiratory total nasal airway resistances. In various studies, mean total nasal airway resistance was found to be from 0.21 to 0,24 Pa/cm3/s, ranging from 0.14 to 0.37 Pa/cm3/s [9]. Total nasal airway resistance reflects the resistance of both side of nasal cavity. The advantage of measuring the total nasal airway resistance is to avoid the effect of nasal cycle over unilateral nasal airway resistance [10].

3.3. Olfactometry

The "Sniffin' Sticks" test is a widely used tool for assessment of olfactory performance. Odor identification comprised common and familiar odorants (recognized by at least 75% of the population). Subjects were presented with single pens and asked to identify and label the smell, using four alternative descriptors for each pen. Between-pen intervals were approximately 20–30 s. The total score was the sum of correctly identified pens, thus subjects could score between 0 and 16 points [11].

3.4. Muco-Ciliary transport time (MCTt)

MCTt was measured with an inert, colored tracer (charcoal powder). We swabbed a small quantity of the mixture onto the head of the inferior turbinate. Because the constituent of this tracer interact with nasal secretions in different ways, it allows a precise evaluation of how an insoluble medium (charcoal) behave in a fluid. The use of this tracer provided us with information on muco-ciliary function objectively (via the appearance of the tracer on the posterior pharyngeal wall). Normal MCTt values in adults are 13 minutes (±3) for charcoal powder [12].

3.5. SNOT-22

The 22-item Sino-Nasal Outcome Test (SNOT-22) is a modification of a pre-existing instrument, the SNOT-20 and it is a validated QoL instrument for the Italian population [13]. The SNOT-22 questionnaire is scored using a Likert scale where 0="No problem", 1="Very mild problem", 2="Mild or slight problem", 3="Moderate problem", 4="Severe problem", and 5="Problem as bad as it can be". Higher total scores on the SNOT-22 survey, obtained by means of the arithmetic sum of the score of the individual items, suggest worse patient functioning, greater severity of symptoms and a deterioration in quality of life (total score range: 0-110) [14]. Given that symptom severity and patient QoL are major drivers in the decision for KOS treatment, the objective of this study was to evaluate the proportion of patients receiving a minimal clinically important difference (MCID) of at least a 9-point improvement on the SNOT-22 after KOS treatment, based on their preoperative QoL level [15].

3.6. I-NOSE

I-NOSE is a reliable, valid, self-administered, symptom-specific questionnaire assessing QoL related with nasal congestion and obstruction. It consists of five self-rated items, each scored from 0 to 4. The NOSE score represents the sum of the responses to the five individual items and ranges from 0 to 20 [16].

3.7. Statistical analysis

Age was summarized by mean and standard deviation (sd), other quantitative variables were summarized by median and first and third quartile (Q1-Q3). Categorical variables were presented as number (n) and percentage (%). TTM scale was categorized as pathologic if >= 17 and as non-pathologic otherwise. Olfactometry was categorized as pathologic if < 11 and as non-pathologic otherwise. Change between pre and post was calculated as "data post- data pre" for each parameter. Chi square test or Fisher exact test when necessary were used to compare categorical variables between the two groups. Mann-Whitney non-parametric test was used to compare the quantitative variables between the two groups and their changes [17]. Mc Nemar test was used to evaluate change between t0 and t1 in KOS group for categorical variables, and Wilcoxon exact test was used for quantitative variables. The proportions of patients in KOS group whose tests result improved has been computed along with 95% Clopper-Pearson Confidence Interval (CI95%) for proportion [18]. For SNOT-22 the improvement has been evaluated in terms of MCID. Lastly, SNOT-22 definition of MCID has been utilized as base for ROC analysis with the aim to evaluate a plausible value of MCID for I-Nose questionnaire. ROC analysis was performed using R software version 4.0.4 with the open-source package "pROC" [19]. All others analysis were performed using Stata 16.1. A p value<0.05 was considered statistically significant.

