

# Comparison between Trans-Cranial Electromagnetic Stimulation and Low-Level Laser on Modulation of Trigeminal Neuralgia

YASSER IBRAHIM SEADA, PT, PhD<sup>1)</sup>, REDA NOFEL, ODM, MD<sup>2)</sup>,  
HAYAM MAHMOUD SAYED, PT, PhD<sup>1)\*</sup>

<sup>1)</sup> Department of Physical Therapy for Neuromuscular Disorders and its Surgery, Faculty of Physical Therapy, Cairo University: 4 Ahmed EL-Zayatt St., Giza, Egypt. TEL: +966504347898, FAX: +96672418322

<sup>2)</sup> Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Al Azhar University

**Abstract.** [Purpose] To determine which of the transcranial electromagnetic stimulation or low level laser therapy is more effective in the treatment of trigeminal neuralgia of multiple sclerosis patients. [Methods] Thirty multiple sclerosis patients of both sexes participated in this study. The age of the subjects ranged from 40 to 60 years and their mean age was (56.4–6.6). Participants were randomly selected from Dental and Neurology Outpatient Clinics at King Khalid Hospital, Najran University, Saudi Arabia. Patients were randomly divided into two equal groups of 15. The Laser group received a low level laser therapy, 830 nm wavelength, 10 Hz and 15 min duration, while the Electromagnetic group received repetitive transcranial electromagnetic stimulation at a frequency of 10 Hz, intensity of 50 mA and duration of 20 minutes. Patients were assessed pre and post treatment for degree of pain using a numerical rating scale, maximal oral mouth opening using a digital calibrated caliper, masseter muscle tension using a tensiometer and a compound action potentials of masseter and temporalis muscles. [Results] There were significant improvements after treatment in both groups, with a significant difference between the Electromagnetic and Laser groups, in favor of the Electromagnetic group. [Conclusion] Repetitive transcranial electromagnetic stimulation at 10 Hz, 50 mA, and 20 minutes duration is more effective than low level laser therapy at reducing trigeminal pain, increasing maximum oral mouth opening, masseter and temporalis muscle tension in multiple sclerosis patients.

**Key words:** Trigeminal neuralgia, Low level laser, Trans-cranial electromagnetic stimulation

(This article was submitted Jan. 28, 2013, and was accepted Mar. 28, 2013)

## INTRODUCTION

Trigeminal neuralgia (TN) is an uncommon disorder characterized by recurrent attacks of facial pain in the trigeminal nerve distribution. Typically, brief attacks are triggered by talking, chewing, teeth brushing, shaving, a light touch, or even a cool breeze<sup>1)</sup>. The pain is nearly unilateral, and it may occur repeatedly throughout the day. Trigeminal neuralgia is characterized by sudden, severe, brief, stabbing, and recurrent episodes of facial pain<sup>2)</sup>. The prevalence ratio is 4 per 100,000 in the population, and commonly affects patients over 50 years, occurring more frequently in women than men with a ratio of 1.5–2:1, respectively<sup>1)</sup>. It is also more common in patients with multiple sclerosis<sup>3)</sup>. TN is associated with decreased quality of life and impairment of daily function. It impacts upon employment in 34% of patients and depressive symptoms are not uncommon<sup>4)</sup>. The condition may be severely disabling with high morbidity particularly among the elderly<sup>5)</sup>. It is evident that trigeminal pain occurs in multiple sclerosis because of pressure on the trigeminal nerve root at the entry zone into the pontine

region of the brain stem<sup>6)</sup>. Compression or insufficiency of blood supply may cause local pressure, leading to demyelination of the trigeminal nerve axon which causes ectopic action potential generation<sup>7)</sup>. TN is almost always unilateral with the maxillary branch being most commonly affected and the ophthalmic branch the least<sup>8)</sup>. Pain attacks usually last from a few seconds to 2 min and may recur spontaneously between pain-free intervals<sup>9)</sup>.

Trans-cranial magnetic stimulation (TMS) is a technique for stimulating of the human brain. A noninvasive stimulation technique, Repetitive Trans-cranial Magnetic Stimulation (rTMS), may be suitable for the treatment of chronic neuropathic pain as it modulates neural activities not only in the stimulated area, but also in remote regions that are interconnected to the site of stimulation<sup>9, 10)</sup>. Prolonged pain relief can be obtained by repeating rTMS sessions every day for several weeks at 10 HZ frequency<sup>11)</sup>.

