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Low power laser biostimulation of chronic oro-facial pain. A double-blind placebo controlled cross-over study in 40 patients

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Summary The efficacy of low power laser stimulation in the treatment of chronic oro-facial pain conditions was investigated in a double-blind placebo controlled modified cross-over study in 40 patients. The laser was an invisible infrared (IR) diode laser with an emission at 904 nanometer (nm). Treatment effect was evaluated by means of VAS-scales and global assessment of pain. Outcome of treatment was correlated to changes in urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA). The clinical impression was that placebo was superior to laser stimulation. No statistically significant difference between the analgesic effect of the laser and placebo irradiation was found on VAS-scales. A significant ($P = 0.05$) increase in 5-HIAA excretion was found in the placebo group. It is concluded that the possibility of a substantial placebo response should be taken into consideration using 904 nm (IR) lasers for pain treatment in patients with this type of chronic oro-facial pain.

Key words: Chronic pain; Placebo; 5-HIAA; 904 nm IR laser; Biostimulation

Introduction

During the last 10–15 years, low power, low level or soft lasers have been commercially available for routine clinical use [3]. Two principally different main areas have been proposed as being suitable for laser treatment: inflammatory diseases or ulcers [23,24,31] and pain conditions of any kind [3,39].

Typical low power lasers today are the 633 nanometer (nm) red He-Ne gas laser, and the infrared (IR) 830 nm Ga-Al-As and 904 nm Ga-As diode lasers [3].

The essential *photobiological* effects in low power laser therapy are unknown. In contrast to surgical lasers, such as the CO_2-laser and the Neodymium : YAG-laser, most low power lasers are not able to raise the temperature in the irradiated tissues by more than 1° C [20]. As a consequence of the low energy delivered to the tissue, a *photothermal* effect is unlikely. A *photochemical* effect cannot, however, be excluded. Light is able to activate different biological molecules – chromophores – depending upon the wavelength of the light. Especially in the ultraviolet and blue parts of the spectrum, numerous different biological structures absorb optical radiation very strongly. In the red and infrared part the dominating absorbing molecules are melanine/DOPA and haem in erythrocytes [17,18]. It has been suggested that the biological effect of low power laser therapy is a result of activation of enzymes in the

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respiratory chain, especially cytochrome *c* in the mitochondria or the Na-K pump. Furthermore it has been claimed that only abnormal biological processes can be influenced by the laser light [23,24].

The effect of laser therapy in wound healing studies and in-vitro studies in cell cultures indicates reaction in terms of faster healing due to increased vascularization, promoted growth of fibroblasts and collagen formation [8,9,28] and changes in the immunological response [31].

Nerve conduction studies in rats have shown that transcutaneous He-Ne laser irradiation doses in the range 4–10 J/cm^2 causes a significant increase in action potential in the sciatic nerve and that this effect is considered to be consistent and long lasting [32]. In another study, scar formation following nerve crush was reduced and again action potential magnitude increased due to He-Ne laser radiation compared to not irradiated contralateral controls [34]. The authors offer no comments as to the neurophysiological nature of the increase in the size of the action potentials. However, a recent study utilizing a convincing rabbit cornea model showed that He-Ne irradiation could not produce any changes in the electrophysiology of corneal Aδ and C fibers [20].

Few controlled clinical trials have been performed. Walker [39] obtained a positive pain relieving effect from He-Ne laser treatment of chronic pain patients with neurogenic and arthrogenic pain after irradiation of the skin overlying greater afferent nerves and the affected nerve or joint itself. In the control group irradiation of skin not overlying nerves was performed. In the experimental group 73% of the patients experienced an average pain reduction of 82%. In the control group only 10% of the patients obtained relief. Furthermore, the responders showed a marked increase in urinary excretion of 5-HIAA, a serotonin metabolite, compared to the non-responders. It was suggested that this pain relieving effect might be a TENS or acupuncture-like effect due to laser stimulation of chromophores in the myelin sheets in low-threshold myelinated nerves. Radiation dose was low; 1 mW for 20 sec, 3 times/week over 10 weeks. In this study and in most of the He-Ne studies [4,27,37,40–42], a maximum output of 1–2 mW have generally been used. However, the irradiance of He-Ne lasers, which can be substantial in magnitude, was not reported in these studies.

