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Clinical Study

Ultrasound Guided Stellate Ganglion Block in Postmastectomy Pain Syndrome: A Comparison of Ketamine versus Morphine as Adjuvant to Bupivacaine

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Background. The postmastectomy pain syndrome (PMPS) is chronic pain after breast cancer surgery and is reported to influence quality of life. The aim of this study was to provide long term reduction of PMPS, improve range of motion of the shoulder, and decrease the need for postoperative analgesia using ultrasound guided stellate ganglion block. *Method.* Sixty patients with PMPS were randomly allocated into 1 of 3 groups: bupivacaine group (group 1), bupivacaine plus ketamine group (group 2), and bupivacaine plus morphine group (group 3). Each patient received 3 blocks with an interval of one week in between. Patients were assessed for: pain visual analogue score (VAS), movement of the shoulder, skin temperature, and the need for analgesic drugs. *Results.* The pain VAS was significantly decreased in group 2 as compared to the other two groups. Shoulder movement improved significantly in the three studied groups with the best results observed after the third block. The need for the analgesic drugs in the form of gabapentin was more in the bupivacaine and bupivacaine plus morphine groups than in bupivacaine plus ketamine group. *Conclusion.* Treatment of PMPS with ultrasound guided stellate ganglion block using ketamine (0.5 mg/kg) as adjuvant to bupivacaine (0.25%) successfully decreased pain VAS and the need for analgesic drugs.

1. Introduction

The postmastectomy pain syndrome (PMPS) is a neuropathic pain that can follow surgical treatment for breast cancer including radical mastectomy, modified radical mastectomy, and segmental mastectomy (lumpectomy) [1]. This syndrome consists of persistent pain in the anterior chest, axilla, and medial and posterior parts of the arm following breast surgery. This pain can be sufficiently severe enough to interfere with sleep and performance of daily activities. Moreover, patients may develop an immobilized arm, which can lead to severe lymphedema, frozen shoulder syndrome, and complex regional pain syndrome. PMPS can result from surgical damage to the intercostobrachial nerve, the lateral cutaneous branch of the second intercostal nerve that is often resected at mastectomy [2].

The etiology of persistent pain after mastectomy is unclear, although it is likely multifactorial [3] and may be partially neuropathic in nature [4]. Previous reports of PMPS have suggested a limited number of potential risk factors, which are inconsistent among studies [3]. While surgical factors, including more extensive surgery (mastectomy), axillary lymph node dissection, and reconstruction have been postulated as important risk factors for chronic pain, many studies do not support this association. Adjuvant treatment, such as radiation, chemotherapy, and hormone therapy, has also been occasionally associated with persistent pain [5]. Among demographic factors, younger age correlates with increased incidence of persistent pain in some studies [6] but not others [7]. Ethnicity may also be a risk factor, as nonwhite race was associated with higher incidence of PMPS [8].

A stellate ganglion block (SGB) is defined as a nerve block which blocks the cervical sympathetic trunks, the vertebral ganglia, the preganglionic and postganglionic fibers of the lower cervical sympathetic ganglia, and the upper thoracic sympathetic ganglia. The SGB is mainly used for the treatment of painful disorders of the head and neck, upper limb, and upper chest [9]. Traditionally, it has been performed blindly by palpating the anterior tubercle of the transverse process of C6 but this method has a relatively high failure rate, with numerous significant and even potentially fatal adverse effects [10]. Image guided nerve block has changed the practice of regional anesthesia and increased safety and accuracy compared with the blind injections [11].

The aim of this study was to evaluate the outcome of ultrasound guided stellate ganglion block using different drugs on postmastectomy pain syndrome. The safety, feasibility, and efficacy of the technique were assessed.

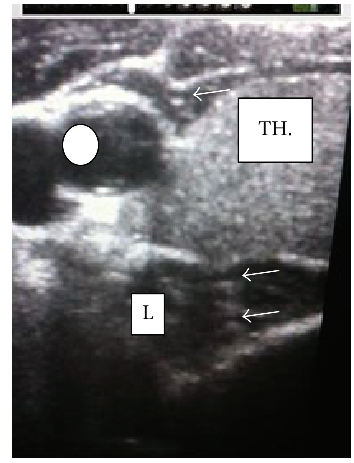

Figure 1: Site of the needle (white arrow). TH: right thyroid lobe. O: right common carotid artery. L: longus collis muscle.