4. Results

In the KOS group, thirty-nine patients were enrolled and treated while 43 patients, treated with conventional medical therapy (topical mometasone furoate), were considered as control group. Respectively, two patients of KOS group and 7 patients of control group have been excluded from the analysis because reported a pre-treatment value of SNOT-22 questionnaire lower than 9 points which prevented the evaluation of MCID; therefore, the final sample size is equal to 73. There was not a statistically significant difference between the two groups in age and sex (Table 1). At baseline, the two groups did not significantly differ for Inspiratory Nasal Airway Resistance, Expiratory Nasal Airway Resistance, SNOT-22 and I-NOSE (Table 2). Moreover, the two groups did

not differ also for the prevalence of pathologic patients in MCT test (78% vs 81%, p=0.727). The control group showed a lower prevalence of pathologic patients (n=8, 22%) than KOS group (n=17, 46%, p=0.033). All the instrumental assessments and QoL questionnaires showed a significant improvement post-KOS treatment after 45 days at t1 (Table 3). Sixteen patients (43%, CI 95% 27;60) reported an improvement across all tests. However, most subject experienced an improvement only on some tests but not all of them. AAR is the test with the lowest number of improvements, for Inspiratory Nasal Airway Resistance 26 patients (70% CI 95 % 53;84) and for Expiratory Nasal Airway Resistance 27 patients (73% CI 95% 56;86) improved. The QoL questionnaires reported the highest improvements: thirty-five patients scored a lower thus better result for I-NOSE (95% CI 95% 81;99) and thirty-four for SNOT-22 thirty-four (92%CI 5% 78;98). However, SNOT-22 MCID, i.e. an improvement of at least 9 points, was achieved only by thirty-one patients (84% CI 95% 68;94). The pathologic prevalence in MCTt went from 81% to 11% with none non-pathological patients change to pathologic and 26 out of 30 patients changed from pathologic to non-pathologic (p<0.001). The pathologic prevalence in olfactometry went from 46% to 8% with none non-pathological patients change to pathologic and 14 out of 17 patients changed from pathologic to non-pathologic (p<0.001). It can be seen that post treatment (t1), most patients reached the maximum score of the test even if starting from different points.

Table 1: Sample analysis: demographic characteristics.

		Control Group		**KOS Group**		**p**
N		36		37		
Age (mean, sd)		48.42	18.42	46.43	16.39	0.628
Sex (n, %)	Female	18	50.0	20	54.1	0.729
	Male	18	50.0	17	45.9	

Table 2: Instrumental assessments of nasal functionality and QoL questionnaires at baseline.

	Control Group		**KOS Group**		
N	36		37		
	median	Q1-Q3	median	Q1-Q3	p
Inspiration resistance	0.34	0.21-0.67	0.30	0.1-0.5	0.1093
Expiration resistance	0.30	0.12-0.67	0.24	0.1-0.5	0.3802
I-NOSE	8.50	5.5-13.0	10.0	5.0-13.0	0.6821
SNOT-22	32.5	22.5-43.0	33.0	23.0-43.0	0.7608

Table 3: Pre and post values in KOS group.

	Pre KOS, t0		**Post KOS, t1**		
N	37		37		
	median	Q1-Q3	median	Q1-Q3	p
Inspiration resistance	0.30	0.14-0.52	0.11	0.05-0.22	<0.001
Expiration resistance	0.24	0.1-0.46	0.13	0.05-0.19	<0.001
I-NOSE	10.0	5.0-13.0	4.0	2.0-7.0	<0.001
SNOT-22	33.0	23.0-43.0	15.0	10.0-24.0	<0.001

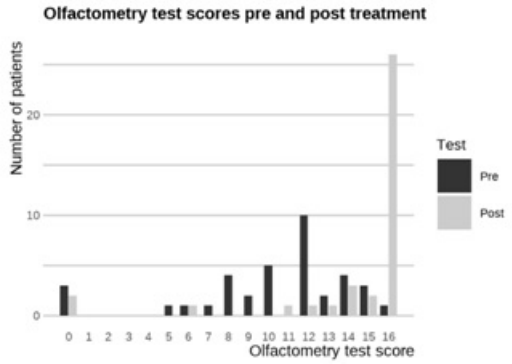

Figure 1: Olfactometry test scores pre- and post-KOS treatment.

