THE UNIVERSITY OF
SYDNEY

A randomised clinical trial on the effectiveness of topical non-steroidal anti inflammatory drug for painful temporomandibular disorders

Aim: The aim of this study was to determine whether a topical non-steroidal anti-inflammatory drug (NSAID) is more effective than placebo for the treatment of painful temporomandibular disorders.

Methods: Forty eight patients (28 females and 20 males) clinically diagnosed with a painful temporomandibular disorder were recruited. Each subject underwent an initial assessment and was then randomly assigned a topical NSAID (Diclofenac 1g/100g) or a placebo. The subjects were reassessed after a two-week period. The primary outcome measure was the change in pain as assessed with an 11-point numerical rating scale. A number of secondary outcomes were also assessed.

Results: The median change in the 11-point numerical pain rating scale in the active group was -1 whilst the placebo group was 0. However, this was not statistically significant, ($p>0.05$).

Discussion and Conclusions: Notwithstanding the limitations of this study including the limited sample size and narrow subject selection, the study suggests that the use of NSAIDs for the treatment of temporomandibular disorders does not provide better results when compared to a non-active topical cream.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used medications[1]. The physiological effect is caused by the reduction of prostaglandin production which sensitises nerve endings at the site of injury. This occurs primarily due to the inhibition of the cyclooxygenase (COX) enzyme that converts arachidonic acid liberated from the phospholipid membrane. There are two forms of COX which exist, COX-1 which is found in the stomach and kidneys and has a physiological role in maintaining tissue integrity. The second form, COX-2, is induced by inflammatory mediators and has a significant role in pain and inflammation. The development of selective COX-2 inhibitors has been a major development in drug therapy. This has enabled the reduction of adverse side effects associated with NSAIDs. This strategy targets the production of prostaglandins specifically involved in pain and inflammation while sparing prostaglandins that exert important physiological roles such as maintaining the integrity of the gastric lining and normal renal function[1]. Nevertheless these drugs have been associated with some adverse events including nausea, vomiting, diarrhoea, constipation, decreased appetite, rash, dizziness, headache and drowsiness. The most serious side effects include kidney failure, liver failure, ulcers and prolonged bleeding.

The development of topical formulations of NSAIDs has been an additional strategy to minimise the adverse effects of NSAIDs. This delivery route can minimise plasma concentrations of drugs and lead to fewer side effects[2]. Bioavailability and plasma concentrations following topical application are 5 to 15% of those achieved by systemic delivery[2]. When NSAIDs are administered topically, relatively high concentrations occur in the dermis, whereas levels in the muscle are at least equivalent to those following systemic administration[2].

The currently accepted pharmacological treatment approaches for temporomandibular disorder (TMD) pain have not been subjected to rigorous scientific examination. This is particularly true in the case of NSAIDS which are used extensively in the treatment

of mild to moderate musculoskeletal pain and are recommended as a first line drug for treatment of TMDs[3,4]. A meta-analysis of TMD management[5] consisting of more than 4000 references which were identified between 1980 and 1992 was published in 1995. Only 1% (n = 50) were randomised controlled trials. Of these, 5 were drug studies, providing an extremely small pool of evidence upon which to base recommendations regarding efficacy of drug therapy and toxicity. The author concluded at the time that it was not clear whether the drug therapies used for TMD provided any benefit over placebo. Currently, there have been very few placebo controlled trials undertaken to evaluate the efficacy of NSAIDs for the treatment of TMD. The aim of this study was to determine whether topical NSAID is more effective than placebo for the treatment of temporomandibular pain.

Methods

Adult patients attending the Orofacial Pain Clinic at the Centre for Oral Health from March 2007 to September 2008 at Westmead Hospital for assessment of facial pain were considered possible for involvement in the study. The human research ethics committee of Westmead Hospital and The University of Sydney approved the study, and all participants gave informed consent.

As part of a normal assessment in the clinic, each patient completed a pain history questionnaire, a psychometric evaluation (Symptom Checklist 90 Revised (SCL-90R) - Derogatis 1983) and musculoskeletal examination (Research Diagnostic Criteria for Temporomandibular disorders, RDC-TMD[6]) of the head and neck. The psychometric evaluation was not used in this study. After assessment, patients who were diagnosed with a localised TMD (myofascial pain with or without arthralgia) where localised pain is defined as three or less sites of palpable pain within the masticatory muscles and temporomandibular joints, were invited to participate.