Later controlled studies have shown that He-Ne laser irradiation of peripheral nerves is capable of suppressing clonus in patients with spastic paralysis [40], of reducing the somatosensory evoked potential [41] and increasing the skin resistance over musculo-skeletal trigger points [37].

More recent double-blind controlled studies have, however, failed to show any difference in tennis elbow [27], in chronic myofascial pain [42] in osteoarthritis of the thumb [4], or in painful arthrosis of the knee [21].

It is interesting that the first enthusiastic reports by Walker [39–41] have not been reproduced by others, and that almost all placebo-controlled studies so far have failed to identify any differences between laser and placebo.

The widespread use of low power laser treatment of pain patients is thus primarily based upon empiric experiences and anecdotal case reports [3,43]. In spite of the almost total absence of scientific documentation of the effect of lasers in dentistry [43] there seems to be a great interest for lasers among private practitioners and a demand for laser treatment from patients. In Denmark, unofficial registrations indicate that having been on the market for 2–3 years, low power lasers are available in between 10% and 30% of all dental clinics.

Purpose

The purpose of this study was primarily to examine the pain relieving properties of a 904 nm IR diode laser in a double-blind, placebo-controlled cross-over study in chronic oro-facial pain conditions. As low power laser irradiation can be considered to be based on a non-surgical and non-pharmacologic principle we wanted, if possible, to reproduce the finding by Walker [39] with regard to the positive association between treatment response and increase in 5-HIAA excretion.

Methods

Subjects

Forty patients with different types of chronic oro-facial pain were recruited for the study. These patients were selected from 70 consecutive pain patients referred to the department over an 18 month period. Inclusion criteria were: oro-facial pain of more than 6 months' duration; no known pathology responsible for the pain. These features fit the DSM-III definitions of chronic, benign, idiopathic pain [2]. Exclusion criteria were severe psychopathology, especially severe depression and anxiety. Severity of depression and anxiety was estimated by means of the extended version of the Beck Self-rating Depression Scale [6]. Patients with a depression score > 15 indicating major depression or an anxiety score > 15 indicating major anxiety [26] were excluded and referred to a psychiatrist.

Thirty-seven females and 3 males participated. Mean age was 59 years (range 25–80 years). Mean duration of pain was 4.9 years (range 0.5–42 years).

Clinical diagnoses *

041.68 Oral dysesthesia, n = 28.
034.68b Odontalgia, n = 5.
006.61 Secondary trigeminal neuralgia from trauma, n = 3.
006.68a Trigeminal neuralgia, n = 1.
033.67b Tension headache, chronic, n = 3.

Initially, a full medical history was taken and a clinical examination was performed. The consumption of analgesics was recorded. In patients with oral dysesthesia it was established that the symptoms could not be associated with allergic reactions to food or environmental factors. Furthermore, no diseases of the oral mucosa (candidiasis, decubitus, etc.) were present. Only patients with precisely localized odontalgia were included in this study. This means that the pain was localized to a single tooth or an equivalent part of the alveolar process. In these cases, X-ray examination revealed no periapical pathology. In the cases of tension headache a conventional bite splint had been used for at least 3 months without subjective improvement.

In general, no patients with generalized diseases which could be suspected to be responsible for the oro-facial symptoms were included in the study. In particular, neurological, hematological, nutritional or endocrinological diseases were taken into consideration.

Pain assessment

Pain intensity was measured by means of a 200 mm VAS scale with end points 'No pain' and 'The worst pain thinkable.'

Pain quality was classified on the basis of the clinical description. A global impression of the total impact of pain experiences was done based on a registration of analgesic consumption, influence of pain in daily life situations, duration of pain and the patient's interest in participating in the study. During the study, evaluation of changes in pain intensity and VAS scale recordings were done at every visit.

