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Original Article

Dexmeditomedine versus Clonidine as an adjuvant to Levobupivacaine in Paravertebral analgesia for acute post mastectomy pain

Sahar A. Tawfik, Maha A. Abd Elaleem, Mohamed M. Hassan, Ahmed H. Mohamed, Sally Mostafa Elhamoly*

Department of Anesthesia and Pain Management, National Cancer Institute, Egypt.

Correspondence: Sally Mostafa Elhamoly, Department of Anesthesia and Pain Management, National Cancer Institute, Egypt. E-mail: drsallyhamoly@gmail.com

ABSTRACT

Background: Acute postoperative pain is a problem after radical mastectomy. Treatment of postoperative pain following mastectomy is an area of increasing interest. The objective of our study is to compare the effect of addition of either dexmedetomidine or clonidine to levobupivacaine for prolongation of analgesia time. Methodology: 126 patients were divided randomly by computer randomization into 3 groups 42 patients each. Group L received 20 mL of 0.25% levobupivacaine. Group LD received dexmedetomedine (1mic/kg) added to 20 mL 0.25% levopubivacaine. Group LC received clonidine (1mic/kg) added to 20 mL 0.25% levopubivacaine. These injected into paravertebral space at T3 level under U/S guidance after finishing surgery while patient still under GA. Heart rate, systolic blood pressure, diastolic blood pressure, Ramsey sedation score, modified VAS, analgesia time, and analgesic requirements were followed. Results: There was no difference between dexmedetomedine group and clonidine group) in modified visual analogue score, analgesia time, and analgesic requirements. But there was significant statistical difference between both interactive (dexmedetomedine and clonidine) groups and control group (levobupivacaine). Conclusion: Addition of clonidine and dexmedetomedine to levopubivacaine in TPVB after modified radical mastectomy reduce postoperative pain scores, prolong duration of pain free periods, delay requirement for first rescue analgesia, and decrease analgesic requirement, with no statistical significant difference in analgesic duration between both additives.

Keywords: Thoracic paravertebral block, radical mastectomy, levobupivacaine, dexmedetomedine, clonidine, analgesia time.

Introduction

Breast cancer represents the 2nd cancer in Egypt according to national cancer registry 2014, and most of these women require breast surgery to remove the primary tumor and axillary staging or dissection [1]. One of the potential suggested strategies in treating cancer, has been mixing two antitumor agents in a nanocarrier [2]. Although several non-invasive techniques have been developed for the treatment of various diseases and cancers, surgery is the gold standard option for most of life-threatening diseases [3]. And, generally, pain can be central or peripheral based on which it can be grouped as central neuropathic pain or peripheral neuropathic pain [4]. Post-mastectomy pain syndrome (PMPS) is a common problem, ranging from 25% to 60%. Pain is localized in the axilla, medial upper arm, breast, and/or chest wall and lasting beyond three months after surgery [5]. Treatment of post- operative pain following mastectomy is an area of increasing interest as this treatment option is now considered a standard of care for those affected by breast cancer [6]. Thoracic paravertebral block (TPVB) is the technique of injecting local anesthetic adjacent to the thoracic vertebra close to where the spinal nerves emerge from the intervertebral foraminae. This results in ipsilateral somatic and sympathetic nerve blockade in multiple contiguous thoracic dermatomes above and below the site of injection. It is

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effective in treating acute and chronic pain of unilateral origin [7]. Ultrasound technology has allowed us to broaden the depth of our knowledge of the anatomy of the paravertebral space in addition to enabling us to visualize the anatomic structures, the needle, and the spread of local anesthetic [8].

Methodology

The randomized, prospective, double blinded study conducted from September 2015 till September 2017. In the first settlement hospital over 126 female patients underwent radical mastectomy, met inclusion criteria and informed consent was obtained. 126 patients were divided randomly by computer randomization program into 3 groups 42 patients each. Preoperatively all the patients were visited**,** full history was taken, full general examination and laboratory investigations were done. GA was commenced in all cases with use of fentanyl as intraoperative analgesia. After the end of surgery while a patient was still under GA, she was brought to lateral position, then injectate was deposited into paravertebral space at T3 level under U/S guidance. Group L received 20 mL of 0.25% levobupivacain alone, group LD received dexmedetomedine (1mic/kg) added to 20 mL 0.25% levopubivacaine, and group LC received clonidine (1mic/kg) added to 20 mL 0.25% levopubivacaine. Heart rate, systolic blood Pressure, diastolic blood pressure, Ramsey sedation score, modified VAS, analgesia time, and analgesic requirements were followed.

