Low intensity laser therapy is comparable to bromocriptine-evening primrose oil for the treatment of cyclical mastalgia in Egyptian females

G.M. SAIED[1], R.M. KAMEL[2] and N. DESSOUKI[3*]
[1]*Department of General Surgery, Faculty of Medicine, Cairo University, Egypt*
[2]*Department of Basic Sciences, Faculty of Physiotherapy, Cairo University*
[3]*Department of General Surgery, St. Bernard's Hospital, Gibraltar*

Abstract: One of the successful treatments for cyclical mastalgia is bromocriptine evening primrose combination. A double blind study was applied on 80 patients with cyclical mastalgia. They were randomly divided into two groups (A and B). In group A, patients were treated by bromocriptine/evening primrose. To group B, LILT with specified dosimetry was applied, using a device that delivers He-Ne laser combined with 4 infra-red diode laser. Evaluation of treatment was both subjective (using VAS) and objective (studying the degree of drop in plasma cortisol level). The drop of plasma cortisol with treatment was studied using the student -*t* distribution. A good response was observed in the laser group in 82.5%, compared to 63.9% in the bromocriptine/evening primrose group. There was a significant deference before and after treatment in both groups ($P<0.05$). This difference was more for the drug treated group than for the laser treated group, but in the latter, it acted on a wider sector of patients. In conclusion, LILT is recommended as a new treatment modality for cyclical mastalgia.

Key words: Low Intensity Laser Therapy, mastalgia, pain, breast, Egypt

Introduction

Breast pain or mastalgia, is the commonest symptom in patients attending a breast clinic (Roberts *et al.*, 1987) and most of the attempts to understand it have occurred only very recently. Previously it was regarded as a part of a psychosomatic disorder (Coopers, 1829) and therefore it was greatly underreported. The recognition of two types of mastalgia, cyclical and noncyclical, was known as early as early 1970s (Preece *et al.*, 1976) and confirmed later (Steinbrunn *et al.*, 1997).

Cyclical mastalgia is the commonest form of breast pain (Gateley & Mansel, 1990). It usually occurs in the second half of the menstrual cycle and is relieved by the onset of the menstruation. It is often bilateral and unilateral cases are more in the left side. The pain is commonly associated with breast heaviness, swelling and bursting sensation (Fentiman & Hamed, 1989). In over half of the patients the pain radiates to axillae and inner aspect of the arm. With time, pain free intervals gradually get shorter until the pain loses its periodicity. The syndrome progresses with time, and disappear with the onset of menopause.

Although a hormonal basis for the syndrome was expected, yet to-date, no definite correlation is proven (Horrobin, 1993). A depressed level of luteal progesterone and a rise in peak prolactin level after stimulation, despite a normal resting value are constantly present (Siturk–Ware *et al.*, 1979; Kumar *et al.*, 1989). Most women require reassurance only, and minority requires treatment. Diuretic therapy given in the luteal phase of the cycle, gives dramatic relief in some women, but it may be ineffective, and should be stopped if no response is evident after two cycles (Preece *et al.*, 1975; Klijn *et al.*, 1991). Oral contraceptive pills have only a mild effect, and may be of value in only a small proportion of the patients. In some patients it may aggravate the symptoms (Wisbey *et al.*, 1983). Bromocriptine, a very effective suppressor of prolactin released from the pituitary gland, is used successfully in cyclical breast pain. It was used empirically in the past for this purpose, even before recognizing the abnormal probating response in those patients (Kumar *et al.*, 1989). It rapidly and regularly relieves the pain (Mansel & Dogliotti, 1990), although, nausea may force patients to discontinue treatment.

Progestrogens have strongly been advocated on the basis of luteal phase insufficiency. Symptomatic relief may be obtained by correcting the depressed progesterone level, by giving it orally in days 10 to 25 of the menstrual cycle. A progesterone cream applied concomitantly daily to the breasts may be of additional value (Mauvais – Jarvis *et al.*, 1979). The relief is rapid and is preferable to give it soon after the onset of symptom. However, some workers deny any effect of the drug on the disease (Maddox *et al.*, 1990; McFadyen *et al.*, 1992).

