Combined platelet rich plasma intra-articular shoulder injection and stellate ganglion block. A new technique for management of chronic post-mastectomy shoulder pain syndrome

Nevert A. Abdel Ghaffar^{1*}, Mohamed A Ghanem²

Lecturer^{1*}, Assistant Professor², Anaesthesia, Intensive Care and pain management, Faculty of Medicine, Mansoura University, 35516, Mansoura, Egypt.

Background: Adhesive capsulitis of the shoulder is common after breast cancer treatment. We aimed to compare the effects of using stellate ganglion block (SGB) with bupivacaine and ketamine alone versus its combined use with intra-articular platelet rich plasma (PRP) injection in patients with post-mastectomy shoulder pain.

Methods: A prospective randomized open blinded end-point pilot study was conducted in Mansoura University Oncology Center, Egypt during the period from August 2017 till April 2018.

Sixty-four patients with chronic post-mastectomy frozen shoulder were enrolled and allocated into one of two groups. Group A received ultrasound guided SGB with ketamine (0.5mg/kg) plus 5ml bupivacaine 0.5% and group B received ultrasound guided SGB using ketamine and bupivacaine in the same dose and intervals as group A plus posterior approach shoulder injection with PRP (3 times with 1-week interval). Numerical rating scale (NRS) at rest and at shoulder movement, range of motions (ROM) of shoulder and disability of arm, shoulder and hand (DASH) questionnaire were recorded. T-test and ANOVA test (for parametric data) and Mann-Whitney test, Wilcoxon rank test and Kruskal-Wallis test (for non-parametric data) were used for analysis.

Results: Group B showed statistically significant improvement in NRS with shoulder movement and DASH score at one, two and three months after injection in comparison to group A ($P \leq 0.001$). Also, ROM improved significantly with PRP shoulder injection after one month from injection.

Conclusion: The combination of intra-articular PRP injection with SGB using ketamine as adjuvant to bupivacaine produces dramatic improvement in post-mastectomy chronic shoulder pain. Their combined use reduces the need for analgesia.

Keywords: Ketamine; pain; platelet rich plasma; mastectomy; shoulder

Introduction

Adhesive capsulitis of the shoulder (frozen shoulder) is a debilitating state characterized by progressive pain and a reduced range of movements about the glenohumeral joint that occurs frequently after breast cancer surgery.¹

Frozen shoulder progresses in three stages: the freezing (2-9 months), adhesive (4-12 months) and thawing stages (5-26 months).² Frozen shoulder management has focused around prolonged courses of physiotherapy to maintain shoulder mobility. Corticosteroids and non-steroid anti-inflammatory medications are also considered as adjuvant therapies in reducing pain and inflammation.³

In refractory cases, there is a controversy about the ideal therapeutic approach. These approaches include intra-articular injections, hydrosilation, manipulation under anaesthesia and surgical capsular release.¹ Among these techniques, stellate ganglion block (SGB) was emerging as an effective technique with an early onset of action.³ However, there is no agreement about its use in

*Correspondence: Nevert A. Abdel Ghaffar

E mail: nevertadel@mans.edu.eg

<https://orcid.org/0000-0002-0345-0870>

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complex regional pain syndrome. Authors reported variable durations of pain relief following this technique from one week up to few months.⁴ Recently, platelet-rich plasma (PRP) have been widely used in treatment of many soft tissue disorders with positive results being rich in alpha-granules containing biologically active moieties (such as transforming growth factor- β and vascular endothelial growth factor) that can stimulate healing of soft tissues and joints.⁵ Positive effects of PRP were reported in treatment of osteoarthritis of the knee; tendinopathies and rotator cuff injuries⁶ with limited trials for post-mastectomy chronic shoulder pain management.

One of the major advantages of PRP technique is its long lasting and healing effect that could extend up to two years.⁷ From this point, a treatment concept using the combined technique (PRP and SGB using bupivacaine and ketamine) in post-mastectomy chronic shoulder pain was tested in the current research.

In the current study, we aimed to compare the effects of using SGB with bupivacaine and ketamine alone versus its combined use with intra-articular PRP injection in post-mastectomy shoulder pain patients.