Goal of the study: To detect benefit of addition of dexmedetomedine and clonidine to levobupivacaine in prolonging duration of postoperative analgesia and reduce analgesic requirements.

Statistical analysis: Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done:

- A one-way analysis of variance (ANOVA) when comparing between more than two means.
- Post Hoc test: Least Significant Difference (LSD) was used for multiple comparisons between different variables.
- Kruskall Wallis test: for multiple-group comparisons in non-parametric data.
- Chi-square (X2) test of significance was used in order to compare proportions between two qualitative parameters.
- Probability (P-value)

P-value <0.05 was considered significant.
P-value <0.001 was considered as highly significant.
P-value >0.05 was considered insignificant.

Results

There was a significant difference between both interactive (dexmedetomedine and clonidine) groups in modified visual Analogue score [table 1], analgesia time, and analgesic requirements [table 2] than control group (levobupivacaine alone). But there were no difference between dexmedetomedine group and clonidine group. Dexmedetomedine group showed more reduction in HR [fig. 1], SBP [fig. 2], DBP and higher sedation score [fig. 3] than clonidine group and levopubivacaine group.

Table 1: Comparison between groups according to modified-VAS.

VAS	Group L (N=42)	Group LC (N=42)	Group LD (N=42)	Kruskall Wallis	p-value
After 1hr.					
Mean±SD	0.00±0.00	0.00±0.00	0.00±0.00	0.000	1.000
Range	0-0	0-0	0-0		
After 2hr.					
Mean±SD	0.00±0.00	0.00±0.00	0.00±0.00	0.000	1.000
Range	0-0	0-0	0-0		
After 3hr.					
Mean±SD	0.05±0.31	0.00±0.00	0.00±0.00	1.000	0.371
Range	0-2	0-0	0-0		
After 4hr.					
Mean±SD	0.14±0.78 [a]	0.76±1.65 [b]	0.00±0.00 [c]	6.196	0.003
Range	0-5	0-5	0-0		
After 5hr.					
Mean±SD	0.07±0.46	0.19±0.59	0.00±0.00	2.056	0.132
Range	0-3	0-2	0-0		
After 6hr.					
Mean±SD	0.10±0.48	0.00±0.00	0.00±0.00	1.624	0.201
Range	0-3	0-0	0-0		
After 12 hr.					
Mean±SD	0.57±0.99 [a]	0.00±0.00 [b]	0.00±0.00 [b]	13.957	<0.001
Range	0-3	0-0	0-0		
After 18 hr.					
Mean±SD	0.05±0.22	0.00±0.00	0.07±0.26	1.457	0.237
Range	0-1	0-0	0-1		
After 24 hr.					
Mean±SD	1.26±1.04[a]	0.00±0.00 [b]	0.00±0.00 [b]	62.153	<0.001
Range	0-3	0-0	0-0		
After 30 hr.					
Mean±SD	0.58± 0.88[a]	0.00±0.00[b]	0.52±1.06[a]	9.454	0.003
Range	0-3	0-0	0-3		
After 36 hr.					
Mean±SD	0.58±0.78	0.48±1.02	0.62±0.99	0.397	0.773
Range	0-3	0-3	0-3		
After 42 hr.					
Mean±SD	0.25±0.42[a]	0.00±0.00[b]	0.24±0.58[a]	6.666	0.014
Range	0-2	0-0	0-2		
After 48 hr.					
Mean±SD	0.17±0.31[a]	0.00±0.00[b]	0.19±0.59[a]	4.014	0.045
Range	0-2	0-0	0-2		
Mean of VAS					
Mean±SD	0.94±0.21 [a]	0.53±0.18 [b]	0.54±0.05 [b]	87.591	<0.001
Range	0.7-1.5	0.36-0.86	0.5-0.64		

(a, b, c) All common characters have no differences
This table shows statistically significant reduction in modified- VAS in intervention groups (dexmedetomedine plus levobupivacaine& clonidine plus levobupivacaine) than control group (levobupivacaine alone) at 4, 12, 24, 30, 42, 48 hours from injection.

