Randomized Trial

# Thermal Versus Super Voltage Pulsed Radiofrequency of Stellate Ganglion in Post-Mastectomy Neuropathic Pain Syndrome: A Prospective Randomized Trial

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**Background:** Breast cancer is the second most common cancer world-wide following lung cancer. Post-mastectomy pain syndrome (PMPS) is one of the chronic post-surgical pain disorders (CPSP) of neuropathic character; nearly 20–50% of patients may develop PMPS. Stellate ganglion blockade has been performed as a diagnostic, prognostic, or therapeutic intervention for different pain syndromes.

**Objective:** The aim of this study is to evaluate and compare the efficacy and safety of thermal versus super voltage pulsed radiofrequency (RF) application of stellate ganglion in neuropathic PMPS in cancer patients.

**Study Design:** A prospective, double-blind, randomized, and controlled trial.

**Methods:** Eighty patients with PMPS after surgery for breast cancer were recruited from the pain clinic of the National Cancer Institute with pain duration of more than 6 months and less than 2 years, visual analog scale (VAS) ≥ 40 mm, and not responding to oxycodone and pregabalin for at least 4 weeks. The pain had to be of positive neuropathic character, as detected by the grading system for neuropathic pain (GSNP; score of 3 or 4). The patients were allocated into 2 equally sized groups:

Group A: Pulsed RF; super voltage pulsed RF was applied with a time of 360 seconds at 42° C, with a pulse width of 20 m/sec and voltage of 60–70 v.

Group B: Thermal RF; thermal RF neurolysis was applied with a time of 60 seconds at 80° C, and was then was repeated twice after needle-tip rotation. Stellate ganglion RF therapy was done under fluoroscopy, integrated by ultrasound guidance. The patients were assessed for pain relief by change in VAS score, functional improvement, and the analgesic concomitant medication (oxycodone and pregabalin) consumption prior to block and at 1, 4, 12, and 24 weeks thereafter. The impact of treatment on quality of life (assessed by short-form health survey questionnaire [SF-36]) and patient function capacity (assessed by the Eastern Cooperative Oncology Group [ECOG]) were also recorded.

**Results:** The percentage of patients who had successful response was significantly higher in the thermal RF group compared to the pulsed RF group at the first week and first, third, and sixth months, with significant difference in post-mastectomy pain intensity, functional improvement, and less rescue analgesia. There was no significant difference in quality of life or patient functional capacity.

**Limitations:** A longer follow-up period may be needed for the evaluation of RF effect on PMPS.

**Conclusions:** Thermal RF of the stellate ganglion is a safe and successful treatment for PMPS. It appears to be more effective than pulsed RF of the stellate ganglion in this pain syndrome.

**Key words:** Cancer breast, post mastectomy pain syndrome, stellate ganglion block, radiofrequency therapy

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Breast cancer is the second most common cancer world-wide following lung cancer. It afflicts about 1.7 million patients annually, i.e., 11.9% of all cancer patients (1). In Egypt, it represents 29% of all National Cancer Institute patients (2). Mathematically speaking, one in each 8 women may develop breast malignancies world-wide, of which 60% mandate surgery of the breast and/or the axilla, and nearly 20–50% of them may develop post-mastectomy pain syndrome (PMPS) (3-5). According to the International Association for the Study of Pain (IASP) ranging, that number is even higher (40–89%) (6).

PMPS may follow breast cancer surgeries, particularly of the upper outer quadrant and axillary nodal dissection, after excluding evident local infection or recurrence (7). The definition and delineation of chronic post-surgical pain (CPSP) disorders is a controversy, and the duration ranges from one month to one year. The IASP definition is that it is the pain that persists after normal healing time (8). Different pathogenesis mechanisms have been implicated in PMPS, such as phantom pain and dysthesia, intercostobrachial neuralgia, neuroma formation (3), complex regional pain syndrome (CRPS), paraneoplastic syndromes, chemotherapy-induced or radiotherapy-induced plexopathy, and/or lymphoedema (3). Various medical and interventional procedures have been tried for treating PMPS, with varying efficacy (9).

Stellate (cervico thoracic) ganglion blockade has been performed as a diagnostic, prognostic, or therapeutic intervention for sympathetic-maintained and neuropathic pain syndromes and integrated in a big list of clinical indications (10,11). Stellate ganglion sympatholysis has proven efficacy in managing PMPS (12). Stellate block has been tried for treating vasomotor syndromes including menopausal syndrome (13). This concept has been extended for relieving both pain and swelling of lymphodema that frequently accompanies PMPS (14). There is growing evidence of stellate ganglion RF in cancer and non-cancer pain fields (15,16).

However, stellate block is not a risk-free maneuver due to nearby vital neurovascular structures such as the vertebral artery, the subclavian artery, pleura, phrenic nerve, recurrent laryngeal nerve, and C8-T1 anterior divisions (11). Various techniques and approaches have been practiced for blocking the stellate ganglion including: local anesthetics, steroids, chemical neurolytic agents (3% phenol in saline) (17), and both pulsed and thermal RF therapy (18,19). RF sympatholysis may be regarded as continuous regional sympathetic block or chemical neurolysis but with long-term efficiency, better safety, more precise localization, and less morbidity and mortality than surgical sympathectomy (20).

Multiple imaging tools have been utilized to guide stellate ganglion block, including magnetic resonance imaging (MRI) and computed tomography (CT) scan (19). However, ultrasound (that clearly visualizes the vascular and soft tissue structures) and fluoroscopy (that clearly delineates C6/C7 bony landmarks) are frequently used practically (21,22).