Danazol, a synthetic gonadotrophin, which depresses the output of follicle stimulating hormone (FSH) and luteal hormone (LH) sometimes, brings symptomatic improvement in those patients (Gateley *et al.*, 1992). Because of its side effects (due to its

*Correspondence: Nazar Dessouki; E-mail: Nazar dessouki@doctors.org.uk

androgenic activity) (Wardle *et al.*, 1983), the drug is reserved as a second-line agent for those responding poorly to bromocriptine.

Patients who fail to respond to one or more of the above measures are minority (18%) and are likely to be anxious or depressed (Gateley *et al.*, 1992). Evening primrose oil, a rich source of gamma-linolenic acid (GLA: 70/0), given at a dose of 3gm daily, brings a remarkable improvement of symptoms. Its use is based on the correction of a definite deficiency of GLA in those patients (Gateley *et al.*, 1992). This essential fatty acid is implicated in the control of prolactin secretion, and steroid hormone/receptor interaction (Horrobin, 1990). It has no side effects, but its action is slow and needs to be given for long times (more than 4 months) before accepting a therapeutic failure.

The analgesic effect of low intensity laser (LILT) is well known since the early days of laser science (Siebert *et al.*, 1987; Basford, 1989; Kert & Rose, 1989). The first documented work on the analgesic effect of LILT was by Walker in 1983 and since then it was used in many fields of medicine. Since the work of Martino *et al.* (1987) many studies about the use of LILT in breast treatment were published. Some of the most important studies include those in Russia (Kovalev, 1990) and German (Schaffer *et al.*, 2000).

Although subjective assessment of treatment is not very difficult, using different pain scales (Huskisson, 1983; O'Brien *et al.*, 1984), objective assessment is always so. Clinical examination does not often help, as the physical features of the breast (size, tenderness, nodularity, and nipple discharge) have no correlation with the severity of patient's symptoms. Estimation of plasma *beta*-endorphin level seems to be very useful. Beta-endorphin, an endogenous opiate, is released into the blood by the pituitary gland in response to pain (Amir *et al.*, 1980). Its release is associated with a gradual onset of both analgesia and elevation of pain threshold that lasts for long periods (Snyder, 1977).

Estimation of plasma beta-endorphin level is possible by a specific radioimmunoassay that is sensitive to 5pg/ml. The normal level by this method is 33.66 pg. /mL at night with a diurnal increase parallel to the circadian rhythm of adrenocorticotropic hormone (ACTH) secretion (Wilkes *et al.*, 1980; Terenius 1987). The hormone alters plasma cortisol level. This alteration may be used as an accurate indirect index of beta-endorphin level. Patients with chronic pain (like mastalgia) tend to have high plasma cortisol levels (Kattabei, 1994) that drop after analgesia (Lush *et al.*, 1972). Some investigators used to measure the degree of drop of serum prolactin level as an index of treatment effectiveness (Russell & Collins, 1985). This method should better be used when mastalgia is associated with hyperprolactinemia, a situation seldom present. Most patients have normal range of serum prolactin, with no change in the spot level after bromocriptine treatment (Russell & Collins, 1985). The objective of this study was to compare LILT and bromocriptine/evening primrose oil in the treatment of cylical mastalgia.

Materials and Methods

Patients and trial design

Eighty patients with no history of diabetes mellitus, renal or hepatic troubles and presenting with cyclical mastalgia were collected from the surgical outpatient clinics at Kasr Al Aini University Hospital and from the private practice in Egypt. Their complaints had to be persistent for the last consecutive three menstrual cycles. They were reassured that their pain was not due to malignancy and any received drugs were discontinued.

Eligible patients were randomly treated either by bromocriptine/ evening primrose oil combination, or by LILT. The trial was double blind. The patients treated by drugs were assigned as group A, while those treated by laser were assigned as group B. Patients of group A were given blue plastic discs while those of group B were given red ones. Similarly coloured labels were put on two glass jars, the blue contains bromocriptine tablets (2.5mg) and evening primrose oil capsules (3gm), while the red labeled jar contained a placebo (vitamin B complex tablets and Cod liver oil capsules that are not known to affect the disease in any way). The medications were given on a single daily dose (2.5mg.) after the main meal, for three consecutive menstrual cycles, but assessment of its effect was done at the end of the 20th day.

