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IZVORNI ZNANSTVENI RAD
ORIGINAL SCIENTIFIC PAPER

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Usporedba amitriptilina sa stabilizacijskom udlagom i placebom u liječenju kroničnih temporomandibularnih poremećaja: pilot-studija

Comparison of Amitriptyline with Stabilization Splint and Placebo in Chronic TMD Patients: a Pilot Study

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Sažetak

Cilj rada: Autori su proveli kliničku studiju kako bi procijenili učinkovitost amitriptilina u liječenju pacijenata s kroničnim temporomandibularnim poremećajima (TMP) te usporedili rezultate liječenja amitriptilinom s onima postignutima stabilizacijskom udlagom. **Materijali i postupci:** U istraživanje je bio uključen dvadeset i jedan pacijent. Pacijenti su nasumično raspoređeni u tri skupine: pacijenti u skupini A primali su amitriptilin, oni u skupini B dobivali su placebo, a u skupini C liječeni su stabilizacijskom udlagom. Ishodi liječenja [bol procijenjena vizualnom analognom ljestvicom (VAS), maksimalno otvaranje usta bez boli, tj. maksimalno ugodno otvaranje (MCO) i kvaliteta života ovisna o oralnom zdravlju (OHIP-14)], zabilježeni su na početku (prije liječenja) te nakon prvog, šestog i dvanaestog tjedna tretmana. **Rezultati:** Nisu zabilježene statistički značajnije razlike među skupinama prije početka liječenja ($p > 0,05$). Rezultati procijenjeni VAS-om značajno su se poboljšali u skupini A ($F = 11,326$, $p = 0,002$, veličina učinka = 0,791) te u skupini C ($F = 7,343$, $p = 0,005$, veličina učinka = 0,647). Srednji rezultati za OHIP-14 značajno su smanjeni samo u skupini A ($F = 4,417$, $p = 0,036$, veličina učinka = 0,596). U skupini B rezultati prema vizualno analognoj ljestvici i prema OHIP-u 14 nisu se s vremenom značajnije promijenili. Pacijenti u skupini C imali su značajniju promjenu rezultata za maksimalno otvaranje usta bez boli u odnosu prema skupinama A i B. **Zaključak:** Prema rezultatima ove pilot-studije može se zaključiti da je primjena nižih doza amitriptilina tijekom 12 tjedana učinkovito smanjila bol i poboljšala kvalitetu života pacijentima s kroničnim TMP-om. Stabilizacijska udlaga pokazala se u istom razdoblju boljom u liječenju ograničenog otvaranja usta.

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Uvod

Temporomandibularni poremećaji (TMP) smatraju se najčešćim orofacijalnim bolnim stanjima nedentalnoga podrijetla. Posljednjih godina TMP se promatra iz višedimenzijske perspektive, što znači da mnogi psihološki, fizički i socijalni čimbenici mogu utjecati na razvoj tih poremećaja (1). Kronična bol može znatno utjecati na socijalno i emocionalno ponašanje pacijenta. Uzimajući to u obzir, postoje određeni dokazi da pacijenti koji pate od kroničnih oblika TMP-a mogu također imati lošiju kvalitetu života (2).

U pomanjkanju znanja o etiološkim mehanizmima koji su u podlozi ovih poremećaja, u liječenju TMP-a glavni je cilj, uz ublažavanje boli i ponovno uspostavljanje mandibularne funkcije, i poboljšanje kvalitete života ovisne o oralnome zdravlju. U liječenju bolesnika s kroničnom orofaci-

Introduction

Temporomandibular disorders (TMDs) are considered the most common orofacial pain conditions of non-dental origin. The current perspective regarding TMD is multidimensional, meaning that many psychological, physical and social factors may have a role in the development of this disorder (1). If the pain becomes chronic, it can have great impact on social and emotional behavior of patient. Taking this into account, certain pieces of evidence prove the validity of the statement that patients suffering from chronic TMD may also have reduced quality of life (2).

In the absence of clear knowledge of the etiological mechanisms that are underlying this disorder, the main goal in TMD management, apart from relieving pain and restoring mandibular function, is to improve oral health related quali-

jalnom boli nužno je procijeniti njezin utjecaj na kvalitetu života, ali i učinak liječenja na cjelokupno poboljšanje kvalitete života (3, 4).

Konzervativni tretmani, uključujući okluzijske udlage, lijekove, strategije samopomoći i fizikalnu terapiju, smatraju se prvim izborom liječenja. Najčešće se odabire stabilizacijska udlaga (5, 6), iako su u uporabi i mnoge druge vrste okluzijskih naprava. One se razlikuju po tomu prekrivaju li potpuno ili djelomično zubni luk preko kojega se nose, te dodiruju li sve ili samo neke zube u nasuprotnoj čeljusti. Općenito se smatra da nošenje okluzijskih udlaga mijenja periferne senzoričke impulse iz receptora u žvačnim mišićima, parodontnom ligamentu i oralnoj sluznici (7) te smanjuje intraartikularni tlak u temporomandibularnom zglobu (8).

Triciklički antidepresivi (TCA) djeluju tako da inhibiraju ponovnu pohranu serotonina u stražnjem rogu leđne moždine čime se uspješno smanjuje brzina prijenosa informacija o boli u mozak. Postoje dokazi da je uporaba amitriptilina u niskim dozama značajno smanjila bol u pacijenata s kroničnim TMP-om i to bez nuspojava (9), ali pacijenti su procjenjivani samo tijekom kraćih razdoblja.