The aim of this prospective, double-blinded, controlled study is to compare the safety and efficacy of super voltage pulsed and thermal RF therapy of the stellate ganglion in PMPS with neuropathic component of the upper chest, shoulder, or upper arm. Our suggested guidance technique is fluoroscopy integrated with ultrasonography.

## Methods

This work was local and did not receive any financial support or funding. After approval of the institutional review board, the supporting CONSORT checklist (S1 and S2 Files) was available as supporting information. Eighty-two patients were able to understand and were willing to follow the study protocol and fulfilled the eligibility criteria that were selected from the pain clinic at the National Cancer Institute at Cairo University in Cairo, Egypt. Before giving informed consent, the aim of the study, the different questionnaires, and the intervention of the study were explained to each patient. Written informed consent regarding risk and benefit of the procedure was obtained from each patient.

### Eligibility Criteria

The patients included in this study had PMPS after surgery for breast cancer, with pain having the following criteria: a) a duration of more than 6 months and less than 2 years, b) moderate and severe pain (visual analog scale [VAS] $\geq$ 40 mm), c) pain described as a refractory one that is defined as pain for which classic biomedical therapy "strong opioids like oxycodone for at least 4 weeks (23) and co-analgesics like pregabalin" has proven ineffective and for which more invasive interventions could be tried after considering the possible psychosocial disorders (24,25), and d) pain is of positive neuropathic character as detected by the grading system for neuropathic pain (GSNP), with a score of 3 or 4 (Table 1, Fig. 1) (26).

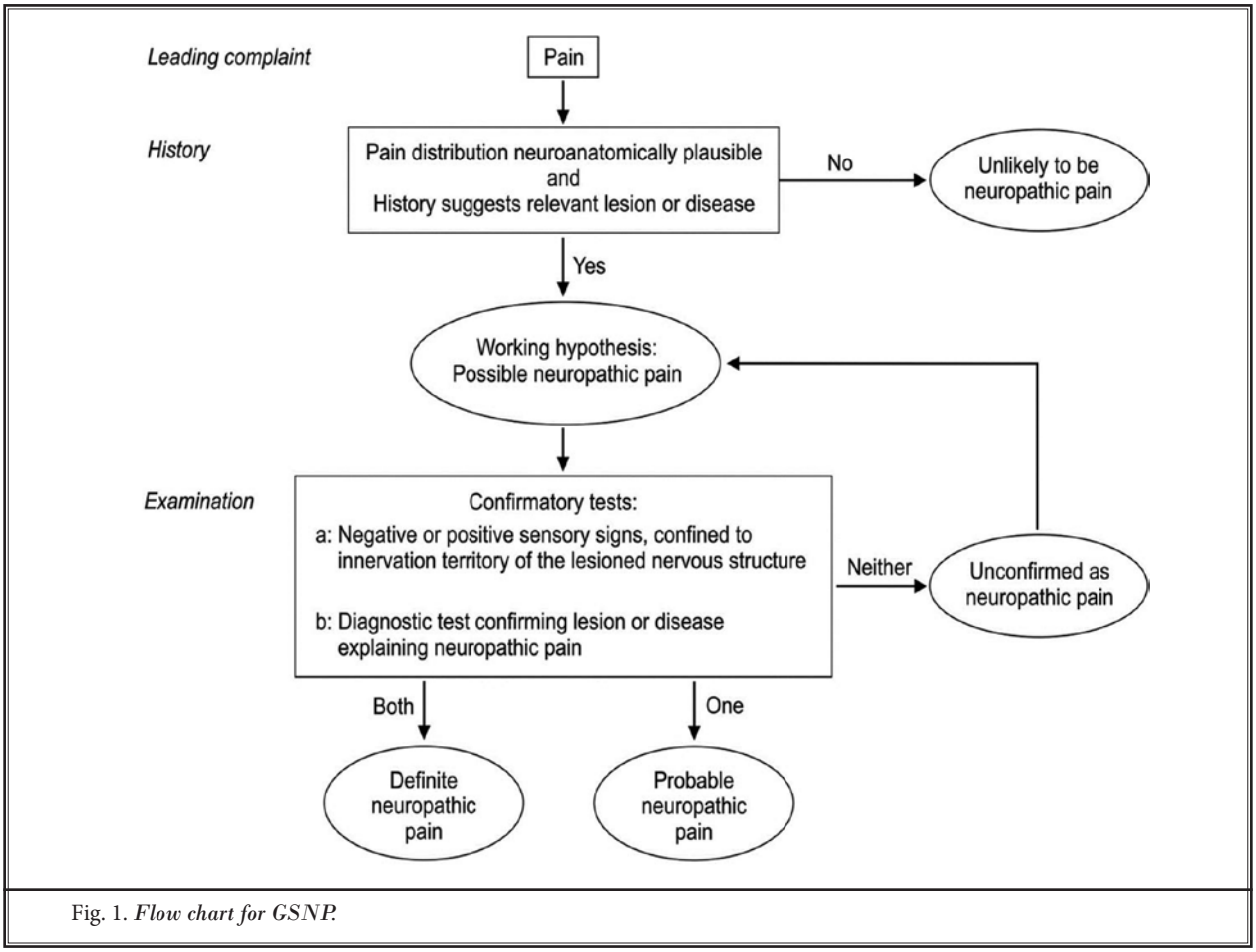


Fig. 1. *Flow chart for GSNP.*

## Exclusion Criteria

Patients were excluded from the study if they had local and systemic sepsis, uncorrectable coagulopathy, local anatomical distortion (which may render the block technically difficult or hazardous), history of contralateral chest disease or pneumonectomy, recent myocardial infarction or severe bradyarrythmias or heart block, allergic to the medications used, or psychiatric illness.