All patients were then taken to the laser room, where the patient lies on the coach under the equipment. The laser device was then switched on only for those having the red label. The procedures were done for each patient individually, not at the same time and patients did not meet and did not know each other.

Laser therapy was given for 20 sessions, once every day, each session is 10 minutes, using a device that delivers He-Ne laser beam in a scanning function, combined with 4 infrared diode laser. The two beams operate together on the whole breast area and shoulder, in an automatic sweeping action. The laser dosimetry:

output wave length 632.8 nanometers, power 15mW, energy density two Joules/cm^2, area of treatment (20x20) cm^2, frequency 5000Hz.pulse 39 duration 200 nanoseconds and pulse energy 10 nano Joules. Total treatment time 200 minutes.

A noon blood sample was taken before the start of treatment and on the 20th day and sent to the laboratory to estimate diurnal plasma cortisol level by radioimmunoassay. Venous blood samples were evacuated in glass tubes containing heparin. The plasma was separated and refrigerated at 5°C. Haemolysed samples were discarded. The tubes were then dealt with by using Gamma Coat^{TM} I^{125} kits. The expected normal values of diurnal plasma cortisol by this method were 7-25 µg/dl (70-250 ng/ml), with a sensitivity standard of 0.21 µg/dl.

The response to treatment was subjectively assessed after 20 days by the Visual Analog Scale (Huskisson, 1983) for quantification of the response, the distance in centimeters from zero point was measured (on a strip of paper scaled from 0 to 10, where 0 is no pain and 10 is worst). A good response is marked as 4 or more (Tavaf-Motamen *et al.*, 1998). The medications were given on a single daily dose (2.5mg.) after the main meal, for three consecutive menstrual cycles, but the VAS was done after 20 days. Blood samples were taken at noon on the 20th day.

Ethical considerations

All patients were informed that they might be subjected to laser therapy, and the nature of this treatment was explained to them. Those who expressed their willingness to participate in the full programme of treatment were included in the study. Attention was paid not to include those having light sensitivity or having cardiac pacemaker.

Results

The average age at presentation was 33.5 years and the average duration of symptoms was 30 months. Only 76 (95%) patients completed the trial (36 in group A and 40 in group B). Of the four missing patients in Group A, in three it was due to unbearable side effects of bromocriptine treatment (Tables 1 and 2).

The response to combined therapy of bromocriptine (2.5mg twice daily) and evening primrose oil (500mg every 6 hours) was appreciable in 23 patients only (63.9%), and in 12 of them (33.3%) the response was not satisfactory. There was no improvement at all in one patient (2.8%). Side effects in the form of nausea, vomiting, epigastric discomfort and dizziness were reported in 15 patients (37.5%), and in three of them these symptoms were severe enough to abandon treatment. All these side effects were attributed to bromocriptine, as evening primrose oil has minimal side effects (Gateley *et al.*, 1981). LILT produced appreciable reduction of pain in 33 patients (82.5%). This reduction was associated with similar reduction in local tenderness, but had no effect on breast nodularity (Tables 2). There was a significant difference ($P \leq 0.05$)

Table 1: Symptoms and clinical findings in patients with cyclical mastalgia (n= 80)

Item		Number	Percent
Physiological status			
	Cancer phobia	68	85
	Anxiety	57	71
	Depression	32	40
Menstrual status	Pre-	68	85
	Peri-	12	15
Affected side	Unilateral (*)	12	15
	Bilateral	68	85
Others	Pain	80	100
	Tenderness	80	100
	Heaviness	80	100
	Interference with sexual activity	27	34
	Associated	3	3.8

(*) No relation to the dominant hand

Data analysis

Comparison of the results between the two groups was done by using the independent samples Student-*t* distribution where the alpha limit was set at $P= 0.05$ or less (an intention-to-treat analysis was used to study drop-outs and patients lost to follow-up.