2. Patients and Methods

After approval from the Local Ethics Committee of Mansoura University, postmastectomy patients recruited from the outpatient pain clinic of the Mansoura Oncology Centre were eligible to participate in this study for stellate ganglion block. Participants had to fulfil the following criteria: postmastectomy neuropathic pain lasting more than 6 months after modified radical mastectomy with any of the following symptoms: allodynia, burning pain, shooting pain, hyperalgesia, visual analog scale (VAS) > 6, and limitation of the shoulder movement at the side of mastectomy. Patients were excluded from the study if one or more of the following criteria were met: patient refusal to participate in the study, bleeding diathesis, sepsis at the site of injection, preexisting neurological (motor or sensory) deficit, or history of using drugs acting on sympathetic nervous system.

All patients were informed about the procedure and its possible consequences and written informed consents were obtained before the procedure. Brief evaluation was done for all patients with regard to their systemic diseases, general condition, and coagulation status. Shoulder mobility was assessed with the patients in sitting position using goniometry and the range of motion was measured in degrees in five positions (extension, flexion, abduction, internal rotation, and external rotation).

Skin temperature was recorded also in the distal portion of the ipsilateral upper extremity using fever scan. Patients were instructed for the use of visual analogue scale (VAS) of 10 points (where 0 points equal no pain and 10 points equal the worst pain imaginable).

With each block, an intravenous cannula was inserted and secured. All suitable resuscitation equipment and drugs were available. Vital signs (heart rate, blood pressure, and oxygen saturation) were monitored throughout the procedure and up to 1 hour after the block performance. Midazolam 0.02 ug/kg was administered intravenously as premedication.

2.1. Technique of the Stellate Ganglion Block. The procedure was done using the classic anterior paratracheal approach at C6. The patient was placed in the supine position with the neck extended by placing a pillow under her shoulder in order to stretch the esophagus away from the transverse process. By asking the patient to keep the mouth slightly open, the neck muscles are kept relaxed. Under complete aseptic technique, a 5–10 MHz linear probe of Siemens ultrasound was initially placed at the level of the cricoid cartilage and the C6 transverse process was identified by the prominent anterior tubercle (Chassaignac's tubercle) (Figure 1). Placement of ultrasound transducer helps retract the carotid sheath and sternocleidomastoid muscle laterally. Pressure was applied with the ultrasound transducer to reduce the distance between the skin and tubercle and to depress the dome of the lung to reduce risk of pneumothorax. A typical sonographic appearance at the C6 level included the transverse process and anterior tubercle of C6, longus colli muscle (LC), longus capitis muscle, carotid artery, and thyroid gland (Figure 2).

A 22-gauge needle was inserted aiming towards the Chassaignac tubercle and after contacting it, the needle was then withdrawn 1-2 mm to bring it out of the longus colli muscle while still staying within the prevertebral fascia. After negative aspiration for blood and CSF, 10 mL volume of prepared solution according to the study group was injected slowly with repeated aspiration evidenced by distension of the longus collis muscle (Figure 3). The head of the patient's bed was elevated, presumably allowing the solution to travel caudally toward the stellate ganglion.

Sixty patients were randomly allocated using closed envelop method into three groups (20 each). In group 1 (bupivacaine group), SGB was done using 5 mL bupivacaine 0.25% in total volume 10 mL. In group 2 (bupivacaine-ketamine), SGB was done using ketamine 0.5 mg/kg added to the same dose of bupivacaine in a total volume of 10 mL. In group 3 (bupivacaine-morphine), the block was done using 1 mg morphine added to the same dose of bupivacaine in total volume 10 mL. One case was excluded from group 2

Figure 2: Indentation of anterior surface of longs collis muscle (black arrow) due to needle insertion inside longus collis muscle. Right transverse process of C6 (white arrow).

Figure 3: Distension of longus collis muscle at the end of procedure. Posterior acoustic shadowing of needle tip during withdrawal (black arrow).

because of failure of injection due to enlarged thyroid gland. The success of the SGB was confirmed by the development of Horner's syndrome (myosis, ptosis, and enophthalmos) at the side of injection and also by the associated nasal congestion and facial anhydrosis.

The SGB was performed three times with an interval of 1 week between each block. Patients were followed up at 2 weeks and 1, 2, and 3 months after last injection. During this period gabapentin was administered once pain VAS was more than 6.