Materials and methods

Study design and participants

Our study was a randomized prospective open blinded end-point pilot level IV study conducted in Mansoura University Oncology Center, Egypt during the period from August 2017 till April 2018. We assessed 70 patients for eligibility. The study was accepted by the responsible institutional research board. The target population of our study was post-mastectomy shoulder pain patients (6 months post-operative) with frozen shoulder. We included patients subjected to modified radical mastectomy with axillary lymph node dissection and received 15 cycles of radiotherapy after surgery aged from 18 to 65yrs and refractory to physiotherapy and non-steroidal anti-inflammatory drugs (naproxen in a dose of 500mg PO every 12 hours).⁸

Six patients were excluded from the study (two declined to participate in the study and four did not meet the inclusion criteria). We included patients in the frozen stage. The patients were labeled as frozen shoulder according to scratch test. Each patient was instructed to scratch his

medial side of the opposite scapula from above and across the neck, from above the same side, and lastly from below. Patients who were unable to perform any of these steps completely (i.e., with limitation in all movements directions), with 50% reduction in their range of motion including passive and active external rotation of the involved shoulder compared to the other shoulder were included.⁹

Exclusion criteria were patient refusal to participate, patients with acute shoulder pain (post-trauma), non-surgically induced adhesive capsulitis of shoulder, previous shoulder pathology before cancer breast surgery, adhesive capsulitis following operations other than mastectomy, diabetes, hypothyroidism or hyperthyroidism, hypersensitivity to amide local anaesthetics, general contraindications to SGB and cardiac and hepatic, renal or respiratory failure. To rule out other causes of adhesive capsulitis, history, clinical, radiological findings (x-ray and MRI) and basic laboratory investigations were evaluated for all patients. Written informed consents were obtained from all study participants.

Sample size was calculated using G *power 3.1 program. Based on a pilot study of (10 patients of each group) and assuming α (type I error) = 0.05 and β (type II error) = 0.2 (power = 80 %), a sample of 64 was assumed (32 for each group) with effect size = 0.6.

Randomization

Each patient was assigned randomly in two groups using block randomization (block size of 4). Group A (n=32) patients received ultrasound guided SGB using ketamine (0.5mg/kg) plus 5ml bupivacaine 0.5% and completed to a total volume of 10ml using normal saline. The SGB was repeated three times at one week intervals between each injection.¹⁰ Group B (n=32) patients received ultrasound guided SGB using ketamine and bupivacaine in the same dose and intervals as group A plus posterior approach shoulder injection with PRP (3 times with 1 week interval). Opaque sealed envelopes technique was used for allocation concealment.

Stellate ganglion block technique

The anterior para-tracheal approach C6 was done. We extended the patient's neck using a pillow under the shoulder while lying in a supine position with slightly opened mouth. Then we placed a linear probe (5-10 MHz) of Siemens

Acuson P300 ultrasound machine at the cricoid cartilage level. The location of C6 transverse process was determined by the prominent anterior tubercle (Chassaignac's tubercle). We inserted a 22-gauge needle and directed towards the Chassaignac's tubercle then redirected inferomedially towards the body of C6 until reach out of Longus Colli muscle while still staying within the prevertebral fascia. After negative aspiration, we injected ketamine in a dose of 0.5mg/kg plus 5ml bupivacaine 0.5% completed to a total volume of 10ml using normal saline and observed the spread of the anaesthetic agents (Figure 1A).¹¹ The solution was allowed to pass caudally toward the stellate ganglion by raising the head of the patient's bed. We confirmed the success of block by the development of Horner's syndrome at side of injection.

Figure 1A: Ultrasound image at the level of the cricoid cartilage shows the spread of the substance injected at the area of the lower cervical sympathetic chain. N= needle; C= carotid artery; Ch= Chassaignac's tubercle; L= lateral.

PRP preparation

PRP was obtained from a sample of patient's blood. Thirty ml venous blood was drawn to yield 5ml of PRP. Citrate dextrose A (an anticoagulant) was added.¹² Preparation of PRP was done by double centrifugation process. At the initial step, three layers were generated: an upper layer that contains white blood cells and platelets, an intermediate thin layer (buffy coat layer) rich in white blood cells, and a lower layer composed mostly of red blood cells. For PRP production, we transferred the upper two layers to an empty sterile tube and then centrifuged to help in soft pellets formation (erythrocyte platelets) at the bottom of the tube. We removed the upper portion of the volume (platelet-poor plasma).