U mnogobrojnim studijama istraživala se uloga stabilizacijske udlage u kontroliranju TMP-a (10 – 12). Međutim, uporaba tricikličkih antidepresiva u liječenju TMP-a nije potpuno istražena, posebice kad je riječ o njihovu utjecaju na kvalitetu života povezanu s oralnim zdravljem. U skladu s tim, cilj ove pilot-studije bio je procijeniti učinkovitost amitriptilina u liječenju pacijenata s kroničnim TMP-om te usporediti dobivene rezultate s onima postignutima liječenjem s pomoću stabilizacijskih udlaga. Nulta hipoteza bila je da nema nikakve razlike između tih terapijskih pristupa tijekom dvanaest tjedana.

Materijali i postupci

Ispitanici

Kliničko ispitivanje provedeno je u Zavodu za mobilnu protetiku Stomatološkoga fakulteta Sveučilišta u Zagrebu. Ispitanici su odabrani među pacijentima koji su se došli zbog orofacijalne boli nedentalnog podrijetla, a prije toga nisu bili liječeni. Dijagnoza se postavljala na temelju kriterija za istraživanje temporomandibularnih poremećaja (DKI/TMP) (dijagnostičke kategorije I ili II u DKI/TMP-u) (13, 14). Podatci o dobi, spolu, trenutačnom bračnom statusu i trajanju boli sudionika dobiveni su upitnikom. Kriteriji za isključivanje iz istraživanja bili su: 1) parodontna bolest, 2) mobilna proteza ili kompletna opskrba fiksnoprotetskim radovima, 3) pacijenti na ortodontskoj terapiji, 4) bol zbog osteoartritisa temporomandibularnoga zgloba (dijagnostička kategorija III u DKI/TMP-u), 5) ostala orofacijalna bolna stanja, 6) psihički ili neurološki poremećaji, 7) bol zbog sistemske bolesti, 8) trudnoća, 9) srčana bolest i 10) poznata netolerancija prema amitriptilinu.

Kliničarka (R. B. B.) vrsna u dijagnosticiranju TMP-a, obavila je sve prve kliničke preglede (T0).

Standardizacija ispitivača

Kako bi se procijenila ponovljivost mjerenja, ista je kliničarka dva puta obavila klinički pregled desetero ispitanika ra-

ty of life. When treating patients with chronic orofacial pain, not only is it necessary to evaluate the impact of pain on the quality of life but also the effect of treatment on overall quality of life improvement (3, 4).

A conservative treatment, including occlusal splint, medication, self-care strategies and physical therapy, are considered the first choice for temporomandibular joint treatment. The most frequently used therapeutic option is a stabilization splint (5, 6), although a variety of other full-arch and partial oral appliances have been in use. It is generally believed that wearing an occlusal splint alters the peripheral sensory input from receptors in the masticatory muscles, periodontal tissues and oral mucosa (7), and decreases the intra-articular pressure in TMJ (8).

Tricyclic antidepressants (TCA) act by inhibiting serotonin reuptake in the posterior horn of spinal cord, and thus successfully decreasing the speed at which pain information is transmitted to the brain. There is some evidence that low doses of amitriptyline daily significantly reduce the pain of chronic TMD without producing side effects (9), but patients were evaluated only for a short period of time.

So far, numerous studies have investigated the role of stabilization splint in TMD management (10-12). However, the use of TCA in the treatment of TMD has not been fully explored, particularly regarding its impact on oral health related quality of life. Accordingly, the objective of this pilot study was to evaluate the effectiveness of amitriptyline in treatment of chronic TMD patients and to compare the obtained treatment results with stabilization splint. The null-hypothesis was that there would be no difference between treatment options in a 12-week treatment period.

Materials and Methods

Subjects

This clinical trial was carried out at the Department of Prosthodontics, School of Dental Medicine, University of Zagreb. The subjects were recruited from patients seeking treatment for non-odontogenic orofacial pain who had not been previously treated. The patients were diagnosed using Research Diagnostic Criteria for temporomandibular disorders (RDC/TMD) (diagnostic categories I or II in the RDC/TMD) (13, 14). The data regarding participant's age, gender, current marital status and duration of pain were collected by a questionnaire. Exclusion criteria were: 1) periodontal disease, 2) removable dentures or complete fixed prosthodontic restorations, 3) ongoing orthodontic treatment, 4) pain due to temporomandibular joint osteoarthritis (diagnostic category III in the RDC/TMD) 5) other orofacial pain conditions, 6) mental or neurological disorders, 7) pain due to systemic disease, 8) pregnancy, 9) cardiac disease and 10) known intolerance to amitriptyline.

At the baseline (T0) all patients were evaluated by the clinician (R.B.B.) who was well trained in diagnosing TMD.

Standardizations of the examiner

To estimate the intra-examiner reproducibility, a clinical examination was made on two separate occasions by the

zličitih od onih uključenih u studiju. Pogreška nije bila statistički značajna (ICC > 0,9). Nisu zabilježene značajne razlike između prvoga i drugoga mjerenja (p = 0,85 - 0,89, t-test za zavisne uzorke).

Etičko odobrenje

Ovu studiju odobrilo je Etičko povjerenstvo Stomatološkoga fakulteta Sveučilišta u Zagrebu. Svi uključeni ispitanici potpisali su informirani pristanak. Eksperimentalni postupci provedeni su u skladu s etičkim standardima Helsinške deklaracije.

Protokol studije

Dvadeset i sedmero pacijenata ispunjavalo je uvjete za uključivanje u studiju, a naposljetku je odabran 21. Oni koji su odbili sudjelovati kao glavni razlog naveli su da smatraju kako će im to oduzeti previše vremena. Prije nasumične raspodjele u skupine svi su pacijenti bili obaviješteni o mogućim nuspojavama amitriptilina i potpisali su suglasnost.