The clinical registrations of effect (VAS and global) were performed by one of the authors (H.J.H.). Based only upon indications of changes in intensity of the pain, changes in exposure time or change of probe were done according to the cross-over procedure and the exposure schedule without breaking the code. The other author (U.T.) performed the randomization and irradiation without being acquainted with the effect of the treatment.

Equipment

A 904 nm IR laser (ORA-LASER) manufactured by Oralia (Konstanz, F.R.G.) was used. The laser diode is located in a probe convenient for intraoral use. In the probe, a red visible guidelight is produced by a light-emitting diode (LED). The laser radiation and the guidelight is delivered through a glass fiber rod. The diameter of the rod is 7 mm and the mean output power delivered by the diode is 30 mW. The laser is pulsed with a pulse width of 200 nsec. The pulse repetition frequency can be either fixed or continuously varied between 1 and 9999 Hz. The irradiance is

* Indices according to 'Classification of Chronic Pain' by the International Association for the Study of Pain [30].

78.9 mW/cm^2 at 9999 Hz. It is classified as a Class 3B laser [19].

Double-blind control

The laser apparatus was delivered from the manufacturer with 2 identical probes; one of the probes was marked with a hidden colored ring, and one was the inactive placebo probe. The code was only known by the manufacturer. We designated the 2 probes A and B. The integrated output power measuring device of the apparatus was disabled. The 904 nm IR light was nearly invisible and totally masked by the guidelight.

Cross-over design

It has been clinically established that laser treatment in pain patients often results in a relatively quick response after 1–3 treatment sessions [39,43]. Furthermore, no late treatment responses have been reported. Long-term follow-up at 2, 4 and 6 months has been performed in the tennis elbow group [27] and in the myofascial pain group [42], and no late changes in treatment response have been reported.

We were, therefore, confident that the following modified double-blind cross-over design with open therapeutic guidance would be acceptable. The patients were allocated at random to treatment with either probe A or B. If a patient had not obtained pain relief after the first 4 treatment sessions with a given probe, the probe was changed without the patient's knowledge. If a patient indicated pain relief after the first 4 treatment sessions, treatment was continued with the same probe throughout the study. At the end of the study the patients were divided into 'responders' and 'non-responders' based on the estimation of changes in pain intensity. 'Non-responders' indicated no changes in pain during the study, whereas those who indicated pain relief were classified as 'responders.' The responders were divided into 'initial responders,' who indicated pain relief after the 4th session, and the 'late responders,' who obtained relief during the last 4 sessions after the cross-over.

The study was performed in accordance with the Helsinki Declaration of 1981 and was accepted by the local ethical committee.

Exposure schedule

In oral dysesthesia the characteristic clinical feature is a burning sensation in the surface of the oral mucosa; typically the dorsum of the tongue, the anterior part of the palate and the inside of the lips [5,11,44]. The clinical appearance of the oral mucosa is normal. Usually no tender spots are present. In these patients, and in the patients with neuralgia, we, in principle, in turn irradiated the afferent nerves innervating the painful area. That would typically be the lingual nerve at the posterior part of the border of the tongue, the mental nerve, the incisal nerve, the greater palatine nerve and eventually the infraorbital nerve, all at the point of emergence from their respective bone canals. In the patients with odontalgia we irradiated the painful spot. In the patients with tension headache we irradiated the myofascial trigger points of the masticatory muscles.

Irradiation time was in accordance with the recommendations from the manufacturer: 60 sec at each spot for the first 2 visits. If the patients did not experience pain relief, the irradiation time was increased to 120 sec at each spot.

Dose

Sixty seconds of radiation correspond to a maximum dose of 4.7 J/cm^2 and 120 sec to 9.4 J/cm^2. The automatic variable pulse repetition frequency setting was, continuously varying the number of pulses/sec between 1 and 9999. The energy delivered to each irradiation point was then estimated to be approximately half the maximal dose indicated above.