2.2. Collected Data. Pain score (VAS) was recorded at the following intervals: before injection, after each injection, and two weeks, one month, two months, and three months after last injection. Range of motion of the arm (flexion, extension, abduction, and internal and external rotation) was assessed after each injection. Horner's syndrome and immediate complications like hoarseness of voice, hematoma, weakness in the limb, and respiratory insufficiency. Skin temperature of the ipsilateral extremity. The number of patients who needed supplemental analgesic was recorded. One patient from bupivacaine group (group 1) died one month after last injection due to chemotherapy-related cardiotoxicity.

Table 1: Patients characteristics (values are mean ± SD).

	Group 1 ($n = 20$)	Group 2 ($n = 19$)	Group 3 ($n = 20$)
Age (years)	56.4 ± 8.9	50.0 ± 12.3	51.4 ± 10.3
Weight (Kg)	81.2 ± 7.9	75.9 ± 9.1	79.8 ± 10.2
Height (cm)	159.2 ± 5.3	161.3 ± 2.7	156.7 ± 9.3

2.3. Statistical Analysis. Data were analyzed with SPSS version 16 for windows. The normality data was first tested with one-sample Kolmogorov-Smirnov test. Descriptive statistics and mean and standard deviation were calculated in each group for continuous variables. Paired comparisons were done with paired t-test for parametric continuous variables and Man Whitney test for nonparametric continuous data. One-way ANOVA was used to compare mean levels in the three groups of the study. Post hoc test (LSD) was done to compare outcome variables across the groups. The statistical difference between groups was considered significant when P value was equal to or less than 0.05.

3. Results

There was no significant difference among the three studied groups for the demographic data of the study subjects (Table 1). The mean values of the visual analogue score of pain were significantly reduced in group 2 (bupivacaine plus ketamine) as compared to the other two groups, while there was no difference in pain scores between bupivacaine (group 1) and bupivacaine-morphine group (group 3) (Table 2).

The movements of the shoulder (flexion, extension, abduction, and internal and external rotation) improved after stellate ganglion block in all groups as shown in Table 3. The flexion movement was better in group 2 than the other two groups. Extension of the arm improved significantly after the second and third injection in the bupivacaine plus ketamine (group 2) and bupivacaine plus morphine (group 3) groups, as compared to the bupivacaine alone group (Table 4). Abduction and internal and external rotation of the arm were comparable in the three studied groups (Tables 5 and 6).

One patient in group 3 (bupivacaine-morphine group) developed small hematoma after the second injection with no need for surgical intervention. Horner's syndrome (a sign for successful block) and nasal congestion were observed after block within 5–10 minutes except in one patient in group 2 (bupivacaine-ketamine group) when it was delayed for 30 minutes after second block.

The skin temperature of the ipsilateral arm to the block got elevated (1–3°C) above basal values in all groups.

Table 2: VAS pain values before and after injections in between the three groups values are mean ± SD.

Injection time (n = 59)	Group 1 (n = 20)	Group 2 (n = 19)	Group 3 (n = 20)
Before injection	7.8 ± 0.74	7.6 ± 0.68	7.8 ± 0.81
After the 1st injection	2.7 ± 0.85	0.8 ± 0.76**	2.4 ± 0.75
After the 2nd injection	2.0 ± 0.79	0.9 ± 0.65**	2.2 ± 0.71
After the 3rd injection	1.9 ± 0.85	0.5 ± 0.5**	2.2 ± 0.52
Two weeks after last injection	2.4 ± 0.68	0.73 ± 0.56**	2.60 ± 0.68
One month after last injection	2.6 ± 0.67	0.9 ± 0.7**	2.8 ± 0.67
Two months after last injection	3.4 ± 1.34	1.1 ± 0.65**	3.0 ± 0.56
Three months after last injection	3.7 ± 1.15	1.2 ± 0.73**	3.5 ± 1.05

**VAS pain values were significantly less in group 2 compared to groups 1 and 3.

Table 3: Flexion of the arm before and after injections among the three groups using goniometry measured by degree (°).

Range of motion (n = 59)	Group I (n = 20)	Group II (n = 19)	Group III (n = 20)
Flexion before injection	94 ± 16.8	98.4 ± 11.2	90.5 ± 20.6
Flexion after the 1st injection	122.5 ± 14.4	124.2 ± 12.16	121 ± 13.7
Flexion after the 2nd injection	126.5 ± 11.8	127.4 ± 10.4	126 ± 8.2
Flexion after the 3rd injection	129.5 ± 8.8	130 ± 10	122.6 ± 24

Table 4: Extension movement before and after injections among the three groups using goniometry measured by degree (°).