Table 2: Comparison between groups according to analgesic requirement

Analgesic Requirement	Group L (N=42)	Group LC (N=42)	Group LD (N=42)	x2	p-value

After 1hr	0 (0.0%)[a]	0 (0.0%)[a]	0 (0.0%)[a]	0.000	1.000
After 2hrs	0 (0.0%)[a]	0 (0.0%)[a]	0 (0.0%)[a]	0.000	1.000
After 3hrs					
Perfalgan 1 gm	2 (4.8%)[a]	0 (0.0%)[a]	0 (0.0%)[a]	4.065	0.131
After 4hrs					
Perfalgan 1 gm	0 (0.0%)[b]	4 (9.5%)[a]	0 (0.0%)[b]	17.085	0.002
Pethidine 50 mg	0 (0.0%)[b]	4 (9.5%)[a]	0 (0.0%)[b]		
After 5hrs					
Perfalgan 1 gm	2 (4.8%)[a]	0 (0.0%)[a]	0 (0.0%)[a]	8.262	0.082
Pethidine 50 mg	2 (4.8%)[a]	0 (0.0%)[a]	0 (0.0%)[a]		
After 6hrs					
Perfalgan 1 gm	2 (4.8%)[a]	0 (0.0%)[a]	0 (0.0%)[a]	4.065	0.131
After 12hrs					
Perfalgan 1 gm	11 (26.2%)[a]	0 (0.0%)[b]	0 (0.0%)[b]	24.104	<0.001
After 18hrs	0 (0.0%)[a]	0 (0.0%)[a]	0 (0.0%)[a]	0.000	1.000
After 24hrs					
Perfalgan 1 gm	17 (40.5%)[a]	0 (0.0%)[b]	3 (7.1%)[b]	29.580	<0.001
2nd 24hrs					
Peffalgan 1g + pthidine 50m	13 (31.0%)[a]	0 (0.0%)[b]	0 (0.0%)[b]		
Prfalgan 2g+ pthidine 50m	4 (9.5%)[a]	0 (0.0%)[b]	0 (0.0%)[b]		
Perfalgan 2 gm	20 (47.6%)[a]	0 (0.0%)[b]	0 (0.0%)[b]	50.785	<0.001
Perfalgan 1 gm	3 (7.1%)[a]	8 (19.0%)[b]	36 (85.7%)[c]		
Perfalgan 3 g	2 (4.8%)[a]	0 (0.0%)[a]	0 (0.0%)[a]		

(a, b, c) All common characters have no differences

This table shows statistically significant reduction in analgesic requirements in intervention groups (dexmedetomedine plus levobupivacaine and clonidine plus levobupivacaine) than control group (levobupivacaine) after 4hrs, 12hrs, 24hrs and 2nd 24hrs.

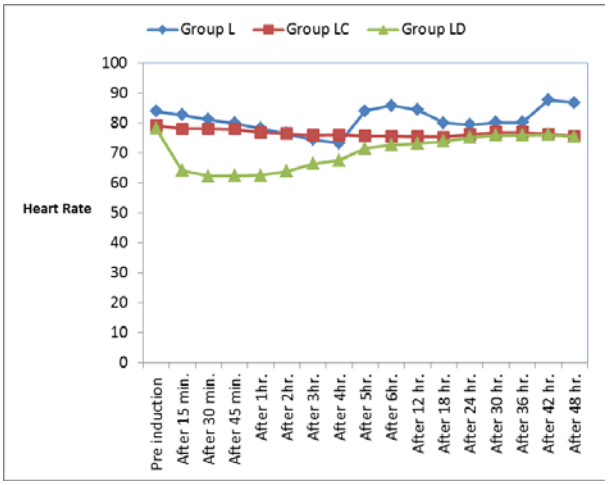

Figure 1: figure shows different results between groups according to heart rate with more reduction in dexmedetomedine than other groups