For a given patient the total time of irradiation could vary from 1 min to a maximum of 18 min, depending upon the number of irradiation points. If a patient reported side-effects to treatment either during treatment or between the sessions, the irradiation time was reduced. Each patient received a total of 8 treatments during a 4 week period with 2 weekly sessions.

5-HIAA

At the first visit the patients were asked to collect the total amount of urine for a 24 h period just prior to the first irradiation. This procedure was repeated after 8 treatment sessions. From

each 24 h urine, a 10 ml sample was taken and frozen at −20 °C. Finally the concentration of 5-HIAA was determined and the total 24 h excretion of 5-HIAA was calculated for each patient. The analysis was performed by means of a 5-HIAA TDX® – biogenic amine assay system from Abbot Laboratories.

Statistics

Non-parametric statistic analysis was used [36], with a 2-sided 5% level of significance. Differences in the area under the VAS curves were tested by the use of the Kruskal–Wallis test. Differences in distributions in groups were analyzed with a Fisher exact test, and changes in 5-HIAA excretion with a Mann–Whitney rank sum test.

Results

Blindness

The code was broken by means of a colored optical glass, HOYA R 72, 2.5 mm, which cuts off all light below 720 nm, and infrared sensors mod. No. Q-12-R by Quantex. We found that probe A was inactive and probe B active. This finding was in contrast to the clinical impression. During the course of the study – after the 4th session – it was found that 11 patients indicated a positive effect from probe A, whereas only 5 patients had a positive effect from probe B (Table I). Furthermore, 8 patients experienced side-effects – intensification of symptoms – during treatment with probe A, but only 3 with probe B. Thus the 'blinding' of the study was successful.

TABLE I

CROSS-OVER PROCEDURE AND GLOBAL ASSESSMENT OF TREATMENT EFFECT ($P = 0.74$; Fisher's exact test)

Number of responders in parentheses.

Start probe	Cross-over procedure	% with effect
Placebo	11 ptt. continue	73% [a] (8)
	10 ptt. change to IR	10% [b] (1)
	5 ptt. continue	80% [a] (4)
904 nm IR laser	14 ptt. change to placebo	21% [b] (3)

[a] '% initial responders.'
[b] '% late responders.'
Total number of responders: 16/40 = 40%.

Estimation of effect

Consumption of analgesics was sparse. One of the patients with tension headache used analgesics (paracetamol, 500 mg p.n. and nozinan 5 mg vesp.) with insufficient effect. The rest of the patients were without relevant medication.

Table I shows the results of the cross-over procedure and the outcome of the estimation of effect at the 4th and 8th session. Due to randomization, 21 patients were treated with the placebo laser and 19 with the active laser from the start. After 4 treatment sessions the effect of the treatment was evaluated. Eleven patients indicated an effect from placebo treatment and 5 from laser treatment. In the initial responders the treatment was continued with the same probe used from the start. For the rest of the patients the probe was switched. After 8 treatment sessions it was found that in 73–80% of those patients who experienced an initial effect from either probe, the effect was sustained during the study. In those patients who did not respond to the first probe, the cross-over to the other probe only resulted in effect in 10–21% of the patients.

Fig. 1 shows the mean VAS-pain recordings for those patients who responded to treatment with the same probe throughout the study: 8 placebo responders and 4 laser responders. A 50% pain reduction was obtained after an average of 3.2 placebo treatments and 3.7 laser treatments. Four patients in the placebo group and 1 in the laser group indicated initial response after 4 sessions, but at the end of the study these patients concluded that no effect had been obtained. Furthermore the VAS-pain scores of the non-responders are shown: 10 in the placebo-to-laser group, and 14 in the laser-to-placebo group. The areas under the VAS curves were used as expressions of the total pain experience during the trial. There were no statistically significant differences between the areas in the responder and in the non-responder groups (Kruskal–Wallis).