Pellets were homogenized in lower third (5ml of plasma) to produce PRP.¹³

Posterior approach shoulder injection technique

The patient was positioned in the sitting position with his ipsilateral hand on the contralateral shoulder. We placed the ultrasound probe (frequency 6-13MHz) just caudal to the acromion over the infraspinatus tendon. The important anatomical points to detect were infraspinatus tendon, humeral head, labrum and joint capsule. The posterior approach target was between the free edge of labrum and the cartilage of humeral head underneath the capsule. Once the target was obtained, we inserted a 22 gauge needle from lateral to medial direction with in-plane technique (Figure 1B) then injected 5ml PRP.¹⁴

Figure 1B: Ultrasound image of the posterior glenohumeral joint shows the needle between the free edge of labrum and the cartilage of humeral head underneath the capsule. N= needle; H= humeral head; IS=infraspinatus muscle; GP= glenoid process; GL= glenoid labrum; L=lateral.

Post-intervention management

The two groups were asked to do stretching exercises at home as finger walk, cross body reach and outward and inward rotations. We asked the patients to warm up their shoulders before performing the exercises by moist heating pad for 10-15mins. During the follow up, we gave paracetamol when numerical rating scale (NRS) was ≥ 4 at a dose of 10mg/kg/dose (max. 2g/day).

Outcome variables

Primary outcome: Pain intensity was measured on 11-point NRS at rest and at shoulder movement before injection, one, two and three months from the first injection (0 equals no pain and 10 equals worst imaginable pain).

Secondary outcome: ROM was measured before and after one month of first injection. Shoulder mobility was assessed while the patient was sitting using goniometry. Also disability of arm, shoulder and hand (DASH) questionnaire was done before injection, after one, two and three months of first injection.

Statistical analysis

The collected data were analyzed using SPSS, version 16. For continuous data, we tested the data for normality using KS test. Parametric data were expressed as means and standard deviations (SD) while non-parametric data were expressed as median and range. On testing significance of parametric quantitative data, t-test and ANOVA test were used. On testing significance of non-parametric data, Mann-Whitney test, Wilcoxon rank test and Kruskal-Wallis test were used. Statistically significant results were considered if $P \leq 0.05$.

Results

Table 1 shows the descriptive data of patients, duration after breast surgery and duration of shoulder pain in both groups. Total paracetamol consumption over three months was statistically lower in group B than group A ($P < 0.001$).

Patient characteristics	Group A N=32 Mean $\pm$ SD	Group B N=32 Mean $\pm$ SD	P value
Age (years)	55.2 $\pm$ 7.9	51 $\pm$ 10.3	0.072
Weight (kg)	77.2 $\pm$ 9.1	80.7 $\pm$ 3.2	0.044
Height (cm)	158.5 $\pm$ 4.3	161.1 $\pm$ 2.6	0.005
Duration after surgery (months)	13.5 $\pm$ 0.67	13.78 $\pm$ 0.7	0.152
Duration of pain (months)	7.44 $\pm$ 0.75	7.34 $\pm$ 0.86	0.647
Total consumption of paracetamol over three months after injection (gram)	86.25 $\pm$ 16.91	51.45 $\pm$ 15.55*	<0.001

Table 1: Distribution of studied patients according to their descriptive characteristics, duration after surgery, pain duration and total consumption of paracetamol NRS values at rest showed no statistically significant difference between both groups (Figure 3A), while with shoulder movement, there was statistically significant improvement in NRS values in group B after one, two and three months of first injection (Figure 3B).

Figure 3A: box and whisker plot chart of numerical rating scale (NRS) of studied groups at rest in different phases of the study

Figure 3B: box and whisker plot chart of numerical rating scale (NRS) of studied groups at shoulder movement in different phases of the study

No statistically significant differences were detected between both groups in ROM before injection. However, after one month of first injection, there was statistically significant improvement in all shoulder movements in group B compared to group A (Table 2).

Table 2: Comparison between group A and group B according to their range of movement (ROM) before injection and one month after first injection

Movement action	Range of movement		Independent t-test	P value
	Group A N=32 Mean (SD)	Group B N=32 Mean (SD)		
Before injection				
Flexion	93.7 (10.8)	91.4 (11.9)	t = 0.817	0.417
Extension	35.6 (6.8)	36.3 (6.1)	t = 0.463	0.645
Abduction	91.8 (11)	92.8 (10.7)	t = 0.393	0.696
Internal rotation	57.9 (10.4)	52.5 (10.5)	t = 2.074	0.042