A low-level laser (LLL) produces photo-biochemical reactions that result in pain relief. Considering the effect of neurotransmitters on nerves, LLLR are expected to be effective in eliminating all kinds of pain that result from nerve irritation and nociceptor excitation (neuropathic pain)<sup>12)</sup>. LLLR can reduce pain of inflammatory origin through their anti-inflammatory properties. Also, low-level lasers have been shown to be effective in alleviating oral

\*To whom correspondence should be addressed.  
E-mail: dr\_hayam98@yahoo.com

and maxillofacial pain<sup>13</sup>). The hypothesis of the current study was that there are no differences between rTMS and LLLR treatments. The purpose of the current study was to determine which of rTMS or LLLR better reduces trigeminal pain, increases low oral mouth opening and improves the power of the masseter and temporalis muscles in TN of multiple sclerosis patients.

## SUBJECTS AND METHODS

### Subjects

This study was conducted at Dental and Neurology Out-patients Clinics at King Khalid Hospital, Najran University, Saudi Arabia. Thirty multiple sclerosis patients with TN (of all branches) of both sexes were randomly selected and participated in this study. Diagnosis was carried out by a neurologist through the use of physical examination and magnetic resonance imaging (MRI). Patients' ages ranged from 40 to 60 years and their mean age was  $56.4 \pm 6.6$  years. The weights of the subjects ranged from 60 to 80 kg, and their mean weight was  $75.00-7.7$  kg. Classical TN was diagnosed according to the International Classification of Headache Disorders 2 Criteria<sup>14</sup>, and the duration of illness ranged from 6 to 12 months (Table 1). Pain during attacks should not be less than six according to a numerical rating scale (NRS), with no satisfactory medical pain relief in the last three months. Patients were conscious, co-operative and free from psychological disorders (as documented by a psychologist), and disabilities secondary to orthopedic problems or special senses impairments. Patients were excluded if they had TN secondary to tumor, herpes zoster or any another causes, i.e. serious cardiopulmonary dysfunction, past invasive treatment (radiofrequency, ethanol, glycerinum injection, Gama-knife microvascular decompression) or coagulation dysfunction. Patients were randomly divided into two equal groups of 15 by a random allocation method (thirty folded papers were allocated in a bag, with two series of 15 papers on which were written either LG or MG and every patient had the chance to choose one folded paper).

The Laser group (LG) consisted of 15 patients whose ages ranged from 40 to 58 years with a mean age of  $48.80-6.3$  years, and a weight range of 65 to 88 kg, with mean weight of  $75.26-6.80$  kg. They were treated with an 830 nm wavelength LLLR<sup>15</sup>.

The Electromagnetic group (MG) consisted of another 15 patients, whose ages ranged from 45 to 60 years, with a mean age of  $46.66-9.608$  years, and a weight range of 60 to 87 kg, with a mean weight of  $74.80-7.27$  kg. They received rTMS at 10 Hz frequency<sup>10</sup>. There were no significant pre-treatment differences between the groups in demographic characteristics ( $p>0.05$ ) (Table 1).

### Methods

An electromyography device (Neuropac Apparatus, Tensiometer: Lafayette, USA 3) was used to measure the motor action potentials of the temporalis and masseter muscles. A calibrated caliper (Chattanooga, USA) was used for mouth opening measurements. An ASA Electromagnetic device

**Table 1.** Demographic characteristics of the patients

Variables	LG (n=15)	MG (n=15)
	M $\pm$ SD	M $\pm$ SD
Age (yrs)	48.8 $\pm$ 6.3	46.6 $\pm$ 9.6
Weight (kg)	75.3 $\pm$ 6.8	74.8 $\pm$ 8.7
Duration of illness (month)	9.12 $\pm$ 0.5	8.95 $\pm$ 0.4

LG: Laser group, MG: Electromagnetic group, M: mean, SD: standard deviation

with the following characteristics; PMT Quattro model, PRO voltage 230 v., frequency 50/60 Hz, absorbed power 850 VA-Class I. Type B, EN 60 601-1 1990. Made in Italy 2002. A Laser device (SN: 5EZ303, Made in Italy).

