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Efficacy of Naproxen-codeine, Naproxen+Dexamethasone, and Naproxen on Myofascial Pain

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Study Protocol, Statistical Analysis Plan, and Results

Study Protocol

This randomized, double-blind prospective clinical study was conducted with 200 voluntary patients who were selected from the individuals who applied with the complaints of myofascial pain to the department of Oral and Maxillofacial Surgery of the Faculty of Dentistry at Van Yuzuncu Yıl University between January 2018 and January 2019.

The voluntary individuals were informed about the study and signed a consent form. The study was approved by the Ethics Committee for Clinical Trials of Van Yüzüncü Yıl University (Protocol Date/No: 16.02.2018/12). The inclusion criteria included the following: patients with myofascial pain that was diagnosed by DC/TMD; patients older than 18 years, who were ASA 1 or ASA 2 (per ASA Physical Status Classification System, according to the anamnesis); complaint of clenching and tooth wear and/or fracture; normal preoperative TMJ MR examination and no TMJ sounds (clicking or crepitation); no interventional and/or surgical procedure related to TMJ; no use of any drug in the last week; and complaints lasting more than 3 months. The exclusion criteria were as follows: smoking; parafunctional habits (determined by asking the patient and by clinical examinations); one or more tooth deficiencies; impacted third molar(s) (to prevent possible impacted toothache being confused with temporomandibular pain); pregnancy or nursing; allergy to study medication; unclear anamnesis; use of different or additional medication; non-compliance with the intended drug dosage; and non-compliance with the follow-up visits once.

Following admission to the clinic, patients were referred to open-closed mouth temporomandibular joint radiography, panoramic radiography, and magnetic resonance imaging for the radiographic evaluation. The clinical evaluation was performed according to the DC/TMD. The included patients were randomly divided into four groups. Online software was used for the randomization (http://www.graphpad.com/quickcalcs/randomize1.cfm). According to the results of the program, closed envelopes containing group numbers were selected by the patients, with supervision of auxiliary staff. Only the auxiliary staff knew the patient's group. Neither the investigator nor the patient knew which drug was given. The groups received the following treatments: Group A: naproxen sodium 550 mg (Apranax fort 550 mg tablet, BID), Group B: naproxen sodium 550 mg + codeine phosphate 30 mg (Apranax plus tablet, BID), Group C: naproxen sodium 550 mg + single-dose dexamethasone 8 mg (Apranax fort 550 mg tablet, BID + Kordexa 8 mg tablet, OD), GroupD (control group): paracetamol 500 mg (Parol 500 mg tablet, QID). The drugs were prepared and bottled by the auxiliary staff and given to patients following

the coding process. Before the initiation of the treatment, occlusal splints were produced for all patients, and patients were instructed to wear them for 8 hrs daily, along with taking the medication. The visual analog scale (VAS) was used for the pain assessment (0 = no pain; 10 = unbearable pain). The follow-up examinations were performed before the start of the treatment and during the treatment at the first, second, and fourth weeks. Study drugs were administered for one week, then patients were instructed to wear the splint for 8 hrs daily and to use only 500 mg paracetamol as an analgesic if they felt it necessary and not to use any other drug. The follow-up of these patients is still ongoing. Thirty-one patients were excluded from the study due to 26 patients having been lost to follow-up, 2 patients used different medication, and 3 patients did not comply with the intended drug dosage.

Statistical Analysis Plan

Power analysis was performed using the G*Power (v3.1.7) program to determine the number of samples. The power of the study is expressed as 1-β (β = type II error probability) and generally, the studies should have 80% power. According to Cohen's effect size coefficients, assuming that the evaluations to be made between two independent groups will have a large effect size (d = 0.80), it was determined that there should be at least 34 people in each group to obtain 90% power at an α = 0.05 level. Considering the possible losses during the study, the groups were formed of 50 people. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used for the evaluation of the study data. The normal distribution of quantitative data was examined and tested with the Shapiro-Wilk test and graphical visualization. The comparison of the normally distributed quantitative variables for three and more groups was done with the one-way ANOVA test and, for two groups, with the Bonferroni test. The comparison of non-normally distributed quantitative variables for three and more groups was done with the Kruskal-Wallis test and, for two groups, with the Bonferroni-Dunn test. The Repeated Measures test (variance analysis for repeated measurements) was used for the intergroup comparison of the normally-distributed variables; paired comparisons were performed with the Bonferroni test; and Pearson's chi-square test was used for the comparison of the qualitative variables. The intergroup comparison of the qualitative data was done with the Cochran's Q test, and the Dunn test was used for the paired comparisons. The accepted level of significance was p <0.05. Statistical analyses were done with NCSS (Number Cruncher Statistical System) 2007 (Kaysville, UT, USA) software package.