External rotation	37.2 (10.6)	42.3 (8.8)	t = 2.12	0.038
One month after first injection				
Flexion	123 (15)	145.9 (12.9)	t = 6.567	<0.001
Extension	62.1 (6.7)	67.7 (8.6)	t = 2.897	0.005
Abduction	116.2 (11)	141.3 (11.6)	t = 8.873	<0.001
Internal rotation	68.6 (7.6)	77.5 (5)	t = 5.525	<0.001
External rotation	67.1 (7.1)	72.8 (5.5)	t = 3.598	0.001

As regards DASH score, within-group comparison revealed statistically significant reduction in the scores of the questionnaire after one, two and three months compared to before injection. On the other hand, between-group comparison revealed statistically significant reduction in DASH score in group B at the three studied periods after injection (Figure 3C).

Figure 3C: Mean and SD of disability of arm, shoulder and hand (DASH) score of the shoulder of the study groups at different phases of the study

Discussion

Increasing attention has been paid for PRP usage in pain management of joint morbidity, however, its true effectiveness has not yet fully established.¹⁵ In the current study, we compared the effect of SGB with ketamine as adjuvant to bupivacaine versus its combination with intra-articular PRP injection for the first time in post-mastectomy shoulder pain.

In current study, patients who received combined PRP and SGB with ketamine and bupivacaine showed statistically significant improvement regarding pain with shoulder movements, ROM and DASH score. This finding could be explained by the growth promoting and healing effects of PRP on the areas of soft tissue damage.¹⁶ This

cooperates with Aslani et al who injected PRP twice in a 45-year-old man with frozen shoulder and found marked improvement in ROM and pain and recommended PRP usage in treatment of shoulder capsulitis in more patients using randomized trials.¹⁷ Kothari et al compared the effect of PRP shoulder injection, ultrasonic therapy and corticosteroids in the treatment of shoulder peri arthritis and found that single injection of PRP resulted in statistically significant improvement over corticosteroids and ultrasonic therapy in visual analogue score (VAS), active as well as passive ROM of shoulder and function (Quick DASH).¹⁸

Moreover, in a recent study, the efficacy of intra-articular PRP injection was tested in frozen shoulder treatment through comparing with local anaesthetic procaine. They found that PRP was more effective and had a more prolonged efficiency in pain and shoulder movement than procaine.¹⁹

An important observation in our study was the significant reduction in the need for the analgesic drug (paracetamol) in group B. This finding confirms the success of the combined technique in alleviating pain in frozen shoulder patients. Moreover, this could reduce the possible side effects of long-term analgesic therapy in those chronic patients.

On reviewing the literature, we found that SGB was tried for treatment of adhesive capsulitis of the shoulder with some success.³ Abdel Dayem et al¹⁰ found significant improvement in pain from 7.6 ± 0.7 to 1.3 ± 0.7 after three months of SGB injection with ketamine as adjuvant to bupivacaine and also found significant improvement in range of motion of shoulder after injection. In addition, there are several studies confirming these findings.^{11,20} To our knowledge, no reports were published about combined PRP and SGB in frozen shoulder patients.

Limitations of the study: A single center pilot study.

Conclusion

The combination of intra-articular PRP injection with SGB using ketamine as adjuvant to bupivacaine produces dramatic improvement in post-mastectomy chronic shoulder pain. Their combined use reduces the need for analgesia. Large-scale clinical trials are required to generalize our findings.