After informed consent had been obtained, all patients participated in several trials with the equipment to be psychologically assured and to familiarize themselves with the treatment steps. The treatment was performed three times per week on consecutive days for eight weeks of total twenty-four sessions.

The pain intensity of all patients was assessed using NRS<sup>16</sup> (0=no pain, 5=moderate pain, 10=worst pain), when patients were not under medication. The masseter and temporalis muscle compound motor action potentials of all patients were measured before and after treatment.

The subjects were seated comfortably upright and were asked not to move their heads during recordings. A stimulating needle electrode was placed intra-orally on the nerve branch at the medial angle of the mandible. The recording electrodes were positioned on the masseter muscle belly parallel to muscular fibres about 3 cm above and anterior to the mandibular angle, two centimeters distance from the two recording electrodes. This electrode placement was demonstrated to be optimal for avoiding cross-talk responses from facial muscles<sup>17</sup>. The electrode over the anterior temporalis was placed just in front of the hairline; the reference electrode was placed just above the eyebrow. The signals were amplified, filtered, and digitized at 1,000 Hz by the Spike 2 system (Cambridge Electronic Design, Cambridge, UK)<sup>18</sup>. For the assessment of maximal Active mouth opening range, patients were asked to open their mouths as much as possible with their heads fixed, and the vertical distance between upper and lower teeth was measured using a calibrated caliper with 1 mm accuracy<sup>19, 20</sup>. For the assessment of muscle power, patients were instructed to tightly clench their mouth as much as possible for assessment of masseter muscle power, and the amount of tension was recorded by a tensiometer.

Subjects in the Laser group were treated with a low power 15mW helium-neon laser of wave length 830A units and a laser beam density of  $150-170$  mw/cm<sup>2</sup> for irradiation. The treatment was first given intra-orally following the path of the nerve branch for 1-2 min, then extra-orally on the most tender points for 10 min. In the sitting position, the contact laser technique was used on the skin overlying the four tender points of the face<sup>21, 22</sup>. Subjects in the electromagnetic group received repetitive TMS at a frequency of 10 Hz, 50 mA intensity, and 20 minutes duration. In the sitting position with all metal objects removed the splenoid was applied

tangentially over the patient's head, and held on one side (contra-lateral to trigeminal pain). A rest period of 10 minutes after application was allowed for all patients<sup>23, 24</sup>. The results of both groups were statistically analyzed to compare the differences within each group and the differences between the two groups. The statistical package of social sciences (SPSS, version 10) was used for data processing and a  $p=0.05$ , as the level of significance.

## RESULTS

The results showed no significant pretreatment differences between the two groups in pain intensity, masseter muscle tension, or maximal mouth opening, masseter and temporalis compound action potentials  $p>0.05$  (Table 2).

There was significant post-treatment reduction in pain intensity in LG compared to the pretreatment mean value, ( $p=0.01$ ), and a highly significant post-treatment reduction in pain intensity in MG when compared to pretreatment mean value ( $p=0.001$ ) (Table 3). Significant differences was found between the post-treatment values of the two groups, with the best result in MG ( $p=0.01$ ) (Table 4).

There was significant post-treatment improvement in masseter tension in LG compared to the pretreatment mean value, ( $p=0.01$ ), and highly significant post-treatment improvement in MG compared to the pretreatment mean value ( $p=0.001$ ) (Table 3). Significant differences was found between the post-treatment values of the two groups, with the best result in MG ( $p=0.01$ ) (Table 4).

There was significant post-treatment improvement in mouth opening in LG compared to the pretreatment mean value, ( $p=0.014$ ), and highly significant post-treatment improvement in mouth opening in MG compared to pretreatment mean value, ( $p=0.001$ ) (Table 3). Significant differences was found between the post-treatment values of the two groups, with the best result in MG ( $p=0.001$ ) (Table 4).