Nasumična raspodjela obavljena je u programu Microsoft Excel nakon kodifikacije svakog pacijenta. Bolesnici su bili podijeljeni u tri skupine liječenja: skupina A primila je 25 mg amitriptilina, skupina B dobila je tabletu placeba iste veličine i izgleda (napravio MAGDIS d. o. o., A. Šenoe 37, Mala Gorica, 10 431 Sveta Nedjelja), a skupina C tretirana je stabilizacijskom udlagom.

same clinician, on 10 subjects, different from those included in the study. The intra-examiner error was not statistically significant (ICC>0.9). No significant differences between the first and second measurement were found (p=0.85-0.89, paired t-test).

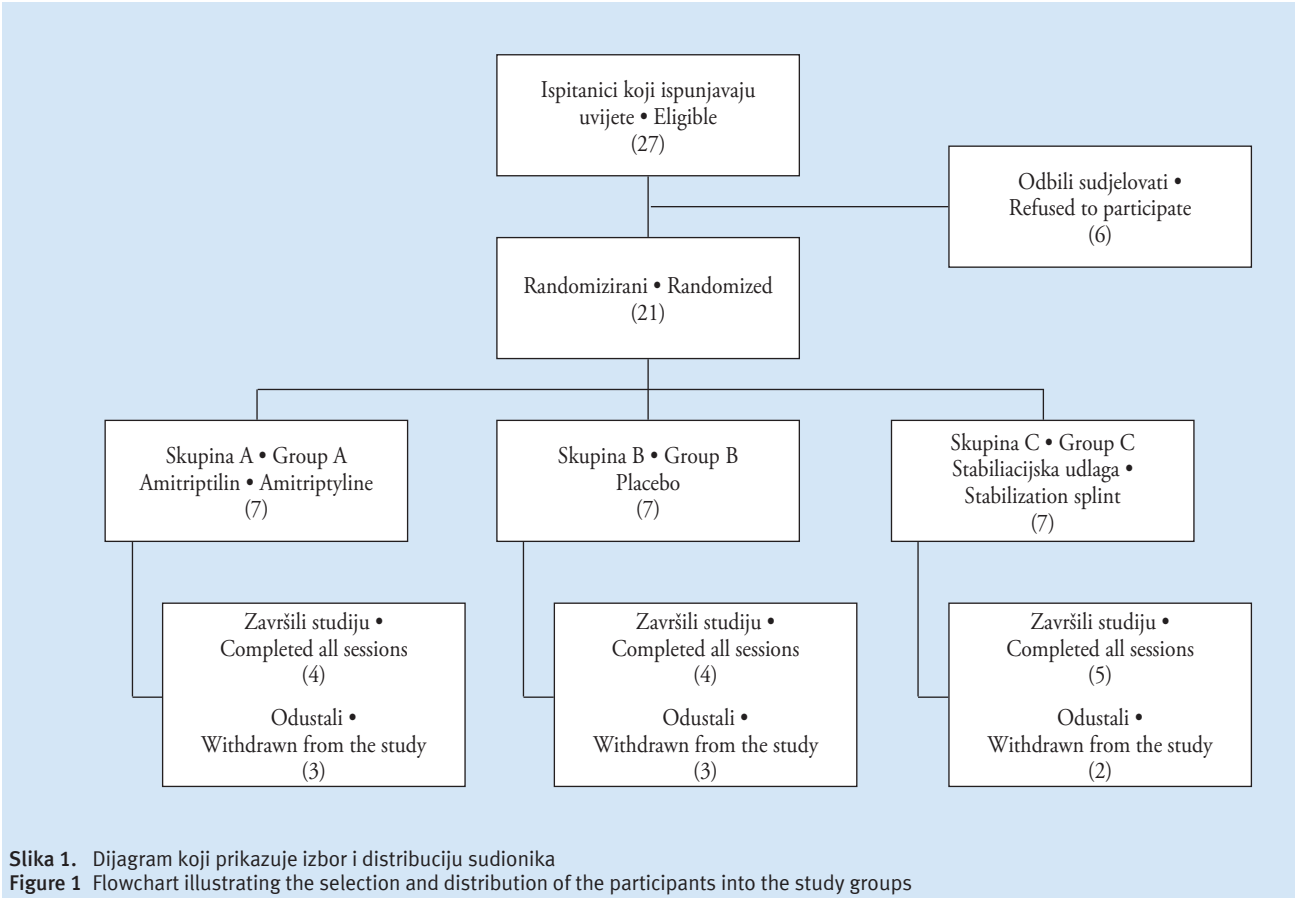
Ethical approval

This study was approved by the Ethics Committee of the School of Dental Medicine, University of Zagreb. Written informed consent was received from all individual patients included in the study. All experimental procedures were conducted in accordance with ethical standards of the Helsinki Declaration.

Study protocol

Twenty-seven patients met the conditions and 21 of them were finally included in the study. The principle reason for patients declined participation in the study was that they thought that participation in the study would take up too much of their time. Prior to randomization all patients were informed about the possible side-effects of amitriptyline. After that they signed written consent form.

The randomization was performed using Microsoft Excel software after the codification of each patient. The patients were allocated into three treatment groups: Group A received 25 mg of amitriptyline), Group B received placebo pill of the same size and appearance (made at MAGDIS d.o.o., A. Šenoe 37, Mala Gorica, 10431 Sv. Nedjelja) and Group C was treated with stabilization splint.