References

1. St Angelo JM, Fabiano SE, editors. Adhesive Capsulitis. Treasure Island (FL): StatPearls Publishing; 2018.
2. Chan HBY, Pua PY, How CH. Physical therapy in the management of frozen shoulder. Singapore Med J 2017;**58**(12):685-689.
<https://doi.org/10.11622/smedj.2017107>
PMid:29242941 PMCID:PMC5917053
3. Cha SM, Kim HS, Ahn KH. The Effects of Stellate Ganglion Block in Adhesive Capsulitis of the Shoulder. J Korean Acad Rehabil Med 1998;**22**(4):950-954.
4. Datta R, Agrawal J, Sharma A, et al. A study of the efficacy of stellate ganglion blocks in complex regional pain syndromes of the upper body. J Anaesthesiol Clin Pharmacol 2017;**33**(4):534-540.
5. Nejati P, Ghahremaninia A, Naderi F, et al. Treatment of Subacromial Impingement Syndrome: Platelet-Rich Plasma or Exercise Therapy? A Randomized Controlled Trial. Orthop J Sport Med 2017;**5**(5):2325967117702366.
<https://doi.org/10.1177/2325967117702366>
PMid:28567426 PMCID:PMC5439655
6. Cole BJ, Seroyer ST, Filardo G, et al. Platelet-rich plasma: where are we now and where are we going? Sports Health 2010;**2**(3):203-210.
<https://doi.org/10.1177/1941738110366385>
PMid:23015939 PMCID:PMC3445108
7. Hall MP, Band PA, Meislin RJ, et al. Platelet-rich plasma: current concepts and application in sports medicine. Journal Am Acad Orthop Surg 2009;**17**(10):602-608.
<https://doi.org/10.5435/00124635-200910000-00002>
8. Dehghan A, Pishgooei N, Salami MA, et al. Comparison between NSAID and intra-articular corticosteroid injection in frozen shoulder of diabetic patients; a randomized clinical trial. Exp Clin Endocrinol Diabetes 2013;**121**(02):75-79.
<https://doi.org/10.1055/s-0032-1333278>
PMid:23426700
9. Alhashimi RAH. Analytical Observational Study of Frozen Shoulder among Patients with Diabetes Mellitus. Joints 2018; **6**:141-144.
<https://doi.org/10.1055/s-0038-1676105>
PMid:30582100 PMCID:PMC6301845
10. Abdel Dayem OT, Saeid MM, Ismail OM, et al. Ultrasound guided stellate ganglion block in postmastectomy pain syndrome: a comparison of ketamine versus morphine as adjuvant to bupivacaine. J Anesthesiol 2014.
<https://doi.org/10.1155/2014/792569>
11. Kulkarni KR, Kadam AI, Namazi IJ. Efficacy of stellate ganglion block with an adjuvant ketamine for peripheral vascular disease of the upper limbs. Indian J Anaesth 2010;**54**(6):546-551.
<https://doi.org/10.4103/0019-5049.72645>
PMid:21224973 PMCID:PMC3016576
12. Welsh WJ. Autologous platelet gel: clinical function and usage in plastic surgery. Cosmet Derm 2000;**11**:13.
13. Sweeny J, Grossman BJ. Blood collection, storage and component preparation methods. Tech Manual 14th ed Bethesda MD Am Assoc Blood Banks 2002;955-958.
14. Peng PWH, Cheng P. Ultrasound-guided interventional procedures in pain medicine: a review of anatomy, sonoanatomy, and procedures. Part III: shoulder. Reg Anesth Pain Med 2011;**36**(6):592-605.
<https://doi.org/10.1097/AAP.0b013e318231e068>
PMid:22005657
15. Hussain N, Johal H, Bhandari M. An evidence-based evaluation on the use of platelet rich plasma in orthopedics--a review of the literature. SICOT-J 2017;**3**:57.
<https://doi.org/10.1051/sicotj/2017036>
PMid:28990574 PMCID:PMC5632954
16. Gautam VK, Verma S, Batra S, et al. Platelet-rich plasma versus corticosteroid injection for recalcitrant lateral epicondylitis: clinical and ultrasonographic evaluation. J Orthop Surg 2015;**23**(1):1-5.
<https://doi.org/10.1177/230949901502300101>
PMid:25920633
17. Aslani H, Nourbakhsh ST, Zafarani Z, et al. Platelet-rich plasma for frozen shoulder: a case report. Arch Bone Jt Surg 2016;**4**(1):90-93.
18. Kothari SY, Srikumar V, Singh N. Comparative Efficacy of Platelet Rich Plasma Injection, Corticosteroid Injection and Ultrasonic Therapy in the Treatment of Periarthritis Shoulder. J Clin diagnostic Res 2017;**11**(5):RC15- RC18.
<https://doi.org/10.7860/JCDR/2017/17060.9895>
PMid:28658861 PMCID:PMC5483763
19. Lin J. Platelet-rich plasma injection in the treatment of frozen shoulder: A randomized controlled trial with 6-month follow-up. Int J Clin Pharmacol Ther 2018; **56**:366-371.
<https://doi.org/10.5414/CP203262>
PMid:29932415
20. Sunder RA, Toshniwal G, Dureja GP. Ketamine as an adjuvant in sympathetic blocks for management of central sensitization following peripheral nerve injury. J Brachial Plex Peripher Nerve Inj 2008;**3**(1):22.
<https://doi.org/10.1186/1749-7221-3-22>
PMid:18950516 PMCID:PMC2584055