Thermal Versus Pulsed Radiofrequency Application of Stellate Ganglion in Sympathetic Mediated Pain in Cancer Patients

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Abstract

Objective: To evaluate the efficacy and safety of Thermal versus pulsed radiofrequency application of Stellate ganglion in sympathetic mediated pain in cancer patients.

Methodology: 60 patients randomly integrated into 2 equal groups:

Group (A): Pulsed and Group (B): Thermal R. Ftherapy was done under fluoroscopy integrated by ultrasound guidance. Patients were assessed for pain relief (VAS score) at 1st day then 1 and 3 months after. Oxycodone and pregabalin consumption were assessed prior to block and at 3 months.

Results: Percentage of patients who had complete pain response was significantly higher in thermal group than pulsed group at first day, first month and three months. There is significant higher number of patients with higher percentage reduction of pregabalin and oxycontin consumption in the thermal group compared to the pulsed group.

Conclusion: Thermal RF of the Stellate ganglion is a safe and successful treatment for cancer patients with sympathetic mediated pain. It appears to be more effective than pulsed RF of the Stellate ganglion.

Key Words: Radiofrequency – Stellate ganglion – Thermal – Pulsed.

Introduction

THE sympathetic nervous system contains some of the afferent and efferent neural pathways necessary for generation, perpetuation, or treatment of certain clinical pain states. Sympathetic neural blockade may be useful in differentiating neuropathic pain processes that involve the sympathetic nervous system (sympathetically maintained / mediated pain-SMP) from those that do not (sympathetically independent pain-SIP). Most, but not all, SMP fulfills the clinical criteria for complex regional pain syndrome (CRPS) type 1 or type 2 [1].

Complex regional pain syndrome (CRPS) is a debilitating condition, characterized by pain in a limb, in association with sensory, vasomotor, sudomotor, motor and dystrophic changes. It commonly arises after injury to that limb. Pain is typically the leading symptom of CRPS, but is often associated with limb dysfunction and psychological distress [2].

Patients undergoing mastectomy may develop chronic neuropathic pain which may be either phantom breast pain or intercostobrachial neuralgia (including postmastectomy pain syndrome) and neuroma pain [3]. It has been found that persistent pain after surgical treatment is quite common and is higher among young patients, those undergoing radiotherapy and axillary lymph node dissection [4]. And about 20-50% women are affected by persistent neuropathic pain after their surgical treatment [5].

Stellate ganglion has been found to be useful in some patients to treat post mastectomy pain syndrome (PMPS) [6].

Various neuro-interventional techniques such as chemical neurolysis, thermal ablation, and neurodestruction have been described for refractory neuropathic pain [7].

Classic targets for sympatholysis are the Stellate ganglion for facial and upper extremity pain.

The anatomy of the Stellate ganglion being in close proximity to various critical structures, renders a number of complications potentially associated with its blockade, some of which are serious and potentially fatal [8]. Many of these complications are not serious, but are associated with patient discomfort. Side effects such as the Horner syndrome that includes ptosis, myosis, enophthalmos,
anhydrosis of the neck and face, conjunctival injection, unilateral flushing, and nasal congestion are reactions to the blockade of the SG [9].

Most complications from Stellate ganglion block occur after diffusion of the local anesthetic (LA) solution onto nearby nerve structures or because of injury to important structures owing to misplacement of the needle, the use of RF techniques may avoid such complications [10].

For these reasons, and in an attempt to avoid these technical difficulties and to improve the safety and efficacy of the block, we tried RF application under fluoroscopic guidance integrated with ultrasound [11].

There is growing interest in the use of radiofrequency ablation (RFA) for management of various painful conditions including malignant pain [12].

Two types of radiofrequency application (RFA) are done for management of chronic pain conditions. Conventional (thermal) TRF uses continuous output of high frequency current with temperature of 70-80°C. Pulsed radiofrequency (PRF) is a newer alternative to conventional RFA with the proposed advantage of avoiding the complication of deafferentation pain and neuritis that sometimes can be seen after the conventional neural ablation [13].

The exact mechanism of action of PRF is unknown. However, it is assumed and demonstrated from studies that it acts by neuromodulation and also affects gene expression in the dorsal horn [14].

Another postulated mechanism of PRF is a reduction in the release of substance P in response to noxious stimuli; thereby leading to both decreased nociceptive behavior and reduced hyperalgesia [15].