Five patients with oral dysesthesia were treated with laser only. In the group of patients treated

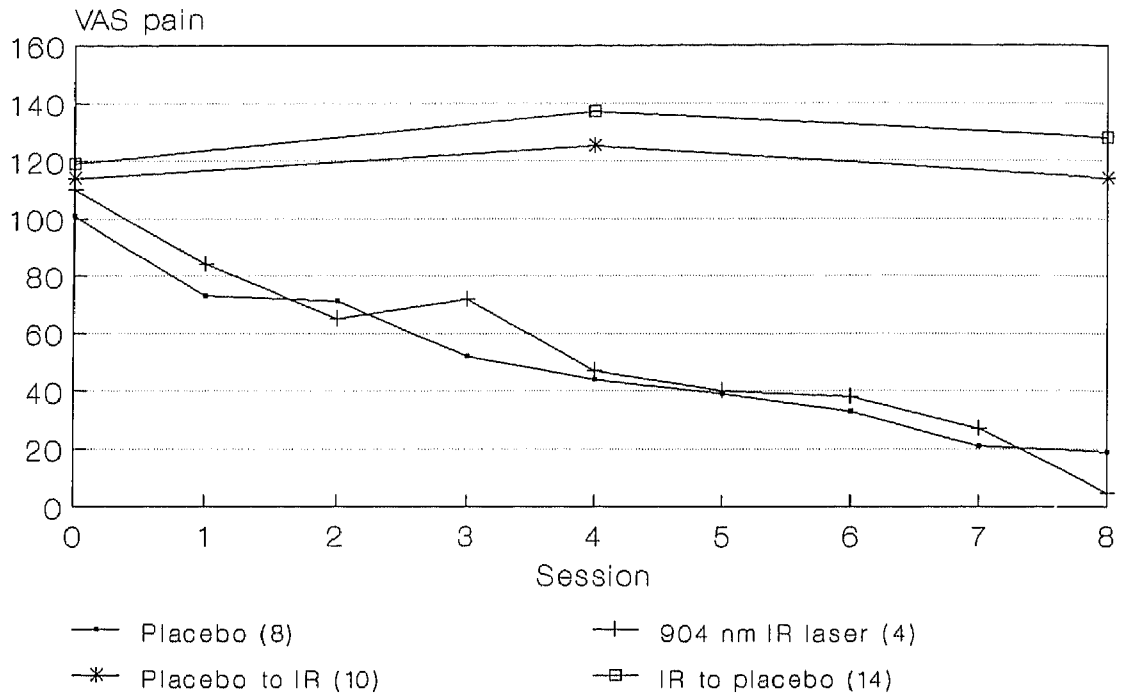

Fig. 1. Mean VAS-pain recordings of pain in patients with chronic oro-facial pain during low power laser treatment. Upper 2 curves, non-responders; and lower 2 curves, responders. Number of patients in parentheses. Cross-over was performed after 4 treatment sessions in the non-responder group, but not in the responder group. Average 50% pain reduction in the responder group at 3.2 sessions in placebo and 3.7 sessions in laser group.

with placebo only, 5 patients had oral dysesthesia, 1 odontalgia, 1 secondary neuralgia, 1 trigeminal neuralgia, and 3 tension headache. The rest of the patients were treated with both laser and placebo. The responders in different diagnostic subgroups were (placebo/laser responder ratio): oral dysesthesia: 5/4, odontalgia: 1/0, neurogenic pain: 1/0, neuralgia: 1/0, muscle pain: 0/0.

It is concluded that no statistically significant differences between laser and placebo can be shown irrespective of the method used for registration of the analgesic effect.

5-HIAA

The concentration of 5-hydroxyindoleacetic acid was determined in 36 patients, 11 responders and 25 non-responders. Of these, 26 patients were treated with the active laser either as the first or the second probe or with the active laser only throughout the study. Ten patients were treated with the placebo probe only. The median 5-HIAA daily excretion before laser treatment was 22.9 μmol (95% confidence interval 19.62–27.20) and after 8 treatment sessions 23.2 μmol (18.00–26.39). Normal daily 5-HIAA excretion is < 40 μmol. Five patients had an abnormally high 5-HIAA excretion before the start of the treatment. In 3 patients this condition was unchanged at the end of the study. The median daily change in 5-HIAA excretion (last visit minus first visit in μmol) was 4.500 in the responder group vs. -1.120 in the non-responder group ($P = 0.12$), and 4.690 in the placebo group vs. -1.620 in the laser group ($P = 0.05$, Mann–Whitney rank sum tests).