Range of motion (n = 59)	Group 1 (n = 20)	Group 2 (n = 19)	Group 3 (n = 20)
Extension before injection	46.5 ± 10.3	51.5 ± 6.8	49.5 ± 13.16
Extension after the 1st injection	63 ± 10.8	68.4 ± 9.5	68 ± 9.5
Extension after the 2nd injection	66 ± 11.87	72.1 ± 7.8*	73 ± 7.3**
Extension after the 3rd injection	67 ± 9.2	73.2 ± 7.5*	76.8 ± 5.8**

*Group II is statistically significant compared to group I.
**Group III is statistically significant compared to group I.

Temporary hoarseness of voice was recorded in three patients of the bupivacaine group (group 1), five patients of the bupivacaine plus ketamine group (group 2), and four patients of the bupivacaine plus morphine group (group 3). No other side effects were detected.

Table 5: Abduction movement before and after injections among the three studied groups using goniometry measured by degree (°).

Range of motion (n = 59)	Group 1 (n = 20)	Group 2 (n = 19)	Group 3 (n = 20)
Abduction before injection	89 ± 18	90.5 ± 12.2	89.5 ± 19.5
Abduction after the 1st injection	119.5 ± 17.6	125.8 ± 9.6	121 ± 15.8
Abduction after the 2nd injection	124.5 ± 12.7	126.6 ± 9.4	127 ± 14
Abduction after the 3rd injection	128 ± 18.8	128.4 ± 8.9	128 ± 8.9

Table 6: Internal and external rotation before and after injections among three studied groups using goniometrymeasured by degree (°).

Range of motion (n = 59)	Group 1 (n = 20)	Group 2 (n = 19)	Group 3 (n = 20)
Internal rotation before injection	59.5 ± 13.1	56.5 ± 8.3	57.5 ± 15.2
Internal rotation after the 1st injection	75 ± 16.4	79.4 ± 9.11	73.5 ± 12.2
Internal rotation after the 2nd injection	78.2 ± 12.4	83.6 ± 6.8	81 ± 12
Internal rotation after the 3rd injection	81.5 ± 12.6	85.3 ± 6.1	84.2 ± 10.2
External rotation before injection	68 ± 11.5	67.9 ± 7.8	70.5 ± 12.2
External rotation after the 1st injection	79 ± 11.2	80 ± 8.8	82.1 ± 8.5
External rotation after the 2nd injection	83 ± 10.3	84.2 ± 7.6	86.3 ± 6.8
External rotation after the 3rd injection	84.5 ± 8.2	87.6 ± 4.2	87.8 ± 4.1

During the follow-up period and specifically at two-week and one-month interval, seven patients (five in group 1 and two in group 3) needed analgesics in the form of gabapentin (300 mg/8 hrs). Only one patient in group 2 needed analgesic drug gabapentin after two months of followup.

4. Discussion

Many patients suffer from pain after breast cancer surgery and are left untreated. This may be due to the lack of interest or information of postsurgery pain among surgeons. In addition, comparison of the results of treatment effects by drug category showed that a high percentage of physicians also felt that the treatment effect was not sufficient even with antidepressants and opioids which are therapeutic drugs for PMPS [12].

There are a limited number of studies of stellate ganglion blockade in PMPS [13]. However, it is widely considered to be an effective therapeutic modality for various diseases such as complex regional pain syndrome (CRPS) of the upper limb and pain in the face or head [14].

In the current study, ultrasound guided stellate ganglion block yielded a significant pain relief in the three groups (bupivacaine group, bupivacaine plus ketamine group, and bupivacaine plus morphine group). This was shown by the decrease in the pain VAS and decrease of the need for postoperative analgesia. These results are in agreement with those of Nabil Abbas et al. [15] who reported that fluoroscopic stellate ganglion block with the classic anterior and oblique approach decreased pain VAS, daily morphine consumption, and areas of allodynia and increased the patient satisfactory score.

On the contrary, Hoseinzade et al. [2] compared the effect of stellate ganglion block and gabapentin on the postmastectomy pain syndrome and found that the stellate ganglion block reduced pain score for short duration while gabapentin was more durable. This could be attributed to the fact that the study authors used bupivacaine alone for ganglion block.