## Randomization, Allocation, and Masking of Study Groups

After assessment of eligibility criteria, a clinical nurse independent of the protocol obtained the randomization number and the patient was then randomized in the pulsed or thermal group. Treatment allocation followed the order of a predetermined randomization list and was generated using random blocks.

Table 1. *Grading System for Neuropathic Pain( GSNP)(26).*

| | |
|---|---|
| Likely | score 1 |
| Possible | score 2 |
| Probable | score 3 |
| Definite | score 4 |

### *Group A*

Super voltage pulsed RF therapy was performed under fluoroscopy, integrated by ultrasound guidance. Analysis of data for 40 patients was performed.

### *Group B*

Thermal RF therapy was performed under fluoroscopy, integrated by ultrasound guidance. Analysis of data for 40 patients was performed. American Society of Anesthiologists-recommended monitors, intravenous line, and $O^2$ (3 L/min) through the nasal canula

were used. Conscious-alert sedation (dexmedetomidine 0.5 ug/kg and fentanyl 1 ug/Kg) was used. The patient was positioned in the supine position over a radiolucent table with the neck extended and a small pillow under the 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 talk or swallow during the procedure.

## Intervention

### Technique of Stellate Ganglion Block

Visualization of C6-C7 level was targeted under fluoroscopic posterioranterior (PA) guidance (C7 level is identified by the nearby T1-transverse process ballooning), and alignment was ensured by caudocephalic orientation. Then, the C-arm was turned 5–10° ipsilateral to visualize the vertebro-transverse junction at C7, which is the target-point of entry. Skin was infiltrated with 1% lidocaine using a 25-gauge needle. Next, the RF needle (Baylis curved, sharp, 22-gauge, 100 mm length, 5 mm active-tip) was inserted under trajectory approach towards the target. Then with real-time ultrasound guidance, using a superficial linear ultrasound probe to guide further needle penetration so that the needle-tip will lie anterior to the longus colli muscle, exclusion of vascular structures was confirmed by duplex (27).

After negative aspiration (for blood, cerebrospinal fluid, or air), 1 mL of omnipaque dye (iohexol) was injected. The contrast agent should trace the retropharyngeal space up and down along the lateral vertebral margin and within the vertebral body (on lateral view) (Fig. 2,3) (4,5).

Subsequently, a 100 mm length Baily RF electrode was inserted and connected to the generator. The RF needle was positioned (perpendicular to the ganglion in pulsed RF technique and alongside the stellate ganglion in thermal RF technique). Stimulation was performed at 2 and 50 Hz to exclude close proximity to the phrenic, recurrent laryngeal nerves, or the segmental nerve of C7. The patient should have been able to say "ee" to preserve the motor function. Negative sensory (up to 1 v) and motor (up to 2 v) responses were anticipated. Afterward, 0.7 mL of (1:1 mixure of lidocaine 2% and dexamethasone 4 mg/mL) was injected (Fig. 4,5) (28).

### Pulsed Technique

Pulsed RF was applied with time of 360 seconds (29), at a temperature of 42° C, with a pulse width of

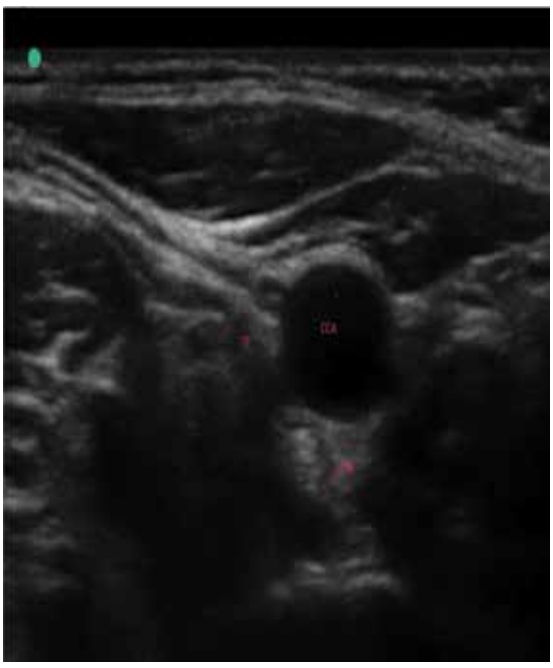

Fig. 2. *The targeted position by ultrasound guidance.* (CCA: common carotid artery; TP: transverse proccess; LC: longus coli muscle.)

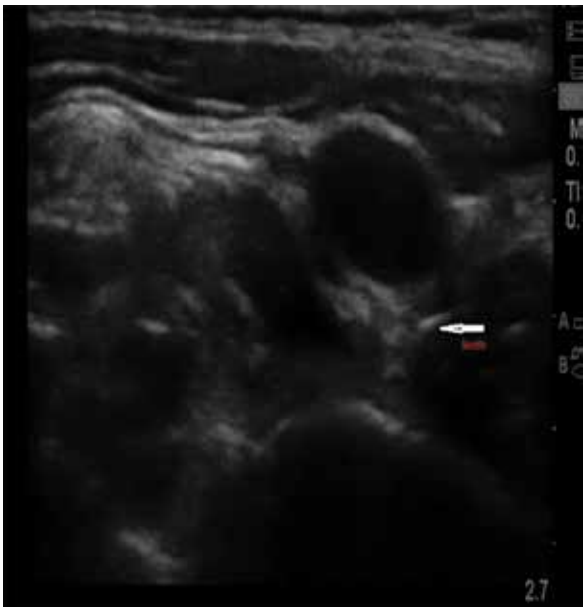

Fig. 3. *The needle at the target stellate ganglion.*

20 m/sec, and voltage of 60–70 v (30), as tolerated by the patient (by adjusting the manual mode of Baily generator).