Discussion

The use of low power infrared diode lasers is widely recommended for clinical use, especially in the treatment of (a) ulcerative or inflammatory diseases [4,21,23,24,28,31], (b) functional disorders

[27,37], and (c) chronic pain conditions [39]. The recommendations are primarily based on positive clinical experiences rather than classical placebo-controlled clinical trials. Only a limited number of controlled studies have been performed. Of these, few [37,39] indicate positive results in pain treatment, whereas several recent studies fail to show any difference between laser and placebo treatment [4,21,27,42].

In the past there has been some discussion as to whether the visible red He-Ne laser or the infrared diode lasers are most suited to treatment of pain and functional disorders [37]. On the basis of previous investigations, especially in vitro studies [23,24,28,31], it seems likely that the He-Ne laser possesses properties other than the infrared diode lasers. The infrared laser radiation penetrates deeper into the tissues than visible laser radiation due to fewer absorbing chromophores in this part of the spectrum [16,33]. On the other hand, hemoglobin and melanine/DOPA if present are strongly absorbing in the 700–1000 nm range [17,18]. Until now no documentation has been presented with respect to differences between different diode lasers.

Whether laser effect is dependent upon the wavelength of the light, irradiance or dose is still unclear. A prerequisition for effect of a given laser source must be its ability to penetrate biological tissues. This penetration will depend upon the optical properties of the skin or oral mucosa, in turn depending upon the type and thickness of the epithelium, reflectance, melanine content and vascularization of superficial parts of the submucosa or subcutis [16]. Secondly, the laser light must be able to reach a relevant target, i.e., the myelin sheets of the nerves. This is a question of the distance to the nerves or pathological processes which are to be influenced. Finally, the photosensitivity of the target is important. This requires the presence of chromophores at relevant positions. In the oral cavity the optical properties of the mucosa have not been investigated. The oral mucosa is highly vascularized in certain areas. The relevant nerves for TENS or acupuncture-like effects are incorporated in the calcified tissues of jawbones and teeth, and therefore not accessible to direct laser irradiation. The influence of low power laser irradiation on the different types of mineralized tissue and the oral mucosa is basically unknown.

In the present study one of the popular 904 nm IR low power lasers was used in a placebo-controlled cross-over study. We deliberately selected patients with stable symptomatology who were suffering from different types of chronic oro-facial pain conditions without known peripheral pathology, or when present, with pain complaints grossly in excess of what could be expected from the physical findings [2]. It is a clinical experience that these conditions are difficult to alleviate. The possibility of spontaneous recovery during the course of the study must, in a group of patients with a mean duration of pain of approximately 5 years, be regarded as negligible. In the case of trigeminal neuralgia, however, spontaneous recovery cannot be excluded. Especially in the patients with chronic oral dysesthesia, who are in the majority in the present study, mean duration of pain in different studies usually amounts to several years at the time of admission [5,11,26,44]. This indicates substantial difficulties in characterizing the etiological cause. In most papers on chronic oral dysesthesia or burning mouth syndrome the etiology is regarded as either multifactorial [5,44], mixed psychosomatic or purely psychogenic [25,38,45,46]. Clinical and neurological examinations of burning mouth syndrome patients have concluded that objective findings in these patients are sparse. It has recently been shown that burning mouth syndrome patients have alterations of heat pain tolerance at the tip of the tongue [14] and alterations in taste thresholds [14] compared to asymptomatic controls. It has been suggested that these sensory alterations in combination with the longstanding intraoral pain condition induces personality alteration similar to those described in other chronic pain patients including elevated scores in the depression, hysteria, psychopathic, paranoia and psychasthenia scales in the MMPI [13].