Patients with contraindications to oral NSAID use were excluded. These patients include those who have a known or suspected hypersensitivity to diclofenac or other NSAIDs, a history of recurrent ulceration, active or recent history of inflammatory diseases of the gastrointestinal tract such as peptic ulcers, gastritis, regional ulcer or ulcerative colitis. Also, those patients with significant hepatic impairment, active liver disease, severely impaired or deteriorating renal function, those who were pregnant or those who were receiving treatment for facial pain were also excluded.

At the first appointment; the following outcomes were measured:

- 11-point numerical rating scale (Turk et al[7]) between 0 (no pain) and 10 (pain as bad as could be)
- Number of sites that were painful on palpation
- Pain free jaw mobility (vertical jaw opening with the incisal edges of the central incisors used as a reference point measured in millimetres without pain)

At the end of the first clinic visit, participants were randomly issued with an identical container of either topical NSAID-diclofenac 1g/100g (Voltaren Emulgel, Novartis) or placebo (sorbolene cream with similar consistency to active drug, Maxi Natural). Each container of approximately 110 grams of gel, was weighed and coded with a 3 digit number. Both clinical researchers and participants were blinded to the container contents. The container codes were kept in a sealed envelope in a locked cabinet and not opened until the conclusion of the entire study. Randomisation was achieved by computer generated software (Excel Microsoft).

Each subject was instructed to apply the cream over the affected area three times daily for a period of two weeks . Specifically, the subjects were instructed to apply a pea-sized amount of the gel to the skin overlying the painful craniofacial sites. Each subject was provided with written instructions on gel application (Appendix 1) and pain assessment measures (Appendix 2) to be completed at home during the two week application period. Patients demonstrated the correct application of a non-study gel to an experimenter prior to leaving the clinic.

Study pain assessment

The patients were reviewed following a 2-week period. Each patient completed a pain diary for 2 weeks, which consisted of an 11-point numerical rating scale (NRS) for facial pain twice daily: 9am and 8pm. In the evening, the patient also rated their level of pain relief for the entire day on a five point pain relief categorical scale (0=no pain relief, 1=a little pain relief, 2= some pain relief, 3= a lot of pain relief, and 4= complete pain relief). At the end of the two week application, the subject was reassessed by evaluating the same measures used at the commencement of the study.

Data Analysis

The primary efficacy end point was determined by the change in pain intensity on the 11-point numerical rating scale for facial pain between the beginning and the end of the study.

A number of secondary outcomes were also assessed.

- The number of days with some pain relief. A two tailed t-test and Mann Whitney test was used to determine if the number of pain relief days was different between the treatment and placebo groups.
- The change in pain on palpation and pain free jaw mobility was also calculated by subtracting values obtained on day 14 from those obtained on day 1 for each patient. A two tailed t-test and Mann Whitney test was be used to compare patients who received treatment with those who received placebo.

Results

Forty eight patients (28 females and 20 males) were recruited. The median age was 42 years with an age range of 17-72 years. Nine patients discontinued prematurely from the study thus leaving a total of thirty nine patients. Four patients did not return to the clinic and could not be contacted or refused further treatment. Three patients developed gastrointestinal problems and thus did not finish. Two patients developed skin irritation to the gel and stopped. The remaining thirty nine patients consisted of twenty two placebo and seventeen active trials. The results of this study are shown in figures 1-4 illustrated below.

Figure 1 illustrates that the median change of the 11-point NRS in the placebo group was 0 whilst the median for change in active group was -1. However, these results did not reach levels of significance ($p>0.05$) as depicted in Table 1 and 2. The results also showed that the number of days with some pain relief for both groups was 4 days. The change in pain free mobility was greater in placebo group (2.68mm) when compared to the active group (2mm). However, utilising a 2-tailed t-test (depicted in Table 1), there were no significant differences between the two groups, ($p>0.05$). Finally, the change in the number of sites that were painful was greater in the active group when compared to the placebo group but group differences were not significant ($p>0.05$).