There were significant post-treatment improvements in masseter and temporalis CAP in LG compared to the pretreatment mean values, (both,  $p=0.01$ ), and highly significant post-treatment improvements in masseter and temporalis CAP in MG compared to the pretreatment mean values (respectively  $p=0.001$  and  $p=0.003$ ) (Table 3). Significant differences was found between the post-treatment values of the two groups, with the best results in MG (masseter,  $p=0.001$  and temporalis CAP,  $p=0.003$ ) (Table 4).

## DISCUSSION

The purpose of the study was to determine which of transcranial electromagnetic stimulation or low level laser therapy is more effective for trigeminal neuralgia of multiple sclerosis patients. Low level laser therapy (LLLT) has been used clinically and some researchers have reported the efficacy of LLLT in the treatment of various pain conditions<sup>21</sup>. In the present study, there were significant improvements in TN compared to pretreatment measurements and the results of NRS indicated a slight but significant reduction in facial pain. Patients also noted a reduction in their anxiety symptoms. Moreover, the present results showed a significant improvement in maximal mouth opening after application

**Table 2.** Comparison between pretreatment mean values of NRS, masseter muscle tension, maximal mouth opening, and masseter and temporalis compound action potentials

Variables	LG	MG
	M $\pm$ SD	M $\pm$ SD
NRS (pain intensity)	7.5 $\pm$ 0.5	7.6 $\pm$ 0.4
Masseter muscle tension (N)	9.7 $\pm$ 2.5	9.5 $\pm$ 2.1
Max. mouth opening (mm)	16.7 $\pm$ 1.1	15.4 $\pm$ 1.7
Masseter CAP (mV)	0.6 $\pm$ 0.1	0.7 $\pm$ 0.1
Temporalis CAP (mV)	0.9 $\pm$ 0.2	0.8 $\pm$ 0.5

NRS: numerical rating scale, CAP: compound action potentials, LG: Laser group, MG: Electromagnetic group, M: mean, SD: standard deviation

**Table 3.** Comparison of the pre-and post-treatment mean values of both groups

Variables		M $\pm$ SD	
		pre	post
NRS	LG	7.5 $\pm$ 0.5	6.2 $\pm$ 0.5*
	MG	7.6 $\pm$ 0.4	5.3 $\pm$ 0.3**
Masseter muscle tension (N)	LG	9.7 $\pm$ 2.5	17.8 $\pm$ 1.6*
	MG	9.5 $\pm$ 2.1	25.2 $\pm$ 1.1**
Max. mouth opening (mm)	LG	16.7 $\pm$ 1.1	23.9 $\pm$ 1.8*
	MG	15.4 $\pm$ 1.7	28 $\pm$ 1.5**
Masseter CAP (mV)	LG	0.6 $\pm$ 0.1	1.6 $\pm$ 0.1*
	MG	0.7 $\pm$ 0.1	2.1 $\pm$ 0.1**
Temporalis CAP (mV)	LG	0.9 $\pm$ 0.2	1.9 $\pm$ 0.2*
	MG	0.8 $\pm$ 0.5	2.4 $\pm$ 0.5**

NRS: numerical rating scale, CAP: compound action potentials, LG: Laser group, MG: Electromagnetic group, M: mean, SD: standard deviation, \*: significant  $p<0.05$ , \*\*: highly significant  $p<0.01$

**Table 4.** Comparison between pretreatment mean values of NRS, masseter muscle tension, maximal mouth opening, and masseter and temporalis compound action potentials

Variables	LG	MG
	M $\pm$ SD	M $\pm$ SD
NRS (pain intensity)	6.2 $\pm$ 0.5	5.3 $\pm$ 0.3*
Masseter muscle tension(n)	17.8 $\pm$ 1.6	25.2 $\pm$ 1.1**
Max. mouth opening( mm)	23.9 $\pm$ 1.8	28 $\pm$ 1.5**
Masseter CAP(mV)	1.6 $\pm$ 0.1	2.1 $\pm$ 0.1*
Temporalis CAP(mV)	1.9 $\pm$ 0.2	2.4 $\pm$ 0.5*

NRS: numerical rating scale, CAP: compound action potentials, LG: Laser group, MG: Electromagnetic group, M: mean, SD: standard deviation, \*: significant  $p<0.05$ , \*\*: highly significant  $p<0.01$

of LLLT. These findings are in agreements with reports of significant reduction in pain and improvements of range of motion after 3 months of LLLT<sup>22, 23</sup>.