Slika 1. Dijagram koji prikazuje izbor i distribuciju sudionika
Figure 1 Flowchart illustrating the selection and distribution of the participants into the study groups

Postupak liječenja

Pacijentima koji su bili podvrgnuti farmakološkom liječenju rečeno je da tijekom dvanaest tjedana prije spavanja uzmu po jednu tabletu. Oni u skupini sa stabilizacijskom udlagom dobili su uputu da pomagalo nose samo tijekom spavanja. Sve terapije propisala je ista kliničarka (I. A.).

Maksilarna stabilizacijska udlaga izrađena je na sadrenom odljevu u artikulatoru ARTEX od tvrdog akrilata (Resilit-S, Erkodent, Siemensstraße 3, 72285 Pfalzgrafenweiler, Njemačka) debljine 1,5 mm na razini prvoga molara. Sve udlage izradio je isti dentalni tehničar. Kliničarka (I. A.) okluzijski je uskladila udlage, pri čemu su zubi nasuprotne čeljusti ostvarivali simultane i simetrične kontakte s udlagom. Ista kliničarka prilagođavala je udlagu, ako je bilo potrebno, i tijekom kontrolnih pregleda.

Mjere ishoda

Kliničarka (R. B. B.), koja nije bila upoznata s vrstom terapije, obavila je klinički pregled svih pacijenta tijekom sljedećih kontrolnih pregleda u prvom (T1), šestom (T2) i dvanaestom (T3) tjednu nakon početka liječenja.

Bol

Za procjenu boli u mirovanju ili tijekom funkcije posljednjih sedam dana korištena je vizualno analogna ljestvica (VAS). VAS je linija duljine 100 mm, s lijevom krajnjom točkom koja označuje stanje bez boli i desnom krajnjom točkom koja označuje najveću bol koju je moguće zamisliti.

Maksimalno bezbolno otvaranje usta

Maksimalno bezbolno otvaranje usta (MCO) definirano je kao maksimalan iznos koji pacijent postigne otvarajući usta bez osjećaja boli. Nakon što je pacijent otvorio usta do te širine, ispitivač bi izmjerio udaljenost između bridova maksilarnih i manidbularnih inciziva.

Procjena kvalitete života ovisne o oralnom zdravlju

Hrvatski upitnik OHIP-14 korišten je za procjenu kvalitete života ovisnu o oralnom zdravlju. Pacijenti su odgovorili na 14 pitanja o kvaliteti života ovisnoj o oralnom zdravlju odabirom jednoga od sljedećih odgovora: 0 – nikada, 1 – gotovo nikada, 2 – katkad, 3 – relativno često i 4 – vrlo često. Mogući rezultati prema tom upitniku bili su u rasponu od 0 do 56. Potencijalna valjanost OHIP-a za procjenu pacijenata s TMP-om i njegova prijašnja uporaba u tu svrhu (15) pridonijeli su prihvaćanju te prethodno validirane verzije u ovoj studiji (16).

Statistička analiza

Preliminarne analize sastojale su se od deskriptivne statistike, testiranja normalnosti distribucije i ispitivanja homogenosti varijanca. Za procjenu razlika prema VAS-u i OHIP-u 14 na početku – T0, T1, T2 i T3, korištena je analiza varijance. Eta-kvadrat (η^2) korišten je za procjenu veličine učinka. Promjene maksimalnog bezbolnog otvaranja usta analizirane su analizom varijance, nakon čega su slijedili *post hoc* Bonferronijevi testovi.

Podatci su analizirani primjenom statističkog softvera SPSS 17.0 (Chicago, IL, SAD). Vrijednost $p < 0,05$ smatrana je statistički značajnom.

Treatment procedure

Patients undergoing pharmacological treatment were instructed to take one pill at bedtime, during 12 weeks. Patients in the stabilization splint group were instructed to wear the splint only during sleep. All therapies were delivered by the same clinician (I.A.).

The maxillary stabilization splint was made on stone cast in ARTEX articulator. It was a hard acrylic splint (Resilit-S, Erkodent, Siemensstraße 3, 72285 Pfalzgrafenweiler, Germany), with a thickness of 1.5 mm at the level of the first molar. The same dental technician made all splints. The clinician (I.A.) adjusted the splint so that the simultaneous and symmetric contacts were obtained in maximum intercuspation. The same clinician adjusted the splint at follow up appointments if there was a need for it.

Outcome measures

The baseline examiner (R.B.B.), blind to a type of therapy, performed clinical examination of each patient at follow up appointments at 1st (T1), 6th (T2) and 12th (T3) week after treatment initiation.

VAS-pain

VAS was used to evaluate the patient's pain at rest or during function in the last 7 days. The VAS is a 100 mm-long line, with left endpoint indicating "no pain at all" and right endpoint representing "worst pain imaginable".

Maximal comfortable mouth opening

Maximal comfortable mouth opening (MCO), the maximum distance the patient could open his/her mouth without feeling pain, was evaluated as the distance between the edges of the maxillary and mandibular incisors.

Oral health-related quality of life evaluation

The Croatian OHIP-14 questionnaire was used to evaluate oral health-related quality of life. Patients expressed their level of agreement with 14 questions about the oral health-related quality of life, by choosing one of the answers: 0-never, 1- hardly ever, 2-sometimes, 3 fairly often -and 4-very often. Possible OHIP-14 scores ranged from 0 to 56. The potential validity of the OHIP for evaluation of TMD patients and its previous usage for this purpose (15) contributed to the adoption of this previously validated version in the present study (16).

Statistics

Preliminary analyses consisted of descriptive statistics, normality tests and tests for homogeneity of variances. A repeated-measurements analysis of variance was used to test the differences in VAS and OHIP-14 scores at baseline-T0, T1, T2 and T3. The eta squared (η^2) was used to estimate the size of the effect. Changes in maximally comfortable mouth opening were analyzed with ANOVA, followed by the post hoc Bonferroni tests.