Fig 1. Change in 11-point pain scale

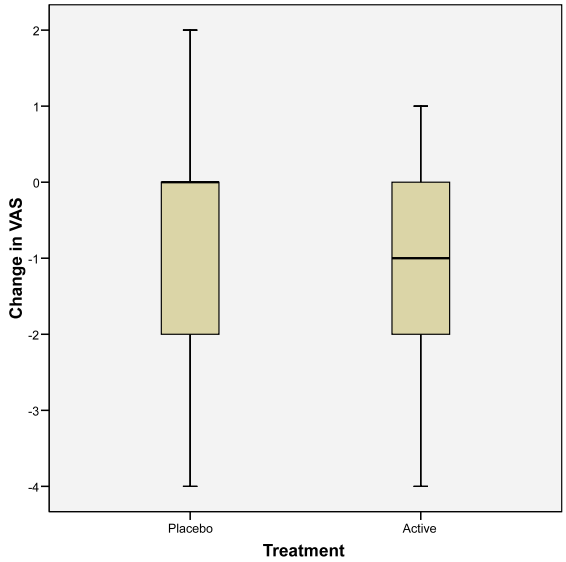


Fig 2. Number of days with some pain relief

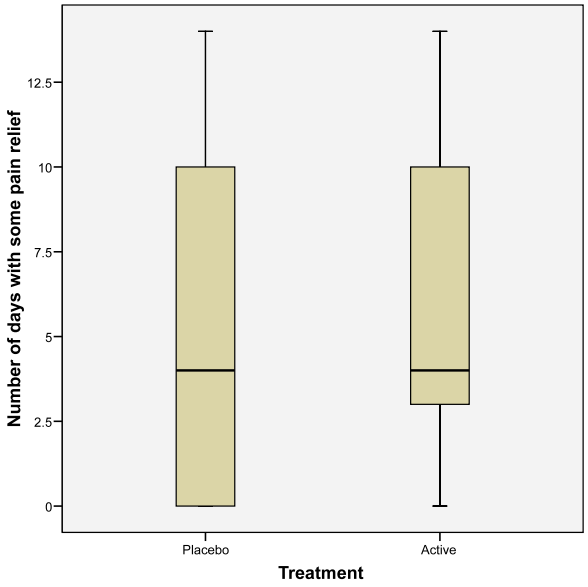


Fig 3. Change in pain free mobility (mm)