Table 2: Subjective improvement after therapy – VAS and objective improvement after therapy by studying the effect on (diurnal) level of plasma cortisol (mg/dl) (n=76)

Type of improvement	Item	Group A (B/Ep)	Group B (LILT)
Subjective	Total no. of patients	36	40
	Improvement >40%	23 (63.9%)	33 (83.5%)
	Improvement <40%	12 (33.3%	7 (17.5%)
	No improvement	1 (2.8%)	0
Objective	Total no. of patients	36	40
	Mean level before treatment	19.04	18.80
	Variance	2.1	1.99
	Mean level after treatment	18.05	1.42
	t distribution (at α = 0.05)	2.03	2.70
	t distribution (at α = 0.01	2.725	3.42
	t-calculate	3.13 (>t distribution at α = 0.05, .01	3.42 (>t distribution at α = 0.05, .01)

There is a significant difference in mean levels before and after both types of treatments at level of significance $\alpha \leq 0.01$) (t calculated > t distribution). The level of significance $\alpha = 0.01$ is the lowest α value mentioned in all statistical tables used to identify t distribution for two sided test. Therefore, t at lower level of significance α (P<0.01) can not be specified

for both groups. This difference was more for group A than for group B.

Discussion

About 80% of mastalgia patients do not require any treatment and the remaining 20% are currently treated with bromocriptine evening primrose oil or by hormonal manipulation (Gateley & Mansel 1990) Bromocriptine and evening primrose oil are the first line drugs used in the treatment and Danazol is kept for failures (Harrison *et al.*, 1989). With this regimen, the overall success rate is around 82 % (Gateley & Mansel, 1990). In four percent of patients a psychiatric element is probably implicated (Preece *et al.*, 1978). This psychosomatic element may be amenable to appropriate therapy. Although Danazol may be recommended as a first line treatment when severe symptoms are present, this should be discussed with the patient in view of its side effects, particularly weight gain, hirsutism, hot flushes and menstrual irregularities (Pollitt, 2004). Danazol failures are treated by bromocriptine but the results are poor and evening primrose oil seems to have no effect under these circumstances.

Low Intensity Laser Therapy is now being successfully used to relieve pain in a range of painful conditions, but its use to relieve pain of cyclical mastalgia was not reported before. Martino *et al.* (1987) found in an open trial, a significant pain reduction in one third of patients having post mastectomy pain and Kamel (1999) reported better results in a series of 40 patients. They attributed the analgesia to the photobiomodulatory effects of laser upon neural function. There is also evidence to suggest that LILT may have significant effects on the synthesis, release and metabolism of a range of neurochemicals including serotonin and acetylcholine. In addition it has proven effects upon the pharmacology of nociceptive process at the level of the primary pain receptor (Maeda & Oshiro, 1990) and also on nerve conduction latency.

With the use of laser in this work, a total subjective improvement of 82.5 % was obtained compared to 63.9 % following first line treatment with bromocriptine/ evening primrose oil, which is the commonest line of treatment used nowadays. In this study, measurement of diurnal plasma cortisol level was used for response assessment in both groups. Measurement of plasma *beta*-endorphin is relatively expensive and is not always available. Using the Student-*t* distribution (which provides comparison between groups), the response to laser (reflected on the effect on diurnal serum cortisol level) was statistically significant. The alterations of serum cortisol parallel those of *beta*-endorphin and may be used as an objective index for the degree of pain relief (Terenius, 1987).

Although statistically speaking the degree of response to LILT is less compared to bromocriptine/ evening primrose oil yet, it gives a satisfactory analgesic effect on a wider sector of patients. Moreover, LILT gives statistically significant subjective and objective pain improvement in cyclical mastalgia, and has no known clinical side effects. Although this single trial is not sufficient we may recommend LILT as a first line treatment and this will limit the use of Danazol to a few patients only. In view of the troublesome side effects of the latter drug, laser therapy is to be considered in all patients refractory to bromocriptine primrose oil treatment.