The present study showed a strong relationship between the application of repetitive transcranial electromagnetic

stimulation and the improvement of TN symptoms. There was reduction of pain according to NRS. These results are in agreement with those of another study that applied the TMS at 5 Hz to treat orofacial pain patients<sup>24</sup>). In the present study, 10 Hz rTMS was applied to treat TN patients and there was a highly significant improvement in maximal mouth opening. This result was confirmed by other result who demonstrated that application of rTMS at 5 Hz or more was able to relieve neuropathic pain<sup>25</sup>), this was also in agreement with the study that applied four different frequencies (0.5 Hz, 1 Hz, 5 Hz and 10 Hz) of rTMS to treat patients with orofacial pain ; the best results was at 10 Hz<sup>26</sup>). The efficacy of rTMS in producing significant analgesia seems to depend on a precise targeting the frequency. It has been reported that application of rTMS sessions over the motor cortex can produce excitatory changes in the brain and induce excitation of the muscles action potentials<sup>27</sup>). The application of low frequency TMS may alter cerebral excitability, brain rhythms, and a variety of human behaviors<sup>28–30</sup>).

The present study found that there were improvements in the masseter muscle tension in both treatment groups with the best results in rTMS group. These findings are supported by other studies that reported significant improvement in the cervical muscle together with significant improvements in the range of motion and relief of pain due to an inhibitory effect on neural discharges around the stimulated cortical areas<sup>31</sup>).

The study concluded that repetitive transcranial electromagnetic stimulation at 10 Hz and 50 mA, for 20 min is considered more effective than low level laser therapy at reducing trigeminal pain, and improving the maximum mouth opening, and masseter and temporalis muscle tensions of multiple sclerosis Patients. It is also considered more useful and safe modality than drugs for other orofacial dysfunctions.

## RECOMMENDATION

We recommend the investigation of the long-term effects of both rTMS and LLLT in various orofacial dysfunctions at different frequencies, durations and intensities, as well as rTMS for other painful neurological disorders.