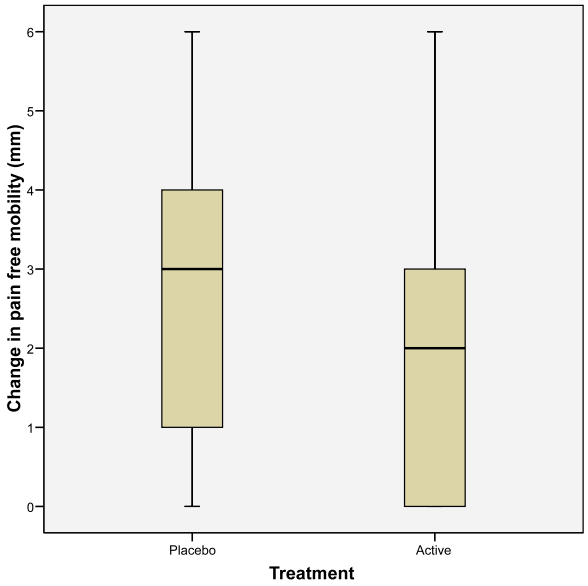


Fig 4. Change in number of painful sites

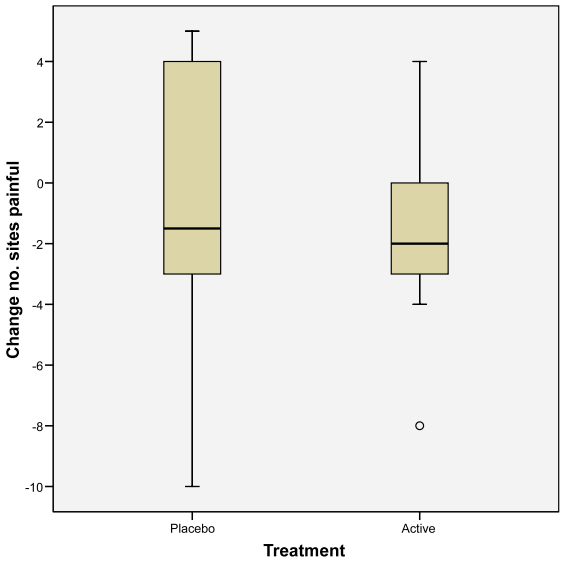


Table 1. t-test of change by treatment

	Treatment	N	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
Change in NRS	Placebo	22	-1.05	1.647	.351	0.928
	Active	17	-1.00	1.414	.343	
Number of days with some pain relief	Placebo	22	5.77	5.191	1.107	0.945
	Active	17	5.88	4.567	1.108	
Change in pain free mobility (mm)	Placebo	22	2.68	2.056	.438	0.286
	Active	17	2.00	1.803	.437	
Change no. sites painful	Placebo	22	-.77	3.939	.840	0.431
	Active	17	-1.65	2.523	.612	

Table 2. Mann Whitney Test

	Change in NRS	Number of days with some pain relief	Change in pain free mobility (mm)	Change in no. of sites painful
Asymp. Sig. (2-tailed)	0.918	0.841	0.267	0.509

Table 3. Distribution of results

	Treatment					
	Placebo			Active		
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75
Change in NRS	0	-2	0	-1	-2	0
Number of days with some pain relief	4	0	11	4	3	10
Change in pain free mobility (mm)	3	1	4	2	0	3
Change no. sites painful	-2	-3	4	-2	-3	0

Discussion

There are a number of confounding factors present within this study. Firstly, there were 6 different operators utilised who assessed the study subjects. Secondly, the active and placebo gels have distinctly different scents which may have introduced bias into the patients responses. The limited sample size may not have been sufficient to detect a significant difference between the two subject groups. Nevertheless, the results of this study are not unlike those of previous studies. Minakuchi et al[8] studied TMD patients with anterior disc displacement without reduction (confirmed by magnetic resonance imaging) and examined the efficacy of systemically administered diclofenac (25mg three times daily) versus non-treatment (control group). Patients were randomly allocated to one of three groups - control, self-care plus NSAIDs, and occlusal appliance plus self-care/NSAIDs. Their results showed within group improvements were made for all variables for all groups. Between group differences were not highly evident with only mean daily activity limitation for the self-care/NSAID group being significantly lower than that of the occlusal appliance + self-care/NSAID group at the two and four week time points. A confounding factor of this study was that both treatment and control groups exhibited a marked improvement in pain during mastication and jaw opening over the study period. One difficulty in studying TMD patients is that there appears to be a natural fluctuation in pain symptoms which may undergo remission and exacerbation. The authors concluded that the gradual reduction in signs and symptoms was non-specific and was related not to the type of treatment, but more to the passage of time.

Gordon et al[9] reported that Ibuprofen (800mg, three times daily) and Piroxicam (20mg daily) were no more efficacious than placebo for the treatment of TMD pain. These studies have only been published as an abstract and examined small groups of TMD patients (n=30 to 40) who appeared to have mostly joint pain. Nevertheless, this suggests that in TMD patients, with predominantly joint-related pain symptoms, NSAIDs may not be particularly effective. However, TMD patients with predominantly masticatory muscle pain have not been reported.

Although considered relatively safe drugs, chronic systemic administration of NSAIDs is associated with significant side effects. In particular the development of gastrointestinal ulceration, renal dysfunction, and in sensitive individuals, the exacerbation of existing hypertension. One approach used to reduce unwanted side effects is the use of creams and more recently topical patches or gels containing NSAIDs to achieve high concentration near the site of tissue pain, but avoiding significant systemic levels.