Acknowledgments

We thank Dr. Azza M. Saied, Faculty of Engineering, Cairo University for doing the statistical analysis. The efforts of the workers at the Physical Therapy Department, Police Authority Hospital were indispensable to the work, and are much appreciated.

References

Amir, S., Brown, Z.W. & Amit, Z. (1980) The role of endorphins in stress. Evidence and speculations. *Neuroscience and Biobehaioural Reviews*. **4**, 77-79.

Basford, J.R. (1989) Low energy laser therapy: Controversies and new research findings. *Laser in Surgery and Medicine* **9**, 1-5.

Coopers, A. (1829) *Illustrations of the Disease of the Breast*. Longman & Co., London. .

Fentiman, I.S. & Hamed, H. (1989) Clinical assessment of patients with mastalgia. *Clinical Practice* **68**, 21-25.

Gateley, C.A. & Mansel, R.E. (1990) Management of cyclic breast pain. *British Journal of Hospital Medicine* **43**, 330-332.

Gateley, C.A., Miers, M. & Mansel, R.E. (1992) Drug treatment for mastalgia: 17 years experience in the Cardiff Mastalgia Clinic. *Journal of Social Medicine* **85**, 12-15.

Gateley, C.A., Pye, J.K. & Harrison, B.J. (1981) Evening primrose oil (Efamol), a safe treatment options for breast disease. *Breast Cancer Research and Treatment* **4**, 161-166.

Harrison, H.J., Maddox, P.R. & Mansel, R.E. (1989) Maintenance therapy of cyclical mastalgia using low dose danazol. *Journal of the Royal College of Surgeons Edinburgh* **34**, 79-81.

Horrobin, D.F. (1990) Gamma linolenic acid. *Reviews in Contemporary Pharmacotherapy* **1**, 2-5.

Horrobin. D.F. (1993) The effects of gamma-linolinic acid on breast pain and diabetic neuropathy. *Prostaglandins Leucotrienes and Essential Fatty Acids* **48**, 101-104.

Huskisson, E.C. (1983) *Pain Management and Assessment*. Ronald Melzack (Ed) New York.

Kamel, R.M. (1999) *The Role of Low Intensity Laser Therapy on Shoulder and Arm Pain in Postmastectomy Patients*. MD Thesis, Faculty of Physical Therapy, Cairo University.

Kattabei, O.M.A. (1994) *Utilization of laser therapy in osteoarthritis*. MD Thesis, Faculty of Physical Therapy, Cairo University.

Kert, J. & Rose, L. (1989) Clinical laser therapy. Low level laser therapy. *Scandinavian Medical Laser Technology*, Copenhagen. .

Klijn, J.G., Van Geel, B. & Jong, F.H. (1991) The relation between pharmacokinetics and endocrine effects ofbuserelin implants in patients with mastalgia. *Clinical Endocrinology* **34**, 253-258.

Kovalev, M.I. (1990) Prevention of lactation mastitis by the use of low-intensity laser irradiation (Article in Russian). *Akush Ginekol (Mosk)* **2**, 57-61.

Kumar, S., Mansel, R.E. & Scanlon, F. (1989) Altered responses of prolactin, luteinizing hormone and follicle stimulating hormone secretion to thyrotropin releasing hormone /gonadotropin releasing hormone stimulation in cyclical mastalgia. *British Journal of Surgery* **71**, 870-873.

Lush, D., Therop, J., Richardson, D. & Bowr, D. (1972) The effect of epidural analgesia on the adrenocortical response to surgery *British Journal of Anaesthesia* **44**, 1163-1169.

Maddox, P.R., Harrison, B.J. & Horobin, J.M. (1990) A randomized controlled trial of medroxy progesterone acetate in mastalgia. *Annals of the Royal College of Surgeons of England* **72**, 71-76.

Maeda, T. & Oshiro, T. (1990) Diode laser restores normal conditions to bradykinin altered rat neural cells: A controlled in vivo study. *Lasers in Surgery and Medicine* **2**, 13-27.

Mansel, R.E. & Dogliotti, L. (1990) European multicenter trial of bromocriptine in cyclical mastalgia. *Lancet* **335**, 190-193.