The data were analyzed using statistical software SPSS 17.0 (Chicago, IL, USA). A value of $p < 0.05$ was considered statistically significant.

Rezultati

Polazni rezultati

Osmero pacijenata odustalo je tijekom istraživanja. Njih trinaestoro (4 u skupini s amitriptilinom, 4 u skupini s placebom i 5 u skupini sa stabilizacijskom udlagom) ostalo je do kraja. Tablica 1. sažeto pokazuje osnovne karakteristike sudionika prema skupini liječenja. Srednja dob za skupinu s amitriptilinom bila je 57,25 ± 8,13 godina, za onu s placebom 46,5 ± 18,15 godina, a za skupinu sa stabilizacijskom udlagom 42,8 ± 12,45 godina. Prosječno trajanje boli za amitriptilinsku skupinu iznosilo je 9,8 ± 2,8 mjeseci, za placebo skupinu 19,5 ± 13,3 mjeseci i za skupinu sa stabilizacijskom udlagom 16,8 ± 7,8 mjeseci. Nisu pronađene značajnije razlike u polaznim karakteristikama među skupinama (p> 0,05).

Results

Baseline scores

Eight patients dropped out of the study. Hence, 13 participants (4 in amitriptyline group, 4 in placebo group and 5 in stabilization splint group) completed the study. The Table 1 summarizes the participant's baseline characteristics, according to treatment group. The mean age for the amitriptyline group was 57.25±8.13 years, for placebo group 46.5±18.15 years, and for stabilization splint group 42.8±12.45 years. The mean pain duration for the amitriptyline group was 9.8±2.8 months, for placebo group 19.5±13.3 months, and for stabilization splint group 16.8±7.8 months. No significant differences in baseline characteristics between groups were found (p >0.05).

Tablica 1. Demografski i polazni podatci o sudionicima
Table 1 Demographics and baseline data of participants

	Amitriptilin • Amitriptyline skupina A • Group A (n=4)	Placebo Skupina B • Group B (n=4)	Stabilizacijska udlaga • Stabilization splint skupina C • Group C (n=5)	F (*p*)
Dob (godine) • Age (years)	57.25±8.13	46.5±18.15	42.8±12.45	3.417 (0.099)
Početna bol (VAS) • Initial pain (VAS)	80.25±14.15	72.75±21.71	70.0±12.5	0.459 (0.645)
Trajanje boli (mjeseci) • Pain duration (months)	9.8±2.8	19.5±13.3	16.8±7.8	1.832 (0.210)
Početni OHIP-14 • Initial OHIP-14	23.5±5.06	23.7±11.26	27.00±9.92	2.487 (0.134)
Početni MCO • Initial MCO	40.00±8.20	30.75±4.64	30.80±7.15	2.497 (0.132)

Učinkovitost liječenja

Promjene intenziteta boli u svakoj skupini nalaze se na slici 2. Varijabla boli procjenjivana je na prvom pregledu (T0) te prvi (T1), šesti (T2) i dvanaesti tjedan (T3) liječenja. Bol je tijekom tog razdoblja kontinuirano slabjela u skupini s amitriptilinom (skupina A) i u skupini sa stabilizacijskom udlagom (skupina C); razlika je bila značajna za skupinu A (F = 11,326, p = 0,002, veličina učinka = 0,791) i za skupinu C (F = 7,343, p = 0,005, veličina učinka = 0,647) (slika 2.).

Promjene u rezultatima prema OHIP-u od početnog do dvanaestog tjedna terapije prikazane su na slici 3. Kvaliteta života ovisna o oralnom zdravlju procjenjivana je na prvom pregledu (T0) te prvi (T1), šesti (T2) i dvanaesti tjedan (T3). Značajno poboljšanje kvalitete života tijekom razdoblja liječenja zabilježeno je samo u skupini A (F = 4,417, p = 0,036, veličina učinka = 0,596).

U placebo skupini (skupina B) rezultati za VAS i OHIP-14 nisu se značajno promijenili tijekom liječenja (p > 0,05).

Ispitanicima u svim trima skupinama zabilježeno je povećano bezbolno otvaranje usta na posljednjem kontrolnom pregledu u usporedbi s početnom vrijednošću (slika 4.). Pri usporedbi skupina pokazalo se da je u skupini C postignuta značajna promjena u bezbolnom otvaranju usta u odnosu na skupine A i B (p > 0,05).

Na posljednjem pregledu ispitanici u skupinama A i C imali su veću, ali ne i značajnu promjenu u rezultatima prema VAS-u (slika 5.) te veću redukciju OHIP-a (slika 6.) negoli oni u skupini B.

Treatment effectiveness

The change patterns for pain in each group are shown in Figure 2. We checked the variable *pain* at four points: baseline (T0), 1st week (T1), 6th week (T2) and 12th week (T3). Pain decreased continuously over time in amitriptyline group (Group A) and in stabilization splint group (Group C); the difference was significant for Group A (F=11.326, p=0.002, effect size =0.791) and for group C (F=7.343, p=0.005, effect size =0.647) (Figure 2).