Di Rienzo et al[10] investigated the efficacy of topical versus systemic diclofenac in the treatment of TMD. In that study, 36 patients were evenly and randomly allocated to two groups. One group received oral diclofenac sodium 50mg tablets twice a day for 14 days. The second group received 16mg/ml of topical diclofenac sodium and were instructed to apply four times daily for a period of 14 days. Patients were asked to complete a questionnaire at the beginning and end of treatment. A graded visual analogue scale (VAS) and questions pertaining to the pain and tenderness of the temporomandibular joint and functional limitation of mouth opening were collected. The results indicated that all patients showed relief from pain after treatment. However, the difference between the two groups was not significant ($p>0.05$). Post-treatment, 16 patients of the first group displayed epigastralgic symptoms. Three patients treated with topical diclofenac showed a modest irritation of the temporomandibular joint region which disappeared spontaneously. Topical diclofenac has the advantage that it does not have adverse systemic effects, whereas oral diclofenac had negative effects on the gastrointestinal system. The authors concluded that there was little difference between topical and systemic application of non-steroidal anti-inflammatory drug diclofenac when used for the treatment of TMD.

Ekberg et al[11] investigated the effect of a systemically applied NSAID, diclofenac, compared with a placebo. In the study, 32 patients with pain localised to the temporomandibular joint (TMJ) were evenly allocated to two groups. Only a visual analogue scale was used at pre-treatment for baseline data collection. The treatment

effect was assessed by the patients' own evaluation of improvement as well as the frequency of joint and muscle pain. The clinical condition was assessed by the degree of tenderness to palpation of the TMJ and masticatory muscles and by mandibular mobility. The results of this study showed a greater reduction of the frequency of joint pain in the group treated with diclofenac as well as a significant reduction of daily TMJ pain. This treatment group also showed a significant decrease in tenderness to palpation of the masticatory muscles in comparison to the placebo group. The patients with short duration of pain showed the best response to diclofenac. It was concluded that there was no evidence in the study to prove that diclofenac should be used as a primary treatment of TMJ pain, but it could be used as a complement to other treatments of acute TMJ pain.

Mason et al[12] conducted a systematic review of topical NSAIDs for chronic musculoskeletal pain. The number of trials included were 15 placebo controlled, 7 active controlled and 3 with both active and placebo controls. The total number of patients involved were 1502 in placebo controlled trials and 764 in active controlled trials. The results showed that in 14 trials with information from 1502 patients, topical NSAIDs were significantly better than placebo. Trials included in this review were of high quality and validity, so minimising the possibility of bias. However, there was insufficient information on different topical NSAID preparations to tell whether one was better than another. Another review of topical NSAIDs in musculoskeletal pain by Lin et al[13] concluded that there was no evidence of superior efficacy beyond two weeks of use.

Vaile et al[14] published a review of the literature investigating topical NSAIDs for musculoskeletal conditions. Human and animal trials indicate that topical NSAIDs display lower plasma concentrations when compared with systemic delivery. Concentrations of active drug therapy in soft tissues are still of a threshold which is considered to have an anti-inflammatory effect. The authors did question the mode of delivery of active drug in the joint therapy that is whether the drug reached the joint due to transcutaneous or systemic route. Adverse reactions were reported with topical

NSAIDs. In approximately 2% of patients there were symptoms ranging from gastrointestinal irritation to irritation of the skin. The authors conclude that the evidence for the usage of NSAIDs in acute and subacute soft tissue injuries is accumulating, however, longer trial periods are necessary.

Ta et al[15] compared the efficacy and adverse effects of a celecoxib, a cyclogenoxygenase-2 inhibitor, with naproxen (NSAID) and a placebo in the treatment of painful TMJs. This study was a randomised double-blind control trial with 68 subjects. They were randomly assigned to one of three groups. Group 1 received celecoxib 100mg twice daily, group 2 received naproxen 500mg twice daily and the third group received a placebo for 6 weeks. Primary outcome measurement was a change in VAS. The results showed that naproxen significantly reduced the symptoms of pain around the joint area. Significant improvements in range of motion was observed with naproxen compared to celecoxib and placebo. Celecoxib did show better pain reduction than placebo but this was not significant for TMD pain. The authors conclude that inhibition of both COX 1 and 2 enzymes are needed to achieve effective analgesia for this type of musculoskeletal pain.

Conclusions

Within the limitations of this study, the results show that the use of NSAIDs for the treatment of temporomandibular pain does not give a better result when compared to a placebo.