The aim of the study is to evaluate the efficacy and safety of pulsed and thermal RF in Cancer patient with chronic sympathetic mediated pain of (head & neck, upper limb and upper thorax).

**Patients and Methods**

After approval of Institutional Review Board and obtaining a written informed consent regarding risk and benefit of the procedure. Patients were randomly selected from the pain clinic at National Cancer Institute (NCI) Cairo University for this study from August 2014 – January 2016. All patients fulfilled the following criteria:

**Inclusion criteria:**
1- Cancer patient with chronic sympathetic mediated pain of upper extremities (head & neck, upper limb and upper thorax).
2- Moderate to severe pain (VAS ≥4).
3- Pain refractory to strong opioid (oxycodone) and adjuvant therapy (pregabalin).
4- Positive Stellate diagnostic block 5ml local anesthetic [16].

**Exclusion criteria:**
1- Patient with local and systemic sepsis.
2- Coagulopathy.
3- Local anatomical distortion.
4- History of contralateral chest disease or pneumonectomy.
5- Glaucoma.
6- Recent MI or severe bradyarrhythmias or heart block.
7- Not allergic to the used medications.

Diagnostic Stellate ganglion block was performed to them by injecting 5ml of local anesthetic (lidocaine 1%) ultrasound guided followed by another block 1 week later using 5ml of local anesthetic (bupivacaine 0.25%) ultrasound guided. Patients who showed a positive diagnostic block in the form of pain score improvement VAS (≤2) and signs of successful sympathetic blockade:


They were then randomly integrated into 2 equal groups:

- **Group (A):** (30 patients) in whom pulsed R.F. therapy was done under fluoroscopy integrated by ultrasound guidance.
- **Group (B):** (30 patients) in whom thermal R.F. therapy was done under fluoroscopy integrated by ultrasound guidance.

ASA-standard monitors (ECG, non-invasive blood pressure and pulse oxymetry) were connected to all patients. I.V. line (G-20) and O2 (3L/min) through nasal prong were used. Midazolam 0.02mg/Kg and fentanyl 1Ug/Kg (conscious sedation) were used. The patient was asked to lie supine over
radiolucent table with the neck extended and a small pillow under shoulders. The field was sterilized with 10% betadine (povidone-iodine) solution and draped. The patient was foretold to communicate by moving the contralateral hand and not to speak or swallow during the procedure.

**Technique:**

**Pulsed-technique:**

Visualization of C6-C7 level was attained under fluoroscopic guidance through P-A view after good alignment was obtained by caudocephalic orientation (C7-level is identified by the nearby T1 transverse process ballooning). Then, the C-arm was turned 5-10º ipsilateral to open the vertebrotransverse junction at C7. At this target marker was applied and point of entry, was infiltrated with 1% lidocaine S.C using 22G needle. Then R.F. needle (curved, sharp, 22G, 50 or 100mm length with 10mm active tip) was advanced using tunnel technique towards the identified bony target under fluoroscopy. After passing through the skin and subcutaneous tissues and stabilizing the needle a 3-12 Mhz linear probe ultrasound Fig. (1) will be used to verify the needle position Fig. (2).

The needle was then advanced with real-time ultrasound imaging so that the needle tip will lie anterior to the longus colli muscle (anterior to the C7 transverse process).

After negative aspiration (For blood, CSF or air), 1ml of contrast agent (omnipaque) was injected.

The contrast agent should outline the retropharyngeal space, longitudinal, within the vertebral shadow (on lateral view), not taking vascular, epidural, intrathecal or muscular pattern Fig. (3).

Then the suitable R.F. Electrode Fig. (4) was inserted and connected to Bailys generator Fig. (5).

Stimulation was done at 2hz with 1-1.5v (motor stimulation) to avoid the phrenic nerve laterally and the recurrent laryngeal nerve anteriorly and medially. The patient should be able to say “ee” to preserve the motor function. There should be no motor response on proper localization.

Then we seek paresthesia for localization. Stimulation was done at 50-100hz with 0.5-1.0v (sensory stimulation), generally the patient should feels paresthesia at a setting of 0.5v (especially upper limb radicular parathesia). The patient should be awake to respond to the stimulation at this stage.