### Thermal Technique

Thermal RF neurolysis was started with time of 70 seconds, at a temperature of 80° C, then repeated after needle-tip rotation to the most medial site and most ventral aspect of C7 transverse process under fluoroscopic guidance, with repeated sensory and motor stimulation before RF lesioning (11,22,28).

A follow-up ultrasound was done 30 minutes after the procedure to exclude any hematoma formation.

### Collected Data

The collection of data and patient assessment were done by a junior doctor who was blinded to the technique performed. In subsequent visits, the patients were not allowed to see their own previous data.

### Demographic Data

The following patient data was recorded: age, weight, duration of the procedure, initial VAS, GSNP, initial total daily dose of oxycodone and pregabalin, baseline quality of life (assessed by short-form 36 [SF-36]), and baseline Eastern Cooperative Oncology Group (ECOG).

### Outcome Data

The outcome data were collected at 1, 4, 12, and 24 weeks.

#### *Primary Outcome*

A) Changes in VAS for assessment of pain relief. A 100 mm horizontal line version was used with 2 ends (left-end means no pain and right-end means the worst pain). This version is preferred in research studies for chronic pain status (31).

B) Functional improvement. This is a self-reported analysis for the primary outcome after performing pain interventions. It is divided into 4 categories (0–25%) ≈ no or minimal functional improvement, (> 25–50%) ≈ mild improvement, (> 50–75%) ≈ moderate improvement, and (>75–100%) ≈ marked improvement (32).

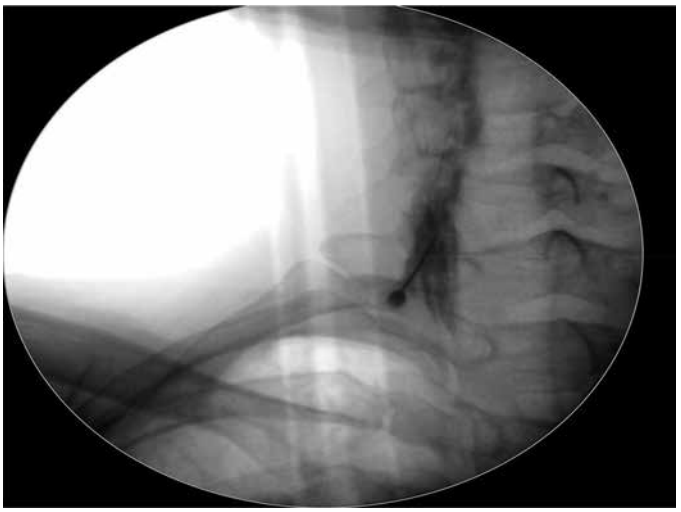

Fig. 4. *P-A fluoroscopic view showing the RF needle at C7 target position after contrast injection.*

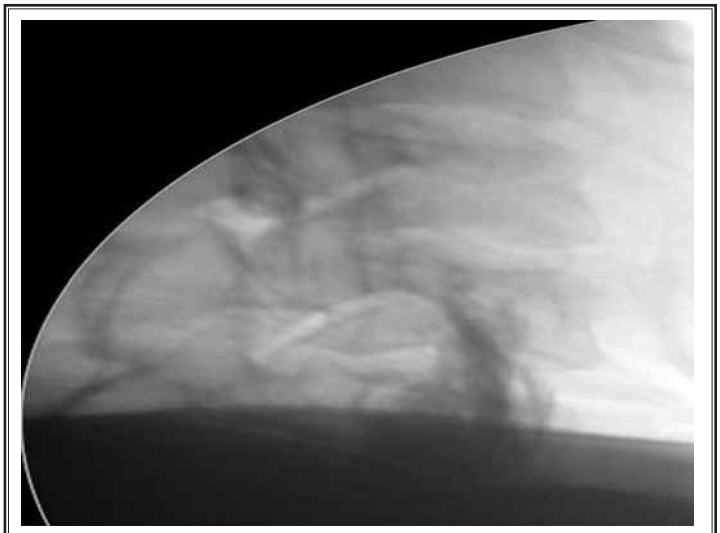

Fig. 5. *Lateral fluorosocopic view after contrast injection.*

C) The analgesic concomitant medications (oxycodone and pregabalin) consumption were assessed prior to the block and at 1, 4, 12, and 24 weeks thereafter.

#### *Secondary Outcome*

A) The impact of treatment on the quality of life of the patient, which was assessed by the SF-36 questionnaire (33).

B) The patient function capacity (disability level) was evaluated according to the ECOG, with 0 meaning fully active, 1 meaning

capable of light effort, 2 meaning in bed less than 50% of the day, 3 meaning in bed more than 50% of the day, and 4 meaning bed-ridden (34).

Any complication was assessed and recorded.

### Sample Size Bases

Based on a success rate of 67% of thermal ablation of stellate ganglion and 21% of stellate ganglion block, a minimum of 25 patients per group was needed to show difference with an alpha error of no more than 0.05 and at least a power of 90% for the test statistics (19). We decided to assign 40 patients to each group to compensate for any drop-outs.

Data were analyzed using SPSS Version 22.0 (IBM Corporation, Armonk, NY). Numerical data were summarized as means and standard deviations 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 2 groups for numerical variables was done using either student's 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.