5. Conclusion

KOS treatment in the nasal cavity consists in a minimally invasive system, based on a cranial nerve stimulation method, conceived to treat NAR symptoms and with promising efficacy for acute migraine and other inflammatory disorders [20]. In a healthy nasal cavity, the airflow is sensed by the nervous system. An inflammatory process could lead to mucosal swelling, which in turn could potentially prevent the nervous system from detecting the airflow passing over the surface. The idea behind the kinetic oscillation stimulation treatment was that applying mechanical oscillations, similar Regarding the SNOT-22 is available the definition on MCID, therefore we compared SNOT-22 clinically significant improvement and the other tests results to assess if was possible to determine similar cut-offs. The ROC analysis suggested that MCID does not reflect consistently in changes in scores of AAR, olfactometry and MCTt. However, it is possible to compare I-NOSE improvements and SNOT-22 improvements. The ROC analysis (AUC = 0.8091) compares patients that achieved or not an MCID based on SNOT-22 with their post-treatment improvement in I-NOSE questionnaire. The optimal cut-off lies at 3 points improvement in I-NOSE questionnaire (TPR 0.77, TNR 0.83) (Figure 2). (Table 4) compares changes in KOS group and in control group. The two groups did not differ for Inspiratory Nasal Airway Resistance and Expiratory Nasal Airway Resistance changes, but the change is higher in KOS group than control group for the two QoL questionnaires, SNOT-22 and I-NOSE (Figures 3 and 4). Because of none of non-pathologic patients for MCTt or olfactometry

changed to pathologic, in both tests we evaluated the percentage of patients that were pathological at baseline and were not at T1. For MCTt there are 28 pathological patients in control group and 30 in KOS group, of these patients an higher percentage of them became non-pathological in KOS group than in control group (87% vs 43% , p<0.001). For olfactometry there are 8 pathological patients in control group and 17 in KOS group, of these patients an higher percentage of them became non-pathological in KOS group than in control group (82% vs 25% , p=0.010).to naturally occurring turbulence, would have a positive effect on the inflammatory condition in the mucosal surface layer [1]. The mechanism behind this effect is not fully understood and further studies are needed, but it has been explained as a possible effect on the sensory nerves and the autonomic nerve system, i.e. the sympathetic part [8]. Also in a pilot study on migraine, authors speculate that KOS, at least in part, may mitigate migraine symptoms through the trigeminal parasympathetic reflex and an associated beneficial impact on autonomic balance [21]. In our study, 43% of patients treated with KOS showed a significant improvement in all objective functional parameters and subjective questionnaires examined. AAR is an objective evaluation important in epidemiological studies and in monitoring of patients with nasal obstruction, such as NAR patients [22]. The treatment of NAR using KOS has proven to be effective immediately in controlling the co-management of the nasal mucosa as is also shown by the results of AAR for both Inspiratory Nasal Airway Resistance and Expiratory Nasal Airway Resistance (70% and 73% of patients improved significantly), similarly to conventional medical therapy. In addition, a number of studies have sought to determine the influences of acute or chronic rhinitis on olfactory function. Moreover, these studies suggest that the degree of olfactory loss is usually associated with the severity of nasal disease, with an improvement of smell function after various treatments [23]. In our KOS group, 92% of patients showed a significant improvement (p-value<0,001) in the score obtained at the olfactometry test performed 45 days after KOS treatment (t1). Because patients with nasal pathologies often exhibit a decreased muco-ciliary clearance [24], evaluated as an increase in the MCTt, expressed in minutes, we also wanted to verify whether an improvement in MCTt was to be found after KOS treatment (t1), which occurred in 84% of the sample treated with KOS. As regards the questionnaires on QoL, I-NOSE and SNOT-22 showed a significant increase in the score obtained after KOS treatment in the majority of patients: respectively in 95% and 92% of the KOS group. In addition, we observed that these increases were higher for KOS group than in the control group, treated with mometasone furoate. In particular, SNOT-22 questionnaire contains different aspects of QoL – rhinological symptoms, ear/facial symptoms, sleep function, and psychological function and in our opinion it could be that either of these sub-scales has a larger impact on the total SNOT-22 score of the patients in this study [14]. In future studies it would be of interest to analyze whether treatment of NAR has a larger impact in one or more of these four sub-scales of SNOT-22.

In our opinion, we believe that, in a subsequent study, it could be significant to divide the study groups into different subgroups, distinct by subtype of NAR (based on cellular infiltration), in order to verify if there is a significant difference in the efficacy of each treatment. Furthermore, it is necessary to verify the improvement of functional results obtained with the KOS procedure in the medium and long term and on a larger sample of patients. In our experience, no treatment was interrupted due to discomfort, reported by the patient and the safety profile of KOS treatment proved to be valid. The most common, anticipated in a written consent, temporary symptom reported throughout the treatments was increased tear secretion, followed by nasal secretion and sneezing. In our experience, there were no adverse events after treatment and no events judged as related to it such as epistaxis, nasal discomfort or cardiovascular effects, as rarely described in previous studies [20, 25]. This also could be due to the extreme attention paid to the correct positioning of the balloon at the level of the middle meatus, placing it in contact with the medial, anterior and posterior compartments of the inferior turbinate and only with the inferior face of the middle turbinate. In conclusion, KOS treatment is a safe and mini-invasive procedure for the treatment of NAR symptoms, well accepted from the patients and with a promising improvement of QoL, as assessed with the improvement of I-NOSE and SNOT-22 score after the KOS application on patients. The procedure can be administered on an outpatient basis without the need for general/local anesthesia or any premedication and it presents an efficacy almost comparable to that of conventional medical therapy.