Then we applied pulsed RF protocol with time=240 seconds, temp 42ºC and pulse width=20 msec.

Then we redirected the electrode to the most medial part of the transverse process in the same plane Fig (6). Then we applied RF again.

Then we redirected the electrode in the ventral aspect Fig (6). Then we applied RF to this point, with same protocol.

**Note:** At each point, we repeated sensory and motor stimulation before lesioning.

**Thermal technique:**

- The patients were prepared as before.
- The same steps were done as before.
- Then 1ml lidocaine 2% plus 2ml dexamethasone (non-particulate steroid) was injected before lesioning.

After 60 seconds we applied thermal RF protocol with time=90sec temp 70ºC 3 cycles at 3 needle positions as showed in Fig. (6).

**Note:** At each point (3 needles positions), we repeated sensory and motor stimulation before lesioning.

**Patient evaluation:**

1. The patients were assessed for pain relief (VAS score) at 1st day then 1 and 3 months after. Oxycodone and pregabalin consumption were assessed prior to block and at 3 months after. A follow-up ultrasound was done 30 minute after procedure to exclude any hematoma.

- Complete response VAS 0-3.
- Partial response VAS 4-6.
- No response VAS 7-10.

Any complication was then assessed.

**Statistical methods:**

Data were analyzed using SPSS win statistical package version 22. Numerical data were summarized as means and standard deviations (SD) or medians and ranges as appropriate. Medians were used mainly for skewedness and not normally distributed data. While qualitative data were described as Frequencies and percentages. Comparison between two groups for numerical variables was done using either student *t* test or Mann-Whitney U-test (non-parametric *t*-test) as appropriate.

Relation between qualitative data was done using Chi-square test or Fisher’s exact test as appropriate.
Fig. (1): RF cannula and linear probe.

Fig. (2): Target needle position by ultrasound imaging [red line (A), end of needle shadow (B): Stellate ganglia]. (CCA: Common carotid artery, IJV: Internal jugular vein, TP: Transverse process, ES: Esophagus, LC: Longus coli muscle).

Fig. (3): Dye distribution in AP and lateral X-ray views.

Fig. (4): RF needle electrode.

Fig. (5): Bailys pain generator.
All patients involved in this prospective double blind study completed this study within the period of August/2014 to January/2016.

Table (1) showed socio-demographic characteristics of the studied group. No significant difference between two the groups as regard sex, weight and diagnosis.

Table (2) showed the pain relief response after performing the procedure at the first day, first month and after three months. Percentage of patients who had complete response was significantly higher in thermal group than pulsed group at first day, first month and three months.

- Complete response VAS 0-3.
- Partial response VAS 4-6.
- No response VAS 7-10.

Table (1): Demographic characteristics of the patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=60)</th>
<th>Pulsed (n=30)</th>
<th>Thermal (n=30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>50.7±11.0</td>
<td>47.6±7.5</td>
<td>53.0±13.0</td>
<td>0.028</td>
</tr>
<tr>
<td>Median (range)</td>
<td>50.0 (30-75)</td>
<td>47.0 (35-60)</td>
<td>53.0 (30-75)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>72.0±7.2</td>
<td>69.0±3.1</td>
<td>75.0±3.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Median (range)</td>
<td>70.0 (60-93)</td>
<td>70.0 (65-75)</td>
<td>74 (60-93)</td>
<td></td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (45.0)</td>
<td>15.0 (50.0)</td>
<td>12.0 (40.0)</td>
<td>0.436</td>
</tr>
<tr>
<td>Female</td>
<td>33 (55.0)</td>
<td>15.0 (50.0)</td>
<td>18.0 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRPS</td>
<td>15 (25.0)</td>
<td>9 (30.0)</td>
<td>6 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Maxillary tumor</td>
<td>7 (11.7)</td>
<td>3 (10.0)</td>
<td>4 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Phantom limb</td>
<td>4 (6.7)</td>
<td>3 (10.0)</td>
<td>1 (3.3)</td>
<td></td>
</tr>
<tr>
<td>PMP</td>
<td>34 (56.7)</td>
<td>15 (50.0)</td>
<td>19 (63.3)</td>
<td>0.559</td>
</tr>
</tbody>
</table>