## Results

We pre-screened 110 patients. Fourteen patients refused to participate in the study and 16 did not meet the inclusion criteria, therefore 80 patients remained and gave written informed consent. These patients were then randomized into the pulsed or thermal group. Out of 80 enrolled patients, 80 were analyzed (n = 40 in each group). Eighty patients were analyzed up to 3 months, and 71 patients were analyzed at 6 months (n = 36 in pulsed RF group [as 4 patients died] and n = 35 in thermal RF group [as 3 patients died and 2 lost contact]) (Fig. 6). The investigation was carried out

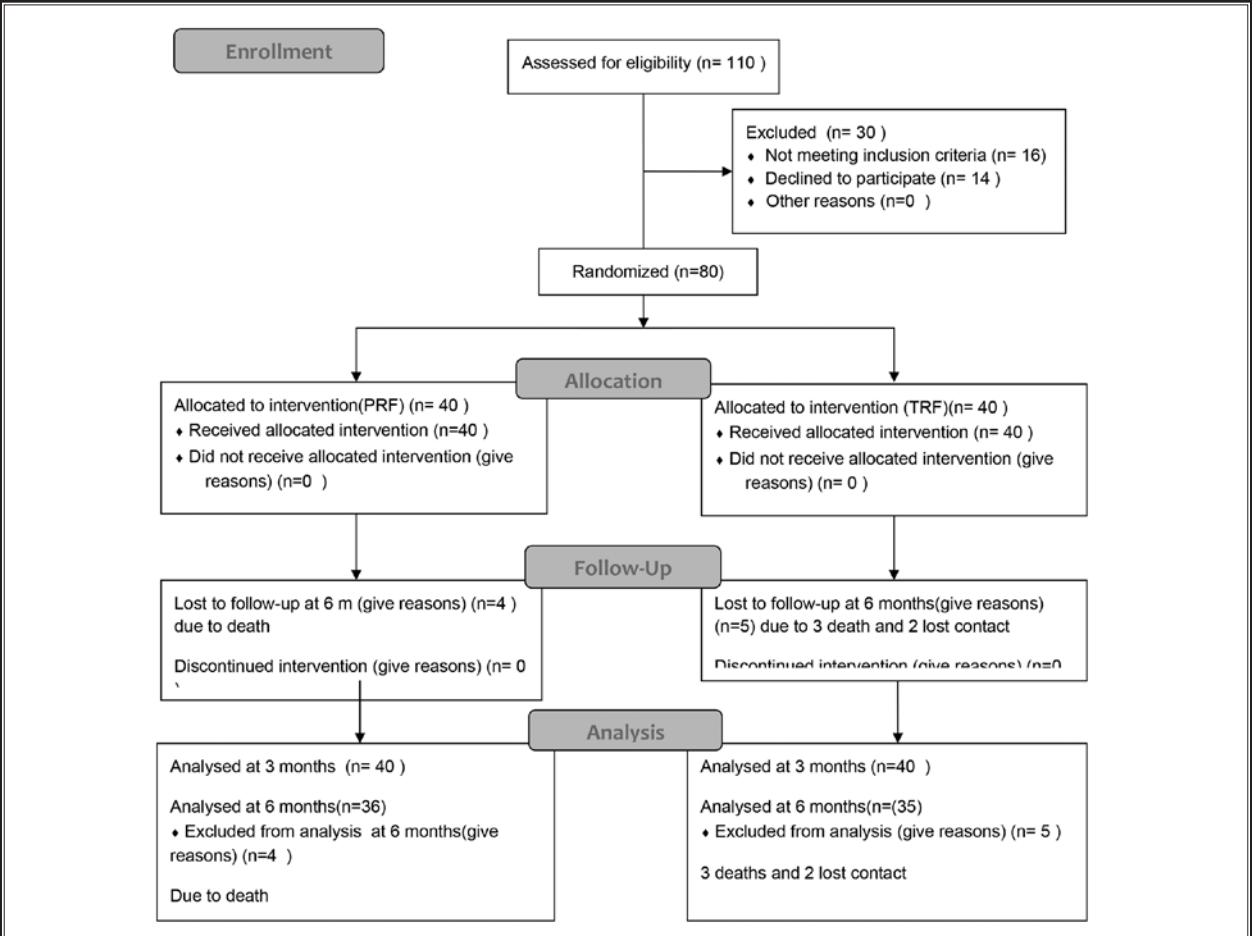


Fig. 6. *CONSORT 2010 flow diagram.*

Table 2. *Demographic and clinical characteristics of the patients.*

| Characteristic | Total (n = 80) | Pulsed (n = 40) | Thermal (n = 40) | *P*-value |
|---|---|---|---|---|
| Age (yrs) | | | | |
| Mean ± SD | 50.7 ± 11.0 | 47.6 ± 7.5 | 50.0 ± 13.0 | 0.082 |
| Median (range) | 50.0 (30.0–75.0) | 47.0 (35.0–60) | 53.0 (30–75) | |
| Weight (kg) | | | | |
| Mean ± SD | 72.0 ± 7.2 | 69.0 ± 03.1 | 71.0 ± 3.9 | 0.065 |
| - Median (range) | 70.0 (60.0–93.0) | 70.0 (65–75) | 72 (60.0–93.0) | |
| Cured | | 12 | 11 | 0.065 |
| Under therapy | | 19 | 21 | |
| Terminal | | 9 | 8 | |
| Initial VAS score (mm) | | 76 ± 8 | 72 ± 9 | 0.068 |
| Basal total daily dose of oxycodone (mg) | | 80 ± 12 | 78 ± 10 | 0.861 |
| Basal total daily dose of pregabalin (mg) | | 325 ± 35 | 350 ± 25 | 0.739 |
| GSNP (grade 3/grade 4) | | (n)30/10 | (n) 31/9 | 0.75 |
| Quality of life (SF-36) | | | | |
| Physical health | Baseline | 72.1 ± 15.5 | 71.0 ± 18.2 | 0.66 |
| Mental health | Baseline | 70.6 ± 16.2 | 71.5 ± 16..2 | 0.60 |
| Duration of procedure (min) | | 23 ± 7.3 | 21.2 ± 6.6 | 0.782 |

Values are means and SDs. No statistically significant difference between groups in any socio-demographic or clinical variable was obtained, indicating that both groups were equivalent for the variables measured.
VAS= visual analog scale; GSNP= grading system for neuropathic pain; SF-36= short-form 36-item questionnaire

from August 2014 to April 2016 for recruitment, and the follow-up and analysis of data was completed in September 2017.