The skewed sex ratio in our investigation is in accordance with other investigations of patients with atypical facial pain and chronic oral dysesthesia in which women usually dominate in the range 80–90% [10,11,25,46].

In spite of the comprehensive literature on idiopathic burning mouth syndrome and atypical facial pain, only few studies deal with placebo-controlled treatment of the condition. Previously we have used tricyclic antidepressants in a double-blind, placebo-controlled trial in 60 patients with chronic oral dysesthesia. Objective psychiatric rating showed that the patients suffered from depression in a light to moderate degree. We found no differences between active treatment and placebo. Placebo treatment was shown to be effective in approximately 40% of the patients [15,26]. A similar placebo response has been found in another study [10].

In the present study, we failed to show any difference between laser and placebo treatment irrespective of the method used for registration. Taken together, the two treatments gave the traditional placebo response in 40% of the patients. The placebo response in this and previous studies may, at least in part, be ascribed to the type of pain patients treated. Firstly, the absence of peripheral inflammatory processes makes an effect from laser treatment unlikely [23,24]. Secondly, in patients with oral dysesthesia, the absence of peripheral pathology in particular supports a view of a psychosomatic origin. Treatment of psychosomatic symptoms of this type in the absence of physical findings are usually regarded as very difficult, also from a psychiatric point of view [35]. Under these circumstances a substantial placebo response might be expected.

We have used a modified cross-over technique in which the cross-over procedure was performed in the middle of the study in the non-responder group without informing the patients. In our opinion this procedure offers maximum benefit for the most effective treatment modality. However, this cross-over method is only acceptable when treatment effect is almost instant. We found a 50% pain reduction after 3–4 treatment sessions in the responder groups. As a result of the procedure 11 patients were treated with placebo and 5 with laser only, which means that 24 patients received the eventual positive effect from both treatment modalities. In this way, none of the treatments has been brought into disrepute by the selected procedure. In our opinion, the method chosen has 2 advantages. First of all, the natural course of the treatment response in the responder group can be followed throughout. A reduction in mean VAS-pain score on a 200 mm VAS scale from 120 mm to 20 mm must be regarded as a successful and effective treatment. Secondly, the lack of response following the intermediate cross-over in the non-responder group supports our view of the treatment response as being primarily placebo-related in nature. During the last 4 sessions a 50% reduction in VAS-pain score should be expected if treatment response was related to treatment per se.

In the statistical analysis of the figures shown in Table I, the calculations are based on the maximal numbers of responders, initial and late responders taken together. If, however, the Fisher exact test was performed on the initial responders only, the P value would be = 1.00.

The sensitivity (statistical power) of the modified cross-over method used will be less than that of a regular cross-over procedure. It has been calculated that the power in the alternative: +/− 50% difference – which for example could be 30% non-responders and 80% responders – will be approximately 50%. The weak power is a natural consequence of the relatively small number of patients in the study.

In the present study, a placebo response could be obtained in 73% of the patients. Then, if a difference between treatments of a magnitude of 15% should not be overlooked, and with a risk of a type I error of 5%, and a risk of a type II error of 10%, then the total sample size in a future study must comprise at least 292 patients.

A sample of this size is regarded as unrealistic and without relevance as the treatment response seems to be related to the individual patient rather than the nature of treatment in question. It is interesting that 73–80% of the patients who responded initially to either placebo or laser had a positive effect throughout the study, whereas only 10% of those who, unknowingly, were switched to laser treatment in the middle of the study had a positive effect at this time. The fact that the initial response is by far the most impressive leads us to the assumption that some patients have a mobilizable placebo response, which may be totally inde-

pendent of laser irradiation. The late responders are regarded as incidental. The placebo response in our study seems to be slightly better than the average placebo response reported in other studies [7]. This difference cannot be explained, as the placebo response is supposed to be determined by several independent factors as the setting of the study, the doctor–patient relationship and the beliefs and anticipation of the patients. The significance of applying a new treatment principle, which has obtained much public interest should not be overlooked. However, the rather constant placebo response independent of the diseases treated and the methods used has led to the assumption that a 'fundamental mechanism in common is operating, one that deserves more study' [7].