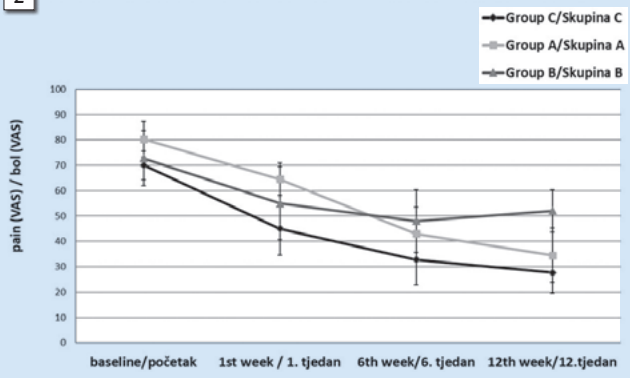
Changes in OHIP-scores from baseline to 12th week of the therapy are shown in Figure 3. We checked the variable *oral health-related quality of life* at four points: baseline (T0), 1st week (T1), 6th week (T2) and 12th week (T3). A significant improvement in the quality of life during the treatment period was found only in Group A (F=4.417, p=0.036, effect size =0.596).

In placebo group (Group B), VAS and OHIP-14 scores did not change significantly over the treatment period (p>0.05).

The subjects in all three groups had an increased MCO at the final visit comparing with baseline (Figure 4). A between group comparison showed that in Group C a significant change in MCO relative to Group A and Group B was found (p>0.05).

At the final visit subjects in Group A and group C had greater, but not significant, change in VAS scores (Figure 5), as well as greater OHIP reduction (Figure 6), than patients in group B.

2



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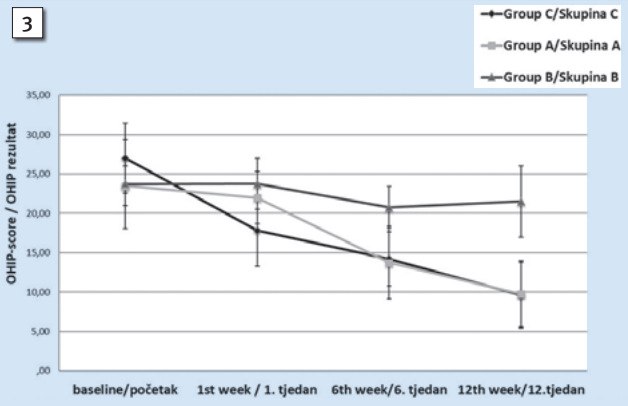

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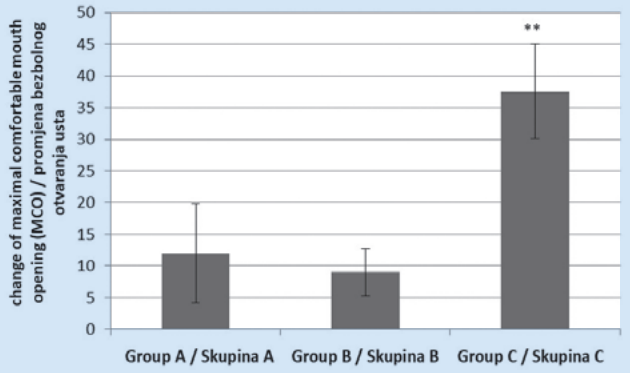

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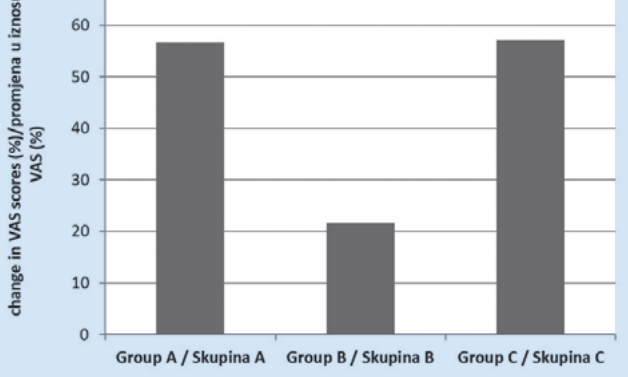

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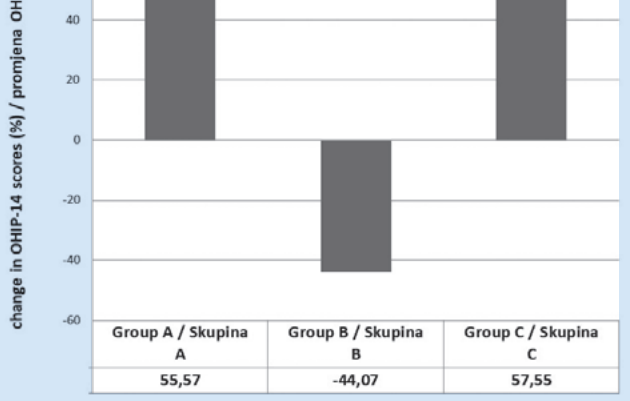

Slika 2. Promjene boli (VAS) od polaznih rezultata do 12. tjedna liječenja
Figure 2 Changes in pain (VAS) from baseline to 12th week of the therapy
Slika 3. Promjene rezultata za OHIP od polaznih do 12. tjedna liječenja
Figure 3 Changes in OHIP-score from baseline to 12th week of the therapy
Slika 4. Učinkovitost terapijskih intervencija procijenjena je prema promjeni u maksimalnom udobnom otvaranju usta nakon 12 tjedana liječenja
Figure 4 The effectiveness of therapeutic interventions was evaluated by assessing the change in maximal comfortable mouth opening following 12 weeks treatment (the whiskers represent standard deviations)
Slika 5. Učinkovitost terapijskih intervencija procijenjena je prema promjeni rezultata prema u VAS-u nakon 12 tjedana liječenja
Figure 5 The effectiveness of therapeutic interventions was evaluated by assessing the change in VAS scores following 12 weeks treatment
Slika 6. Učinkovitost terapijskih intervencija procijenjena je prema promjeni rezultata za OHIP-14 nakon 12 tjedana liječenja
Figure 6 The effectiveness of therapeutic interventions was evaluated by assessing the change in OHIP-14 scores following 12 weeks treatment

Rasprava

Stabilizacijska udlaga je *zlatni standard* u liječenju temporomandibularnih poremećaja. No tijekom godina iskušani su i mnogi drugi načini liječenja TMP-a. Eksperimentalni dokazi, temeljeni na nasumičnim kliničkim ispitivanjima, kontroverzni su i do danas nije dokazano da je neki tretman bolji od bilo kojega drugoga kad je riječ o TMP-u. Ova studija procijenila je učinkovitost amitriptilina u usporedbi sa stabilizacijskom udlagom i placebom kod bolesnika s kroničnim temporomandibularnim poremećajima.