Results

A total of 169 patients were included in the study and 132 of them were female while 37 were male. The groups A, B, C, and D consisted of 42, 40, 40, and 47 patients, respectively. Their mean age was 27.04±10.56 years (18-69 years). 35.5% of patients (n=60) were married and 64.5% (n=109) were single. Regarding their occupation; 20.1% (n=34) were unemployed, 13.0% (n=22) were government employees, 29.6% (N=50) were housewives, 10.1% (n=17) private-sector employees and 27.2% (n=46) were students. Regarding the left occlusions of patients; 74% (n=106) had class I closure, 18.3% (n=31) class II closure, %7.7 (n=13) class III closure. 75.5% (n=108) of right side occlusions consisted of class I closures, 16.0% (n=27) of class II closures and 8.9% (n=15) of class III closures. There was no statistically significant difference between the groups for age, gender, marital status, occupation, occlusion type of left/right side distributions; Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) scores ($p>0.05$). Only, there was statistically significant difference between the groups for occupation ($p<0.05$). There was no drug side effect reported by the patients in the groups.

Evaluation of the Baseline VAS Measurements According to the Groups:

There was a statistically significant difference between the groups regarding the baseline VAS measurements ($p<0.05$). The VAS values in Group D were lower than Group C ($p<0.05$). Other paired comparisons did not reveal any statistically significant difference ($p>0.05$).

Evaluation of the Changes in VAS Measurements According to the Groups:

The evaluation of the changes between baseline and first-week VAS measurements showed that the change in Group B was greater than Group A and D, and the decrease in VAS values of the subjects in Group B was greater than the subjects in Group A and D ($p<0.01$). Other paired comparisons did not reveal any statistically significant difference ($p>0.05$).

The evaluation of the changes between baseline and second-week VAS measurements revealed that the change in Group B was greater than Group A, C, and D, and the decrease in VAS values of the subjects in Group B was greater than the subjects in Group A, C, and D ($p<0.01$). Other paired comparisons did not reveal any statistically significant difference ($p>0.05$).

The evaluation of the changes between baseline and fourth-week VAS measurements showed that the change in Group B was greater than Group A, C, and D and the decrease in VAS values in the subjects of Group B was greater than the subjects of Group A, C, and D ($p<0.05$). In addition, the change in Group A was greater than Group D and, the decrease in

VAS values in the subjects of Group A was greater than the subjects of Group B ($p<0.05$). Other paired comparisons did not reveal any statistically significant difference ($p>0.05$).

According to the evaluation of the changes between the first-week and second-week VAS measurements, the change in Group B was greater than Group D, and the decrease in VAS values in the subjects of Group B was greater than the subjects in Group D ($p<0.01$). Other paired comparisons did not reveal any statistically significant difference ($p>0.05$).

The comparison between the first-week and fourth-week VAS measurements showed that the change in Group B was greater than Group C and D, and the decrease in VAS values in the subjects of Group B was greater than the subjects of Group C and D ($p<0.01$). The change in Group A was greater than Group D, and the decrease in VAS values in the subjects of Group A was greater than the subjects of Group D ($p<0.01$). Other paired comparisons did not reveal any statistically significant difference ($p>0.05$).

The comparison between the second-week and fourth-week VAS measurements showed that the change in Group A was greater than Group C and D ($p<0.01$). Besides, the change in Group B was greater than Group C and D ($p<0.01$). Other paired comparisons did not reveal any statistically significant difference ($p>0.05$).