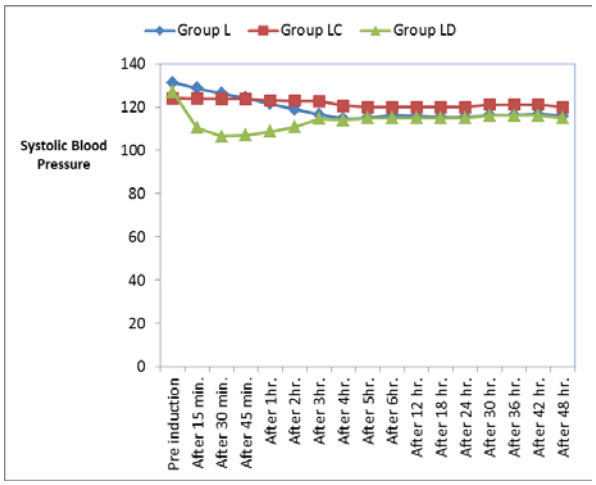

Figure 2: Figure shows different results between groups according to systolic blood pressure with more reduction in dexmedetomedine group

Figure 3: Figure shows different results between groups according to sedation scale with higher scores observed in dexmedetomedine group

Discussion

Breast surgeries done for malignancy are known to be associated with considerable postoperative pain [7]. There has been a growing interest in the use of thoracic paravertebral block (TPVB) to combat this pain, producing an effective block of the pain pathway, characterized by unilateral regional blockade of several dermatomes. Local anesthetic deposited in this space deep to the superior costotransverse ligament and superficial to the pleura can spread multiple levels superior and/or inferior to level of injection. This technique generally results in ipsilateral blockade of somatic and sympathetic nerves [8]. 126 patients participated in this prospective randomized controlled trial, randomly divided into 3 groups, 42 patients each, Group L (control group) that will receive 20 mL levopubivacaine (0.25%) alone. Group LD in which 1 mcg/kg dexmeditomedine will be added to 20 mL levopubivacaine (0.25%). Group LC in which 1mcg/kg clonidine will be added to 20 mL levopubivacaine (0.25%). Our study results revealed no significant statistical difference between all groups regarding demographic data. Group LD showed more reduction in heart rate after 15, 30, 45 minutes, 1, 2, 3, 4, 5, 6 hours from injection (fig 1). Dexmedetomidineacts on α2 receptors in the brain and spinal cord cause inhibition of protein kinase A and

subsequent phosphorylation, activation of potassium channels and hyperpolarization of plasma membrane, inhibition of adenyl cyclase activity, reduction of neuronal firing as well as inhibition of voltage-gated calcium ion channels. Effects in the nucleus tractussolitarius lead to inhibition of sympathetic activity and reduce peripheral vasoconstriction produces hypotension and bradycardia [9]. Clonidine also an (α-2)-adrenoreceptor agonist which produces analgesia by a non-opioid mechanism. It acts through stimulation of pre- and post-synaptic α2 agonists in many areas of the central nervous system leading to sedation, analgesia, and reduction of sympathetic tone it also has been shown to prolong the duration of analgesia when administered in the paravertebral space [10].

Group LD showed higher sedation scale for 1 hour after injection than LC group and group L. There are α2 adrenoceptors in the locus coeruleus in the floor of the fourth ventricle, where α2 agonists act to cause sedation. The locus coeruleus also has afferent connections from the rostral ventrolateral medullary nuclei and efferent connections to noradrenergic fibers connecting to the thalamus and elsewhere [11]. Reduction of modified VAS score values after injection in all groups, with significant reduction of analgesic requirement seen in group LD and group LC than group L, with prolongation of block duration seen in both group LD and group LC extended to 48 hours after injection compared with group L which extended only to 24 hours (P value < 0.001). But there was no difference in pain free period between group LD and group LC.

Conclusion:

Addition of dexmedetomedine and clonidine to levopubivacaine in thoracic paravertebral block reduced pain scale, analgesic requirements and prolonged analgesia time after radical mastectomy.

Conflict of Interest:

The author declared no conflict of interest.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee**.**

Informed consent:

Informed consent was obtained from all individual participants included in the study.

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