Appendix 1

PARTICIPANT INSTRUCTIONS

Study Title: *The effectiveness of a non-steroidal anti-inflammatory drug on jaw pain*

Chief Investigator: Dr Tuan Dao Department of Oral Restorative Sciences

How to apply the cream to your face

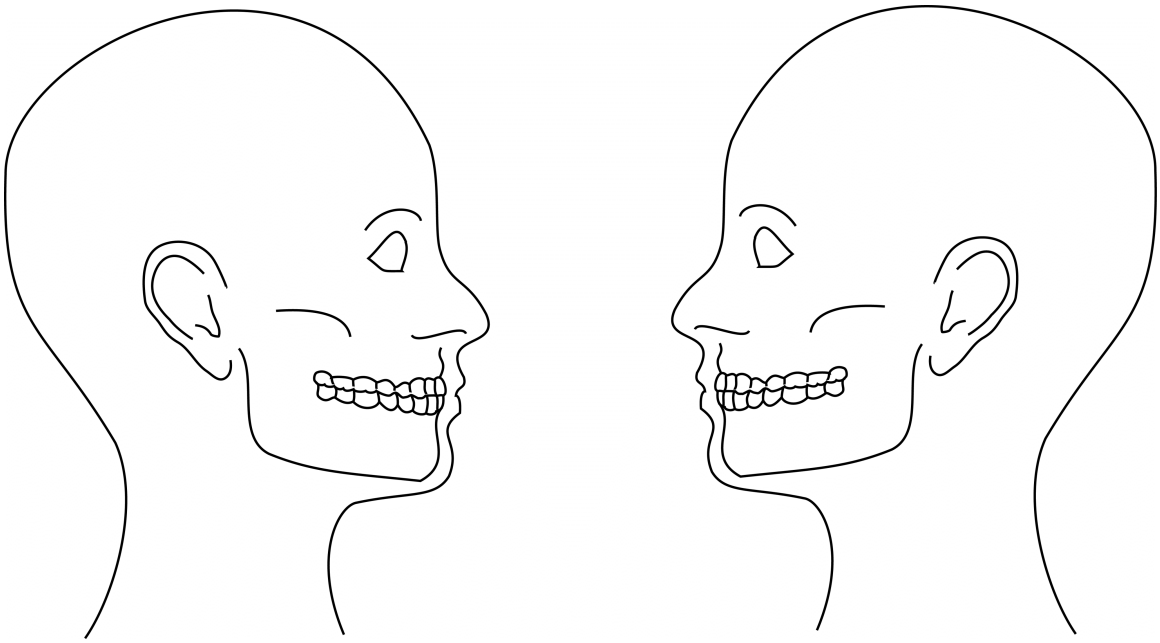
1. You will be taught how to apply the cream to painful sites on your face at your initial appointment. Below is a diagram with the locations where we wish you to apply the cream.

2. Place a pea-sized amount of cream (as shown in the clinic) onto your index finger and rub it gently into the painful sites of your face three times a day (9am, 2pm, & 8pm).

3. Do not apply it inside your mouth or in or around your eyes, and remember to wash your hands immediately after applying the cream to your face.

4. Remember to record in the diary that you were given your facial pain level twice a day; once at 9am and once at 8pm, and also the amount of pain relief your felt for the day.

5. Discontinue use and consult the Chief Investigator if a rash or other symptoms develop.



Appendix 2

Complete this at **9 A.M.**:

How would you rate your facial pain on a 0 to 10 scale at the present time, that is, **right now**, where 0 is "no pain" and 10 is "pain as bad as could be"?

No pain										**Pain as bad as could be**
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Complete this at **8 P.M.:**

How would you rate your facial pain on a 0 to 10 scale at the present time, that is, **right now**, where 0 is "no pain" and 10 is "pain as bad as could be"?

No pain										**Pain as bad as could be**
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

How would you rate your pain relief for the **entire day**, where 0 is "no pain relief" and 4 is "complete pain relief"?

No pain relief	**A little pain relief**	**Some pain relief**	**A lot of pain relief**	**Complete pain relief**
0	**1**	**2**	**3**	**4**

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