Changes in 5-HIAA excretion are supposed to reflect fluctuation in serotonin metabolism, including the CNS serotonin. Major serotonin pools of the human body, however, are the thrombocytes and the argentaffine cells of the small intestine. It has been demonstrated that chronic pain patients have low concentrations of 5-HIAA in the cerebrospinal fluid, indicating a low turnover rate in central serotoninergic systems. Also, a positive correlation between duration of pain and 5-HIAA in CSF has been demonstrated [1]. Previously we have shown that chronic pain patients, including patients with chronic oral dysesthesia, have a decreased number of ^{3}H-imipramine binding sites on thrombocytes as is the case in endogenously depressed patients [29]. These binding sites are supposed to be associated with serotonin transport across the cell membranes in thrombocytes as well as in serotoninergic neurons. In the present study we found a statistically significant increase in urinary 5-HIAA correlated to placebo treatment and treatment response. Somehow we then succeeded in reproducing the findings of Walker [39], who showed that an increase in 5-HIAA excretion is indicative of positive treatment response. In our study, however, the majority of the responders were placebo responders, in contrast to He-Ne laser responders in the study by Walker. In general, it seems difficult to explain why the TENS-like effect suggested by Walker [39] on CNS metabolism of serotonin should be able to influence the total excretion of the metabolite of an essential amino acid. Furthermore, the CNS contribution to urinary 5-HIAA cannot be separated from the contribution from other sources. However, if the 5-HIAA excretion is regarded as a more generalized physiological serotonin-mediated placebo phenomenon [22] it might be understandable that amino acid metabolism outside the CNS can be influenced. Accordingly, the increase in urinary 5-HIAA excretion in our study might be explained as a consequence of down-regulation or blockade of serotonin receptors by unknown mechanisms increasing the serotonin turnover in general. In future investigations of 5-HIAA in pain patients, the number of ^{3}H-imipramine binding sites on thrombocytes should be taken into consideration as this might offer possible explanations to this problem.

In conclusion we have investigated the 904 nm IR laser in the treatment of certain types of chronic oro-facial pain. We have recorded no specific effects of laser irradiation whatsoever, but a substantial placebo response. It must be stressed that our conclusions are limited to the above-mentioned conditions. Thus, it is not possible to draw any conclusions with respect to effect in ulcers or inflammatory diseases. Furthermore, it cannot be concluded, for instance, that a 830 nm IR diode laser is superior to the 904 nm IR diode laser with respect to treatment of pain conditions since scientific support for this view is still missing.

Future research should include placebo controlled studies, and the generalized biochemical reactions of the placebo response per se should be dealt with in particular. The effect of different wavelengths, frequency, irradiance and irradiation schedules have to be taken into consideration in relation to different well-defined pathological conditions. Also, the long-term effects in responder groups need to be evaluated.

In conclusion, however, placebo response represents a natural, safe and effective method of treatment which can be utilized in approximately 40% of the patients. Perhaps it would be of greater interest if more effort were made to investigate and characterize this treatment modality than that of low power lasers.

Addendum

The following cases are reported as other examples of the enthusiastic anecdotal reports which seem to be the leading type of 'documentation' dominating this field.

During the study, the impression that probe A was the active one became evident, and 6 patients, not included in the study, were treated with this probe, which turned out to be the placebo probe, by one of the authors (H.J.H.). Four patients had trigeminal neuralgia. They were not included because they were under carbamazepin (Tegretol®) treatment, however, with insufficient effect. One patient obtained considerable sustained relief, another transient relief and two no relief.

Two patients were suffering from Sjögren's disease. They were irradiated on the auriculotemporal nerve bilaterally. One patient experienced increased salivary secretion, and the sialometry was positive for the first time in many years after 6 treatments. The other Sjögren patient experienced no positive effect.

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