Martino, G., Fava, G. & Galperti, G. (1987) CO_2 laser therapy for women with mastalgia. *Lasers in Surgery and Medicine* **7**, 78-82.

Mauvais-Jarvis, P., Siturk-Ware, R., Kuttenn, F. & Sterkers, N. (1979) Luteal phase insufficiency: A common pathophysiological factor in the development of benign and malignant breast disease. *Commentaries on Research in Breast Disease* **1**, 25-59.

McFadyen, I.J., Forrest, A.P., Chetty, U. & Raab, G. (1992) Cyclical breast pain - some observations and the difficulties in treatment. *British Journal of Clinical Practice* **46**, 161-164.

O'Brien, W.J., Rutan, F.M., Sanborn, C. & Omer, G.E. (1984) Effect of transcutaneous electric nerve stimulation (TENS) on human blood beta-endorphin levels. *Physical Therapy* **64**, 1367-1374.

Pollitt, J. (2004) Management of benign disease of the breast. *Surgery* **22**, 164-168.

Preece, P.E., Mansel, R.E. & Hughes, L.E. (1978) Mastalgia: psychoneurosis or organic disease? *British Medical Journal* **1**, 29-30.

Preece, P.E., Richards, A.R. & Owen, G.M. (1975) Mastalgia and total body water. *British Medical Journal* **4**, 498-500.

Preece, P.E., Hughes, L.E. & Mansel, R.E. (1976) Clinical syndromes of mastalgia. *Lancet* **11**, 6470-6473.

Roberts, M.M., Robinson, S.E. & French, K. (987) Consultation for breast disease in general practice and hospital referral patterns. *British Journal of Surgery* **74**, 1020.

Russell, I.S. & Collins, J.P. (1985) Double blind controlled clinical trial of bromocriptine and clopamide versus placebo for the treatment of mastalgia. *The 11th World Congress of Gynaecology and Obstetrics*. Berlin.

Schaffer, M., Bonel, H., Sroka, R., Schaffer, P.M., Busch, M., Sittek, H., Reiser, M. & Duhmke, E. (2000) Magnetic resonance imaging (MRI) controlled outcome of side effects caused by ionizing radiation treated with 780nm-diode laser -preliminary results. *Journal of Photochemistry and Photobiology* B **59**, 1-8.

Siebert, W., Siechert, N. & Siebert, B. (1987) What is the efficacy of soft and mid-lasers in therapy of tendopathies? *Archives of Orthopedic & Traumatic Surgery* **106**, 388-393.

Sitruk-Ware, R., Sterkers, N. & Mauvas, J.P. (1979) Benign breast disease hormonal investigations. *Obstetrics and Gynaecology* **53**, 457-460.

Snyder, S. (1977) Opiate receptors and internal opiates. *Scientific American* **236**, 44-56.

Steinbrunn, B.S., Zera, R.T. & Rodrigue, J.L. (1997) Mastalgia. *Postgraduate Medicine* **102**, 183-198.

Tavaf-Motamen, H., Ader, D.N., Matrice, W.B. & Shriver, C.D. (1998) Clinical evaluation of mastalgia. *Archives of Surgery* **133**, 211-213.

Terenius, L. (1987) Endorphins and cortisol in chronic pain. In: *Handbook of Chronic Pain Management*: Graham D., Diana E. (ed), Amsterdam, New York, Oxford, pp. 33-36.

Walker, J.B. (1983) Relief from chronic pain by low power laser irradiation. *Neuroscience Letters* **43**, 339-344.

Wardle, P.G., Whitehead, M.I. & Mills, R.P. (1983) Non reversible and wide ranging voice changes after treatment with danazol. *British Medical Journal* **278**, 946.

Wilkes, M.M., Stewart, R.D. & Bruni, J.F. (1980) A specific homologous radioimmunoassay for human beta-endorphin: direct measurement in biological fluids. *Journal of Clinical Endocrinology and Metabiology* **50**, 309-315.

Wisbey, J.R, Kumar, S. & Mansel, R.E. (1983) Natural history of breast pain. *Lancet* **2** (8351), 672-674.