6. Conflict of Interest Statement

The authors have no conflicts of interest to declare.

7. Funding Sources

There was not any funding of this work.

Table 4: Change comparison between KOS group and control group, t1.

	Control Group		**KOS Group**		
N	36		37		
	median	Q1-Q3	median	Q1-Q3	p
Inspiration resistance	-0.536	(-0.41)-(-0.07)	-0.133	(-0.3)-0.0	0.1057
Expiration resistance	-0.431	(-0.32)-(-0.05)	-0.087	(-0.27)-0.0	0.1403
I-NOSE	-1	(-2)-0.0	-4	(-7)-(-1)	<0.001
SNOT-22	-3	(-6)-(-1)	-16	(-23)-(-10)	<0.001

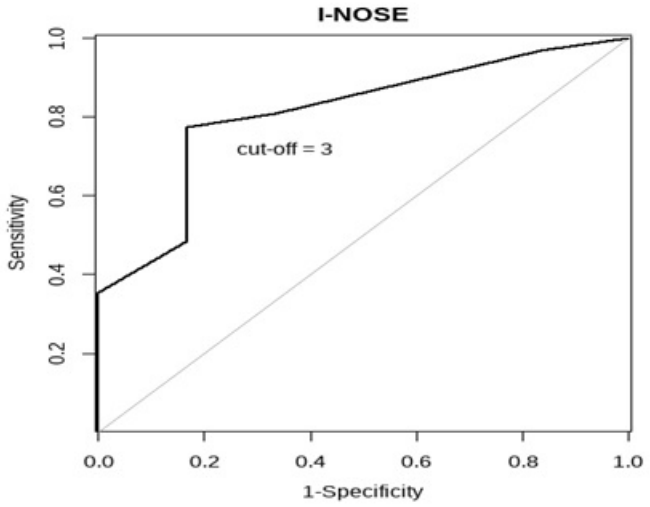

Figure 2: Comparison of SNOT-22 and I-NOSE questionnaires scores: ROC analysis.

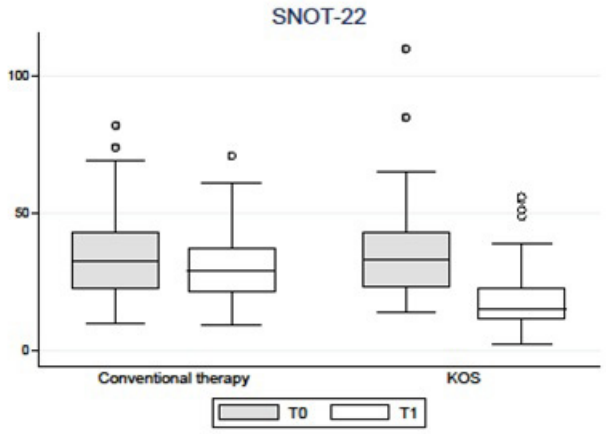

Figure 3: Comparison of change of SNOT-22 score in KOS group and in control group.

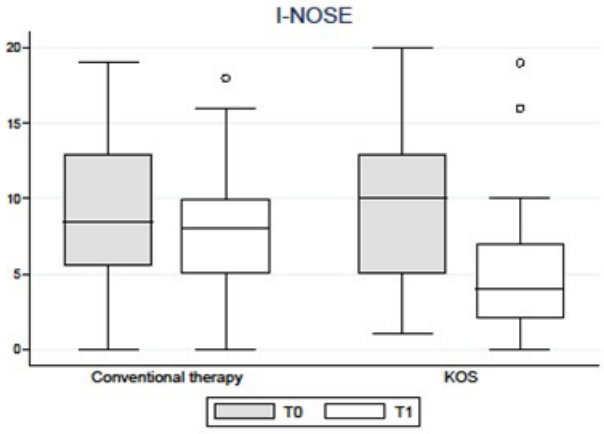

Figure 4: Comparison of change of I-NOSE score in KOS group and in control group.

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