Among the three groups of the study population, the mean values of pain VAS were significantly decreased in the ketamine group after block and up to 3 months as compared to the other groups. These results are similar to Sunder et al. [16] who reported that ketamine appears to be a good adjuvant for SGB and achieves a prolonged sympathetic blockade for pain relief. Another study [17] observed a fall in pain VAS from 10 to <1 following addition of 0.5 mg/kg ketamine to bupivacaine for SGB with significantly prolonged duration of analgesia. The mechanism of action of ketamine may be supraspinal by systemic absorption and peripheral through NMDA receptors located on the somatic nerve and dorsal root ganglion. Blockade of peripherally located NMDA receptors is a potential target in the management of neuropathic pain. As there are changes in Na^+ and Ca^{++} channels in neuropathic pain, a combination of Na^+ channel blocker (bupivacaine) and NMDA receptor antagonist (ketamine) appears to be superiorly for treatment of neuropathic pain [18].

The addition of morphine did not produce significantly different effects on pain scores than bupivacaine alone which was in agreement with Glynn and Casale [19]. This study showed that morphine did not produce any demonstrable effects on the sympathetic nervous system nor did it provide pain relief. Consistently, Rashid et al. [20] stated that the analgesic potency of morphine is reduced in neuropathic pain. However, O'Connor and Dworkin [21] recommended opioid analgesics as second-line treatments for neuropathic pain and to be only considered for first-line use in selected clinical circumstances.

Yucel et al. [22] also found that SGB had successfully decreased pain VAS and also increased the range of movement of the wrist joints in patients with complex regional pain syndrome type l. In the current study, the different types of motion (flexion, extension, abduction, and internal and external rotation) were increased after injection of SGB in all groups compared to before injection. The improvement of movement was comparable among the three studied groups with the best results achieved after the third block. This lack of differences can be explained by the fact that the range of motion of the shoulder is not only dependent on pain relief but also on the physical therapy. Jewell et al. [23] concluded that physical therapy, specific exercise, and mobilization techniques tend to produce the fastest result and the greatest improvement and prevent further tightening of the shoulder.

The skin temperature of the ipsilateral arm to the block was elevated by 1 to 3° above the baseline measurement value after injection indicating the success of the technique because of the increase in the blood flow due to the sympathetic effect of SGB. This was clarified by Yamazaki et al. [9] who used laser-Doppler blood flowmetry to confirm changes in blood flow following SGB.

In the study of Huntoon [24], it was found that arterial vessels other than the vertebral artery which also supplies the anterior spinal cord and brain stem pass directly anterior to the transverse processes at the site of the conventional anterior paratracheal approach. Therefore, the accidental injection or induced spasm of these vessels (and not the vertebral arteries) is responsible for some cases of seizure, hematoma, or other vascular complications during the conventional SGB. The usage of ultrasound guided technique in SGB decreased the complication as only one patient developed small hematoma after the 2nd block in the bupivacaine plus morphine group which did not need surgical intervention throughout period of monitoring. This is in agreement with Rastogi et al. [25] and Yoo et al. [26] who concluded that the ultrasound guided nerve blockade has changed the practice of regional anaesthesia and that ultrasound guided SGB offers a superior accuracy and improved patient safety.

The hoarseness of voice observed in the current study probably occurred because of the spread of the LA to the recurrent laryngeal nerve (RLN). However, Hardy and Wells [27] reported an incidence of 10% with 10 mL local anesthetic solution and up to 80% with 20 mL solution in the classic approach. Kapral et al. [28] reported RLN palsy in only 1 patient of 12 patients in whom ultrasonography showed the spread of the LA between the carotid sheath, thyroid gland, and the esophagus (the anatomic site of the RLN), which is why bilateral stellate block is not advisable at the same setting.

Vomiting was observed in 7 patients following administration of ketamine which necessitates antiemetic therapy (metoclopramide intravenous injection). This symptom could be explained by the systemic absorption of ketamine. This was in agreement with Thorp et al. [29] who found that the administration of ketamine was associated with vomiting.

We concluded that the treatment of PMPS with ultrasound guided stellate ganglion block using adjuvant ketamine (0.5 mg/kg) to bupivacaine (0.25%) successfully decreased pain VAS values and increased shoulder-joint ranges of motion and decreased the need for analgesic drugs, as compared to bupivacaine alone or bupivacaine plus morphine.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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