Table (2): The pain relief response after performing the procedure at the first day, first month and after three months.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=60)</th>
<th>Pulsed (n=30)</th>
<th>Thermal (n=30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At first day:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>27 (45.0)</td>
<td>0 (0)</td>
<td>24 (80.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partial response</td>
<td>21 (35.0)</td>
<td>0 (0)</td>
<td>3 (10.0)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>12 (20.0)</td>
<td>30 (100.0)</td>
<td>3 (10.0)</td>
<td></td>
</tr>
<tr>
<td>At first month:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>33 (55.0)</td>
<td>9 (30.0)</td>
<td>21 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partial response</td>
<td>12 (20.0)</td>
<td>6 (20.0)</td>
<td>3 (10.0)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>15 (25.0)</td>
<td>15 (50.0)</td>
<td>6 (20.0)</td>
<td></td>
</tr>
<tr>
<td>At three month:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>18 (30.0)</td>
<td>6 (20.0)</td>
<td>12 (40.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partial response</td>
<td>15 (25.0)</td>
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<td>12 (40.0)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>27 (45.0)</td>
<td>21 (70.0)</td>
<td>6 (20.0)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Our study included 60 cancer patients with sympathetic mediated pain. 60% of them were complaining of post mastectomy pain syndrome (PMPS) while 25% were diagnosed as complex regional pain syndrome (CRPS). As per the estimates of the International Association for the study of Pain (IASP) the prevalence of pain in breast cancer ranges from 40-89% [17].

In our study we used the technique of fluoroscopic guidance integrated with ultrasound [11]. Fluoroscopic guidance for identification of bony landmark. While ultrasound for identification of vessels (inferior thyroid, vertebral artery, common carotid, internal jugular vein), thyroid gland, traghea, oesphgus and longus colli muscle to avoid their injury.

The ultrasound guidance allowed us to use low volume of injectate (LA & steroid) (2-3ml) whether before lesioning or in diagnostic block to avoid false positive results and to avoid spread to the nearby structures as phrenic and recurrent laryngeal which is not available with fluoroscopic or CT guidance.

In our study, we reported in the thermal group at day 1 complete, partial and no pain relief in 80%, 10% and 10% of cases respectively. After one month we reported complete response in 70%, partial response in 10 and no response in 10% of cases. While after 3 months it changed to 40% of cases showing complete pain relief, 40% of cases partial relief and 20% no response. While in the pulsed group, we reported at day 1 no response in 100% of cases. After 1 month it changed to 30% of patients showing complete response, 20% partial response and 50% no response. After 3 months
follow-up, we founded complete response in 20% of patients, 10% partial response and 70% no response.

The potency and long term efficacy of thermal RF compared to pulsed RF may be justified by the concept that the thermal RF is classified as a method of neurodestruction while the pulsed RF is a method of neuromodulation 18 which has been shown in our study the higher percentage of complete response in the thermal RF group than pulsed group.

The delayed response of pulsed RF compared to the thermal RF is due to its different mechanism of action (neuromodulation) which may takes several weeks to reach its maximum effect [18].

We used in the thermal group, 1m lidocaine 2% & 2ml dexamethasone before lesioning to avoid local neuritis, which may develop after thermal RF. While we didn’t inject it in the pulsed group to see the actual efficacy of pulsed technique rather than the effect of local anaesthetic and steroid as Eugene reported the long term efficacy of PRF compared to SGB in case report in a patient diagnosed as post traumatic distress syndrome [19].

The partial response of thermal RF may be due to the mixed nature of the type of pain which was not only sympathetic mediated pain but there was also an element of a somatic pain which need a different treatment than sympathectomy.

While the no response of the thermal RF recorded after 3 months follow-up may be justified by, that in such cases there was a continuous progression of the disease with changing in the pattern of pain whether somatic, neuropathic and sympathetic mediated pain. Which needed a further change in pain management modality other than sympathectomy or even a re-sympathectomy to be tried.

Our results agreed with Forouzanfar et al., who conducted a retrospective series of thermal RFA of Stellate ganglia for chronic pain syndromes, they reported complete pain relief in 37.8% of patients, partial pain relief in 41.3% and no pain relief in 20% of patient suffering from complex regional pain syndrome type 2, ischemic pain, cervicobrachialgia or post thoracotomy pain at 1 year follow-up [20]. Successful pain relief for 3 years has been reported, where stellate ganglion thermal RFA was done 5 times [21].