Naši preliminarni podatci govore u prilog primjeni niskih doza amitriptilina u razdoblju od dvanaest tjedana za kontroliranje boli uzrokovane kroničnim TMP-om. Davanje toga lijeka rezultiralo je smanjenjem boli prema VAS-u od 56,68 %. Ovaj rezultat u skladu je s onima dobivenima u nekoliko drugih studija (17 – 20). No, kao i kod bilo kojega drugog lijeka, primjena amitriptilina može povećati rizik od neželjenih nuspojava.

Pokazalo se da je triciklički antidepresiv amitriptilin bolji od placeba za neke vrste kronične boli (21, 22). U istraživanju koje su proveli Plesh i suradnici (20) smanjenje intenziteta boli uočeno je kada se propisalo 30 mg amitriptilina. Nadalje, kod pacijenta koji su primili amitriptilin u kombinaciji s kognitivno bihevioralnom terapijom, smanjivanje boli prema VAS-u nastavilo se čak i kada je terapija prekinuta (19). Istraživanje Sharava i suradnika (21) pokazalo je da nema razlike u analgetičkom učinku između niske (30 mg) i visoke (150 mg) doze amitriptilina, ali da se dogodilo značajno smanjenje boli nakon primjene amitriptilina u usporedbi s placebom. U prvoj studiji McQuaya i suradnika (17), u skupini koja je primala 25 mg amitriptilina, značajno je smanjena bol nakon tri tjedna u odnosu prema skupini koja je dobivala placebo. U drugoj studiji uspoređivali su isti autor i njegovi kolege (18) primjenu niske (25 mg) i visoke (75 mg) doze amitriptilina u odnosu na placebo i pokazali da visoka doza ima jači učinak, ali veličina uzorka bila je malena. Rizzati-Barbosa i suradnici (9) potvrdili su značajno smanjenje intenziteta boli nakon 25 mg amitriptilina u odnosu na placebo poslije dva tjedna liječenja. Naši rezultati pokazali su da je placebo učinak na bol bio uočljiv samo u ranoj fazi primjene lijeka. Nakon trećega kontrolnog pregleda nije potvrđeno nikakvo daljnje poboljšanje u placebo skupini, a u onima s amitriptilinom i stabilizacijskom udlagom znatno se smanjivao intenzitet boli tijekom trajanja cijele studije.

Postoje naznake da pacijenti koji pate od temporomandibularnih poremećaja mogu imati i lošiju kvalitetu života povezanu s oralnim zdravljem. U studiji koju su proveli Almoztino i suradnici (2) rezultati za OHIP-14 bili su lošiji za pacijente s TMP-om negoli u normalnoj populaciji. Blanco-Aguilera i suradnici (23) pokazali su da je percepcija oralnoga zdravlja lošija kod bolesnika koji dulje pate zbog kroničnе boli. Prema sustavnom pregledu (24) čini se da su mnoge metode liječenja u određenoj mjeri poboljšale kvalitetu života bolesnika s TMP-om. Rezultati ove studije pokazali su poboljšanje u rezultatima za OHIP-14 u amitriptilinskoj skupini te neznatno, ali ne i statistički značajno, poboljšanje u skupini sa stabilizacijskom udlagom, a u placebo skupini re-

Discussion

Currently, the stabilization splint represents the "gold standard" for treatment of temporomandibular disorders. However, many other treatment modalities for TMD have been tried over time. Experimental evidence, based on randomized clinical trials, is controversial and till today no single treatment has been proven to be better than any other for TMD. The present study evaluated the effectiveness of amitriptyline compared to stabilization splint and placebo in chronic TMD patients.

Our preliminary data support the use of low doses of amitriptyline over a period of 12 weeks for the management of the pain caused by chronic TMD. Administration of amitriptyline resulted in 56.68% reduction in the VAS scores. This result is in agreement with several other studies (17-20). However, as with any other medication, the use of amitriptyline may increase the risk of adverse effects.

Tricyclic antidepressant amitriptyline has been found to be better than placebo for some chronic pain conditions (21, 22). In the study of Plesh et al. (20), the reduction of pain intensity was observed when using 30 mg of amitriptyline. Furthermore, patients who received amitriptyline combined with cognitive behavioral therapy continued to improve according to the VAS even when therapy was discontinued (19). The findings of Sharav et al. (21) showed that there is no difference in analgesic effect between low (30 mg) and high (150 mg) dose of amitriptyline but there was a significant reduction in pain intensity among amitriptyline and placebo. In the first study of McQuay et al. (17), the use of 25 mg of amitriptyline resulted in a significant reduction of pain intensity after 3 weeks versus placebo group. In the second study, McQuay et al. (18) compared low (25 mg) and high (75mg) doses of amitriptyline versus placebo and showed that high dose has a greater effect. However, the size of sample was relatively small. The findings of Rizzati-Barbosa et al. (9) showed a significant reduction in pain intensity after administering 25 mg of amitriptyline versus placebo group after 2 weeks of treatment. Our findings showed that the placebo effect on pain was high only at early periods of drug administration. After the third follow up visit, no further improvement in the placebo group was found, while amitriptyline and stabilization splint group had significant decrease in pain intensity during the entire study.