## REFERENCES

- Krafft RM, Northeastern O: Trigeminal Neuralgia. *Am Fam Physician*, 2008, 77: 1291–1296. [Medline]
- Katusic S, Beard CM, Bergstralh E, et al.: Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota. *Ann Neurol*, 1990, 27: 89–95. [Medline] [CrossRef]
- Tölle T, Dukes E, Sadosky A: Patient burden of trigeminal neuralgia; results from a cross-sectional survey of health state impairment and treatment patterns in six European countries. *Pain Pract*, 2006, 6: 153–160. [Medline] [CrossRef]
- Marbach JJ, Lund P: Depression, anhedonia and anxiety in temporomandibular joint and other facial pain syndromes. *Pain*, 1981, 11: 73–84. [Medline] [CrossRef]
- Love S, Coakham HB: Trigeminal neuralgia: pathology and pathogenesis. *Brain*, 2001, 124: 2347–2360. [Medline] [CrossRef]
- Nurmikko TJ, Eldridge PR: Trigeminal neuralgia, pathophysiology, diagnosis and current treatment. *Br J Anaesth*, 2001, 87: 117–132. [Medline] [CrossRef]
- Devor M, Govrin R, Rappaport ZH: Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery. *J Neurosurg*, 2002, 96: 532–543. [Medline] [CrossRef]
- Woolfall P, Coalthard A: Pictorial review, trigeminal nerve anatomy and pathology. *Br J Radiol*, 2001, 74: 458–467. [Medline]
- Lefaucheur JP, Hatem S, Nineb A, et al.: Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. *J Neurol*, 2006, 253: 198–204.
- Avery DH, Holtzheimer PE, Fawaz W, et al.: Transcranial magnetic stimulation reduces pain in patients with major depression: a sham-controlled study. *J Nerv Ment Dis*, 2007, 195: 378–381. [Medline]
- Reid P, Pridmore S: Improvement in chronic pain with transcranial magnetic stimulation. *Aust N Z J Psychiatry*, 2001, 35: 252. [Medline] [CrossRef]
- Sanseverino NT, Sanseverino CA, Ribeiro MS: Clinical evaluation of the low intensity laser antialgic action of Ga Al As in the treatment of temporomandibular disorder. *Laser Med Surg*, 2002, 18: 205–207.
- Eckerdal A, Bastin L: A double blind placebo controlled investigation of patients with trigeminal neuralgia. *Laser Ther*, 2003, 12: 112–120.
- International classification of Headache Disorders. Headache classification, subcommittee of the international headache society, 2004. 2nd ed. Cephalgia. 24 (SI), pp 8–152.
- Eckerdal A, Lehmann B: Can low relative laser therapy be used in treatment of neurogenic facial pain? A double blind placebo controlled investigation of patients with trigeminal neuralgia. *Laser therapy*, 1996, 8: 247–252.
- Breivik EK, Bjornson GA, Skovlund EA: A comparison of pain rating scale by sampling from clinical trial data. *Clin J Pain*, 2000, 16: 22–28. [Medline] [CrossRef]
- Galo R, Vitti M, Santos CM, et al.: The effect of age on the function of the masticatory system, an electromyographical analysis. *Gerodontology*, 2006, 23: 177–182. [Medline] [CrossRef]
- Peyron MA, Oliveire B, James P, et al.: Influence of age on adaptability of human mastication. *J Neurophysiol*, 2004, 92: 773–779. [Medline] [CrossRef]
- Neiva PD, Kirkwood RN: Measurement of neck range of motion among mouth-breathing children. *Rev Bras Fisioter*, 2007, 11: 355–360.
- Pehling J, Sciffman E, Look J, et al.: Interexaminer reliability and clinical validity of the temporomandibular disorders index: A new outcome measure for temporomandibular disorders. *J Orofac Pain*, 2002, 16: 296–304. [Medline]
- Kogawa EM, Kato MT, Santos CN, et al.: Evaluation of the efficacy of low-level laser therapy (LLLT) and the microelectric neurostimulation (MENS) in the treatment of myogenic temporomandibular disorders: a randomized clinical trial. *J Appl Oral Sci*, 2005, 13: 280–285. [Medline] [CrossRef]
- Çetiner S, Sevil AK, Sule Y: Evaluation of low-level laser therapy in the treatment of temporomandibular disorders. *Photomed Laser Surg*, 2006, 24: 637–641. [Medline] [CrossRef]
- Seyyed AS, Pooya O, Zohreh D: Low level laser therapy (LLLT) for orofacial pain. *J Lasers Med Sci*, 2011, 3: 97–101.
- Siebner HR, Lang N, Rizzo V: Preconditioning of low frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *J Neurosci*, 2004, 24: 3379–3385. [Medline] [CrossRef]
- Mylius V, Reis J, Knaack A, et al.: High frequency rTMS of the motor cortex does not influence the nociceptive flexion reflex but increases the unpleasantness of electrically induced pain. *Neurosci Lett*, 2007, 415: 49–54. [Medline] [CrossRef]
- Rollnik JD, Wustefelds S, Dauper J, et al.: Repetitive transcranial magnetic stimulation for the treatment of chronic pain. A pilot study. *Eur Neurol*, 2002, 48: 6–10. [Medline] [CrossRef]
- Passard A, Attal N, Benadhira R: Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic wide spread pain in fibromyalgia. *Brain*, 2007, 130: 2661–2670. [Medline] [CrossRef]
- Khedr EM, Kotb H, Kamel NF, et al.: Long lasting analgesic effects of daily sessions of rTMS in central and peripheral neuropathic pain. *J Neurol Neurosurg Psychiatry*, 2005, 76: 833–838. [Medline] [CrossRef]
- Lefaucheur JP, Drout X, Nguyen JP: Interventional neurophysiology for pain control: duration of pain relief following rTMS of the motor cortex. *Clin Neurophysiol*, 2001, 31: 247–252. [CrossRef]
- Rokyta R, Fricova J: Neurostimulation Methods in the Treatment of Chronic Pain. *Physiol Res*, 2012, 61: S23–31. [Medline]
- Kozel FA, George MS, Simpson KN: Decision analysis of the cost-effectiveness of repetitive transcranial electromagnetic stimulation versus electroconvulsive therapy for treatment of non psychotic severe depression. *CNS Spectr*, 2004, 9: 476–482. [Medline]