There was no significant difference between the 2 groups regarding age, weight, duration of the procedure, VAS score, GSNP scores, and initial total daily dose of pregabalin or oxycodone (Table 2). The percentage of patients who had successful response was significantly higher in the thermal group than in the pulsed group at the first week and at the first, third, and sixth months (Table 3). The VAS score was significantly lower in the thermal RF group compared to baseline at all follow-up periods, while in the pulsed RF group it was significantly lower only at the first month. The change in VAS from baseline in the thermal RF group was significantly higher than the change in the pulsed RF group at one week and at the third and sixth months (Table 4). The mean daily dose of oxycodone and pregabalin were significantly lower in the thermal RF group at the first week and first, third, and sixth months compared to baseline values, while it was significantly lower in the pulsed RF group at one month only. Compared to the PRF group, the mean daily dose of oxycodone and pregablin was significantly lower in the thermal RF group at the first week and third and sixth months (Tables 5,6).

There was no statistically significant difference shown between the pulsed and thermal treatment groups, in quality of life (measured by SF-36) at any of the follow-up periods (Table 7). No statistically significant difference was shown between the pulsed and thermal treatment groups in performance status (assessed by ECOG) apart from statistical significant improvement in the thermal RF group compared with the pulsed RF group at one week (Table 8). No complications were reported in the pulsed group, whereas in the thermal group, transient ptosis (for weeks) was reported in (6.6%, 2/30) of cases.

## Discussion

Our study included 80 patients who underwent surgery for breast cancer, complaining of PMPS. For detection of neuropathic component of PMPS, we utilized the GSNP score, which is based on diagnosing the lesion or disease process that affect the neuroanatomical somatosensory system. Physical examination is mandatory for verifying neuropathic character of pain,

Table 3. *Functional improvement recorded at the first week, first month, third month, and sixth month.*

| Characteristic | PRF (n = 40) (%) | TRF (n = 40) (%) | *P*-value |
|---|---|---|---|
| At first week | | | |
| Successful response | 9 (22.5%) | 24 (60%) | |
| (75–100%) Marked | 2 (5%) | 9 (22.5%) | |
| (50–75%) Moderate | 7 (17.5%) | 15 (37.5%) | |
| Fair response | 31 (77.5%) | 16 (40%) | < 0.001 |
| (25–50%) Mild | 17 (42.5%) | 10 (29%) | |
| (0–25%) No or minimal response | 14 (35%) | 6 (15%) | |
| 4 wks | | | |
| Successful | 25 (62.5%) | 29 (72.5%) | |
| (75–100%) Excellent | 8 (20%) | 11 (27.5%) | |
| (50–75%) Good | 17 (42.5%) | 18 (45%) | |
| Fair response | 15 (37.5%) | 11 (27.5%) | < 0.001 |
| (25–50%) Mild | 9 (22.5%) | 6 (15%) | |
| (0–25%) No or minimal response | 6 (15%) | 5 (12.5%) | |
| At 12 wks | | | |
| Successful | 15 (37.5%) | 24 (60%) | |
| (75–100%) Excellent | 4 (10.0) | 10 (25.5%) | |
| (50–75%) Good | 11 (27.5%) | 14 (35.5%) | |
| Fair response | 25 (62.5%) | 16 (40%) | < 0.001 |
| (25–50% ) Mild | 15 (37%) | 10 (25%) | |
| (0–25%) No or minimal response | 10 (25%) | 6 (15%) | |
| At 24 wks | | | |
| Successful | (n = 36) 11 (30.5%) | (n = 35) 19 (54.3%) | |
| (75–100%) Excellent | 3 (8.30%) | 9 (25.7%) | |
| (50–75%) Good | 8 (22.20% | 10 (28.6%) | |
| Fair response | 25 (62.5%) | 16 (45.7%) | < 0.001 |
| (25–50%) Mild | 14 (39.0%) | 10 (28.6%) | |
| (0–25%) No or minimal response | 11 (30.5%) | 6 (17.1%) | |

with diagnosis level being either probable or definite (26). Diagnostic tests were not done routinely for all patients to verify level 4 (definite) GSNP, but some investigational information were detected during cancer work-up, e.g., brachial plexus infiltration or fibrosis as detected by MRI or axilla or positron emission tomography scanning and/or sensory/motor delay at station of brachial plexus during electromyography testing. We did not perform diagnostic blocks in our study prior to RF lesioning due to many considerations: first, diagnostic and prognostic procedures performance are not mandatory in the field of cancer pain management (35); second, cancer patients with moderate and severe pain (VAS > 40 mm) may not tolerate the delay of the diagnostic then therapeutic blocks; finally, the psychosocial bias is higher than expected in cancer pain patients.

Local anesthetic, in form of lidocaine 1%, was injected in both groups prior to RF application to alleviate pain during thermal RF ablation and to also get benefit of the vasodilator and neuro-protective (Na-stabilizer) effects of lidocaine if unwanted neurovascular contact occurred during needle insertion.

Steroids were used in our study to augment the analgesic, antihyperalgesic effects of the procedure through expressing the anti-inflammatory cytokines (IL-10) and counteracting proinflammatory cytokines (TNF & IL-1B) and to reduce local neuritis which may follow thermal RF (36). Dexamethasone was selected to avoid the vascular thromboembolic hazards of particulate steroids.