Certain pieces of evidence prove the validity of the assumption that patients who suffer from temporomandibular disorders may also have a reduced oral health-related quality of life. In the study of Almoznino et al. (2) OHIP-14 scores were worse for patients with TMD than in normal population. Blanco-Aguilera et al. (23) showed that perception of oral health is worse in patients who suffer from chronic pain for a longer period of time. According to a systematic review (24), it appears that many treatment modalities led to an improvement in the quality of life in TMD patients. The present results revealed a significant improvement in OHIP-14 score in amitriptyline group, a slight, but not statistically significant improvement in stabilization splint group, while in placebo group OHIP-14 scores did not change significantly over time.

zultati za OHIP-14 nisu se značajno promijenili u tom razdoblju.

Od svih vrsta liječenja, samo je stabilizacijska udlaga imala značajan učinak na poboljšanje iznosa otvaranja usta jer je kod pacijenata liječenih tom udlagom zabilježena značajno veća promjena u bezbolnom otvaranju usta u usporedbi sa skupinom liječenom amitriptilinom i placebom. Kod pacijenata liječenih amitriptilinom i stabilizacijskom udlagom zabilježena je veća promjena u rezultatima prema VAS-u te veća redukcija OHIP-a, iako razlike u usporedbi s placebom nisu bile statistički značajne.

Ova pilot-studija ima određena ograničenja koja umanjuju snagu naših zaključaka, a najveće je mali broj ispitanika. No ona potiče na provedbu cjelokupne studije jer su rezultati vrlo povoljni. Mjere ishoda liječenja orofacijalne boli vrlo su subjektivne, što zahtijeva strogo poštovanje kliničkog protokola koji uključuje neinformiranje kliničara o vrsti liječenja. Provedba tih protokola vrlo je zahtjevna i probir pacijenata zahtijeva mnogo vremena i truda. Zato smatramo da su preliminarni rezultati naše pilot-studije vrijedni, iako je broj pacijenata bio malen.

Zaključak

Čak i uz ograničenja, rezultati ove pilot-studije pokazuju da amitriptilin i stabilizacijska udlaga mogu biti učinkoviti u smanjenju intenziteta boli i poboljšanju kvalitete života pacijenata s kroničnim TMP-om. Stabilizacijska udlaga pokazala se boljom za liječenje ograničenoga otvaranja usta. Bilo bi korisno i dalje istraživati tu temu na uzorku odgovarajuće veličine.

Zahvala

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Sukob interesa

Nije bilo sukoba interesa.

Of all the treatment options, only the stabilization splint had a significant effect on the amount of mouth opening, whereas patients treated with stabilization splint had a significantly greater change in the comfortable mandibular opening relative to amitriptyline and placebo group. Patients in amitriptyline and stabilization splint groups showed better reduction in VAS and OHIP-14 scores, although the differences, when compared to placebo group, were not statistically significant.

The present pilot study has certain limitations that reduce the strength of our conclusions, the biggest limitation being a small sample size. However, this pilot study encourages execution of a full scale study since our results are favorable. The outcome measures of orofacial pain treatment are very subjective, which warrants the adherence to strict clinical protocol involving blinding. Execution of those protocols is very cumbersome and the recruitment process is time consuming. For this reason, we feel that the results of our preliminary pilot study are valuable, although the number of patients is small.

Conclusion

Even with the abovementioned limitations, the results of this pilot study show that amitriptyline and stabilization splint may be effective in decreasing the intensity of pain, thus improving quality of life of patients with chronic TMD. The stabilization splint showed superiority in the management of limited mouth opening during the same period. Further research using adequate sample size would be of value.

Acknowledgement

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Results of this study were presented as an abstract at PER-IADR Meeting in Dubrovnik, Croatia in 2014.

Conflict of interest

None declared

Abstract

Objective of work: The authors conducted a clinical study to evaluate the effectiveness of amitriptyline in treatment of chronic TMD patients and to compare treatment results with stabilization splint. **Materials and Methods:** Twenty-one patients with chronic TMD were included and randomly distributed into 3 groups: patients in Group A received amitriptyline, patients in Group B received placebo, and those in Group C were treated with stabilization splint. Treatment outcomes (pain assessed by a visual analogue scale (VAS), maximal comfortable mouth opening (MCO) and oral health related quality of life (OHIP-14)) were taken at baseline (before treatment), and at 1st, 6th and 12th week of treatment. **Results:** No statistically significant differences between the groups at baseline were found ($p>0.05$). VAS scores improved significantly in Group A ($F=11.326$, $p=0.002$, effect size $=0.791$) and in group C ($F=7.343$, $p=0.005$, effect size$=0.647$). Mean OHIP-14 scores decreased significantly only in Group A ($F=4.417$, $p=0.036$, effect size $=0.596$). In Group B, VAS and OHIP-14 scores did not change significantly over time. Subjects in Group C had a significant change in MCO relative to Group A and Group B. **Conclusion:** From this pilot study it can be concluded that the use of low doses of amitriptyline for a period of 12 weeks is effective for pain management and quality of life improvement in chronic TMD patients. Stabilization splint demonstrated superiority in the management of limited mouth opening during the same period.

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Key words
Amitriptyline; Temporomandibular Joint Disorders; Occlusal Splints; Chronic Pain

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