Kastler et al., reported complete pain relief in 60% of patients for 2 years duration with Thermal RFA stellate ganglion under computed tomography guidance in patient suffering from complex regional pain type 1.22. We reported in our study almost the same results (40%) in 3 months follow-up. Furthermore, we need in the future a study comparing the 2 techniques U/S versus CT guidance regarding safety and efficacy.

Jan van Zundert studied the articles done on Stellate ganglion block/Neurolysis (thermal radiofrequency). List of indications were RSD/CRPS of the face and upper extremity, facial causalgia, phantom tongue pain and causalgia, cluster headaches, postherpetic neuralgia of a trigeminal, cervical or thoracic dermatome, and vasospastic disorders, he reported that all studies received a 1C grade (strong recommendation, very low quality). Ten of the 11 were case reports, case series, and a retrospective study, but were performed for the aforementioned diagnosis. The study by Price et al., was prospective, double-blinded, and placebo-controlled, but included only 4 patients and therefore received 1B grade (strong recommendation grade, moderate quality) [23].

A case report of complex regional pain syndrome II of upper limb reported complete pain relief from PRFA of Stellate ganglion for 2 months duration was reported in [24].

Other indications for Stellate ganglion block have been reported recently; for the treatment of vasomotor symptoms in symptomatic women (hot flashes) with cancer breast [25]. A case report demonstrated the benefits of Stellate ganglion block for intractable lymphedema of the upper limb after breast cancer surgery. The circumferences of the mid-point of their each upper and lower arms were measured on every visit to the pain clinic. A decrease of the circumference in each patient was observed starting after the second injection. A series of blocks were established to maintain a prolonged effect. Patients were satisfied with less swelling and pain [26]. These primary results will encourage to use our Radiofrequency technique to achieve long term result.

Although complications such as cardiac arrhythmia, nerve injury, bleeding, infection, neuraxial and intravascular injection, pneumothorax are expected yet, no complication were reported after PRFA of Stellate ganglion [27].

In our study we didn’t report any complication in the pulsed group.

Whereas in the thermal group, transient ptosis (few weeks) was reported in (6.6%, 2/30) of cases.
And by following them we founded it not disabling them even it improved with time, no other complications were reported. Kastler et al., reported transient ptosis in (5.8%, 1/34) of cases in his study [22]. Also Charles Gaucci noted that after thermal RF of SG there is, a theoretically possibility of Horner’s syndrome, and he noted in his practice that it usually clears spontaneously within a few weeks [18].

This very low rate of complication was obtained because close attention to safety precautions was given on each patient. First, in order to avoid inadvertent vertebral puncture U/S were used. Second, the use of stimulation mode before the RF lesioning is crucial in order to detect the nearby motor nerve (phrenic, recurrent laryngeal nerve and cervical nerve root) so avoiding them.

Hoarseness of voice, lump sensation was not reported in our study. Hardy and Wells reported an incidence of 10% with 10mL LA solution and up to 80% with 20mL solution in the classic approach. Kapral et al., reported RLN (recurrent laryngeal nerve) palsy in only 1 patient in whom ultrasonography showed the spread of the LA between the carotid sheath, thyroid gland, and the esophagus (the anatomic site of the RLN) [28]. In our study we avoided it by direct visualization of solution during injection by real time U/S guidance, using RF technique and using the least volume of LA (2-3ml).

The frequency of retropharyngeal hematoma after SGB was reported in a large retrospective review done by Higa et al., who carried out Medline and Japanese database literature searches over a 40-year period on the topic of SGBs to establish the incidence of retropharyngeal hematoma. The overall incidence was approximated at 1 per 100,000 SGBs. The researchers found a total of 27 instances in which complications of hematoma and airway compromise had occurred. They also mentioned the possibility that other vessels from the thyrocervical trunk or the inferior thyroid artery might possibly be implicated, as the vertebral artery had no apparent damage noted at either autopsy or surgery in those cases in which autopsy was performed [29]. However, Kapral et al., reported a much higher incidence of asymptomatic hematoma especially with the blind technique [28]. In our study, there was no hematoma reported.

At the end, thermal RF of the Stellate ganglion is a safe and succeceful treatment for cancer patients with sympathetic mediated pain. It appears to be more effective than pulsed RF of the Stellate ganglion.

References


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