Table 4. *VAS after RF therapy and changes from baseline values.*

| Post-Procedure Time | Pulsed RF (n = 40) | Thermal RF (n = 40) | Change from Baseline Pulsed RF | Change from Baseline Thermal RF | *P*-value |
|---|---|---|---|---|---|
| 1 wk | 52.5 ± 9.8 | 32.4 ± 5.4* | 24.5 ± 6.4 | 44.5 ± 5.7 ¶ | < 0.001 |
| 4 wks | 33.7 ± 8.3* | 25.5 ± 5.3* | 43.5 ± 5.6 | 45.7 ± 6.4 | 0.194 |
| 12 wks | 62.3 ± 8.7 | 28.3 ± 7.5* | 14.6 ± 7.3 | 45.5 ± 4.8 ¶ | < 0.001 |
| 24 wks | (n = 36) 65.4 ± 7.6 | (n = 35) 31.3 ± 6.9 | 11.4 ± 6.2 | 45.2 ± 5.6 ¶ | < 0.001 |

All data values are means ± SD. VAS= visual analog scale (0–100 mm)
* $P < 0.05$ compared to baseline values, ¶$P < 0.05$ change in VAS from baseline in the thermal RF group compared to the change in VAS from baseline in the pulsed RF group.

Table 5. *Mean (mg) daily consumption of oxycodone.*

| Oxycodone Consumption (n = 80) | Pulsed RF (n = 40) | Thermal RF (n = 40) |
|---|---|---|
| Pre-procedure | 80 ± 12 | 78 ± 10 |
| 1 wk post-procedure | 75 ± 14 | 48 ± 12* ¶ |
| 4 wks post-procedure | 45 ± 18* | 42 ± 10* |
| 12 wks post-procedure | 80 ± 12 | 46 ± 18* ¶ |
| 24 wks post-procedure | (n = 36) 83 ± 13 | (n = 35) 52 ± 21* ¶ |

Data are presented as means ± SD.
* $P < 0.05$ compared to baseline values.
¶ < 0.05 compared to pulsed RF group.

Table 6. *Mean pregabalin (mg) daily consumption.*

| Time | Pulsed RF (n = 40) | Thermal RF (n = 40) |
|---|---|---|
| Pre-procedure | 325 ± 35 | 350 ± 25 |
| 1 wk post-procedure | 295 ± 24 | 145 ± 12* ¶ |
| 4 wks post-procedure | 145 ± 18* | 135 ± 10* |
| 12 wks post-procedure | 318 ± 18 | 146 ± 14* ¶ |
| 24 wks post-procedure | (n = 36) 337 ± 21 | (n = 35) 163 ± 17* ¶ |

Data are presented as means ± SD.
* $P < 0.05$ compared to baseline values.
¶ < 0.05 compared to pulsed RF group.

Table 7. *Effect of pulsed and thermal RF on quality of life by SF-36.*

| SF-36 | Follow-up | Pulsed RF (n = 40) | Thermal RF (n = 40) | *P*-value |
|---|---|---|---|---|
| Physical Health | Baseline | 72.1 ± 15.5 | 71.0 ± 18.2 | 0.66 |
| | At 4 wks | 66.8 ± 19.2 | 69.3 ± 19.6 | 0.81 |
| | At 12 wks | 75.4 ± 16.5 | 75.8 ± 16.8 | 0.82 |
| | At 24 wks | (n = 36) 75.3 ± 18.5 | (n = 35) 76.5 ± 16.6 | 0.83 |
| Mental Health | Baseline | 70.6 ± 16.2 | 71.5 ± 16.2 | 0.60 |
| | At 4 wks | 68.9 ± 19.2 | 74.0 ± 18.9 | 0.62 |
| | At 12 wks | 79.3 ± 19.5 | 77.1 ± 14.2 | 0.87 |
| | At 24 wks | (n = 36) 76.2 ± 17.5 | (n = 35) 74.5 ± 12.7 | 0.85 |

No statistically significant difference was shown between the pulsed and thermal treatment groups, at any of the study times.

Table 8. *Comparison of changes in functional capacity "ECOG" between the 2 groups.*

| Follow-up Points | Pulsed RF Group (n = 40) | Thermal RF Group (n = 40) | *P*-Value |
|---|---|---|---|
| At preoperative visit | 2.0 (1–5) | 2.0 (1–4) | 0.183 |
| At 1 wk | 2.0 (0–3) | 1.0 (0–2) | 0.002 |
| At 4 wks | 2.0 (0–3) | 1.0 (0–2) | 1.000 |
| At 12 wks | 1.0 (0–2) | 1.0 (0–2) | 0.411 |
| At 24 wks | (n = 36) 1.0 (0–3) | (n = 35) 1.0 (0–2) | 0.411 |

The values are presented as median (range).
$P < 0.05$ is significant.
ECOG= Eastern Cooperative Oncology group.

The present study revealed that a higher percentage of patients in the thermal RF group achieved the primary outcome of at least 50% pain relief (assessed by change in VAS score and functional improvement measurement) all through the study period. In the thermal RF group, the recorded VAS pain scores at all post-procedure assessment points were statistically lower compared with baseline value. Also, oxycodone and pregabalin consumption was lower compared to the pre-procedure value. While in the pulsed RF group, the VAS pain scores and oxycodone consumption were only lower than baseline at 4 weeks. When comparing pain improvement from baseline, the thermal RF group showed superior improvement compared to the pulsed RF group at 1, 12, and 24 ($P < 0.001$) weeks. Regarding secondary outcome measurements: quality of life and functional capacity results- all were comparable but not strict representatives of the VAS score changes apart from ECOG which showed statistical significant improvement in the thermal RF group compared with the pulsed RF group. The discrepancy between the primary outcome and the secondary outcome is well-documented in cancer pain studies and is attributed to a variety of factors such as the hidden psychological pitfalls, the progress of advanced disease or the occurrence of distant metastases, and/or unrelated pain, such as low back or joint pain. Moreover, these barriers against improvement in secondary outcome following pain relief may still be active even in cured cancer patients.

We reported more efficacy and longer-term relief of thermal compared to pulsed RF. This could be justified by the fact that thermal RF is a neuroablative tool which is frequently used in sympatholysis, particularly in cancer pain cases. This concept has been confirmed by many authors (11,19,28,37-40).

The concept of the longer and more potent effect of thermal RF in neuroablation has been widely practiced in many clinical procedures such as percutaneous

cervical cordotomy (41), trigeminal gangliotomy (42), secondary glossopharyngeal neuralgia due to oropharyngeal cancer (40,43), and facetal medial branch denervation (32). Furthermore, pulsed RF neuromodulatory mechanism "C-Fos expression and/or reduced release of substance p in the dorsal horns leading to reduced nociception and hyperalgesia (44)" are of delayed response up to several (4–6) weeks (36,45). Hence, this neuromodulatory, pulsed RF, which is frequently used in sensory neuropathy (36), has a time-lag that might not be tolerated in this patients' category of intractable cancer pain (VAS > 40 mm).

Again the fair response to RF treatment in the remaining studied patients may be explained by other involved mechanisms of PMPS which may be sympathetically-independent or involving other pains "myofacial or somatic" which need other interventions rather than sympathectomy. The regression in pain relief after thermal RF which is recorded at the third and sixth month may be explained by the disease progression, change in pain pattern (which necissate other treatment modality), or sympathetic fibers regeneration that demands re-sympathectomy.

The reported successful response of 72%, 60%, and 54.3% of patients in the thermal group at1, 3, and 6 months follow-up, respectively, in our trial, coincided with Kastler et al (19) who reported improvement in 67% of cases following CT-guided thermal RF of stellate ganglion in CRPS-I (19). Forouzanfar et al (46) published a retrospective study of thermocoagulative RF of stellate ganglion in a variety of chronic pain syndromes. They reported complete pain relief in about 37.8%, partial relief in 41%, and no relief in 21% of the patients at the one-year follow-up.

Significant pain relief has been recorded following thermal RF repeated 5 times per 3 years (47). Van Eijs et al (28) has stratified stellate blockade to receive 1C grade (strong recommendation, very low quality) (10). Thereafter, the procedure of stellate block received 2B+ grade (recommended, moderate quality).

Recently, a case report of CRPS-II of the upper arm showed excellent pain relief for 2 months following pulsed RF of stellate ganglion (48). Our protocol design specified pulsed RF technique with duration of 6 minutes which is the least time for pulsed RF to exert its anti-allodynic action in neuropathic disorders (29).We also tried the high (super) voltage method by adjusting the manual mode of the Baylis generator at 60–70 volt assuming to augment the pain-relieving effect of pulsed RF (30).

We recorded a low rate of adverse events in our work (transient ptosis in 2/40 patients, only for few weeks, in the thermal RF group and no adverse events reported in the pulsed RF group), as ultrasound can precisely locate the blood vessels (carotid, vertebral, thyroid vessels), nerves (phrenic, recurrent laryngeal, cervical nerve roots), and other soft tissue structures (longus coli muscle, trachea, oesphagus, and thyroid) together with the pre-stimulation prior to RF therapy to avoid the nearby nervous structures. This rate of ptosis incidence correlates with the rates reported by Kastler et al (19) (1/34) and Gauchi (36). The absence of lump sensation and hoarseness of voice in our study could be attributed to the small volume of local anesthetic/steroid mixture used (0.7 mL) and monitoring injection using real-time ultrasound to lessen spread into the space bounded by the carotid sheath, the thyroid gland, and the esophagus where the recurrent laryngeal nerve locates (49). In one study, the rate of recurrent laryngeal nerve blockade was 10% when 10 mL volume of local anesthetic was injected and 80% when 20 mL was injected (50). Similarly, no retropharyngeal hematomas were reported in our study due to ultrasound (with Duplex capability) practice to avoid vascular penetration especially of thyrocervical or inferior thyroid vessels which are mostly injuried (49,51). Narouze et al (21) showed that ultrasound is essential to identify the thyroid gland and vessels, vertebral vessels, nerve roots, longus colli muscle, and the esophagus. Ultrasound is the only tool to exclude penetrating the oesphageal diverticulae (27). Moreover, ultrasound may reduce radiation exposure and improve the success of stellate block as it avoids injection within the longus coli muscle substance (its thickness varies greatly anatomically and under imaging) (52). The real-time monitoring of local anesthetic (dexamethasone mixture) injection under ultrasound guidance, together with the small volume (0.7 mL) used, helped to avoid false-positive results due to blockade of nearby somatic cervical nerves. Finally, ultrasound-guided precise positioning of the RF needle-tip is essential for sizable theromocoagulative lesion generation since the thermal RF lesion is quite small (about 1.5 times the RF needle radius, i.e., 1.8 mm for 22-gauge RF needle) (32).

## Limitations and Recommendations

A larger scale, multi-center meta-analysis is needed to verify our hypothesis.

A more prolonged period of follow-up may be needed for evaluation of RF effect on PMPS.

## Conclusion

Our prospective, double-blinded, randomized controlled trial has revealed that thermal RF of the stellate ganglion is a safe and successful treatment for PMPS with neuropathic component. It appears to be more effective, more rapidly onset, and a longer duration than the super voltage pulsed RF of the stellate ganglion. In our opinion, the combined integrated use of both fluoroscopy and ultrasound guidance is assumed to be of added value in performing stellate ganglion block.

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