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Original Article

Effectiveness of Preoperative Eutectic Mixture of Local Anaesthetic [EMLA] Application and Postoperative Wound Infiltration of Ropivacaine in Patients Undergoing Modified Radical Mastectomy [MRM]: A Randomised Single Blind trial

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Abstract
Aims: *To assess analgesic efficacy of preoperative EMLA cream and postoperative wound infiltration with ropivacaine in modified radical mastectomy.*
Method: *This is a prospective randomised single blind trial done in ASA-PS 1 and 2 for unilateral MRM aged between 18-60 years. 60 patients are randomised into four groups. First group, preoperatively EMLA cream is applied over the incision. In second group, preoperative EMLA cream with postoperative infiltration with ropivacaine. Third group, only postoperative wound infiltration with ropivacaine. In the fourth group no such interventions. All patients are operated under general anaesthesia. Intraoperatively heart rate variability (HRV) and blood pressure variability (BPV) and postoperatively VAS at rest and movement, degree of arm movement, opioid requirement are noted to assess analgesic efficacy. Statistical analyses is performed by using a statistical software package SPSS, version 20.0*
Results: *Time to the initial dose of paracetamol and rescue fentanyl dose requirement is significantly lower in groups 2 and 3. HRV and BPV at the time of incision was more in group 3 and 4, so also the intra-operative analgesia. VAS at rest, at 0 hour, at discharge and drain removal was significantly low with group 2 and 3.Similarly VAS on movement, significantly reduced in group 2 and 3 at the time of discharge and drain removal. There was significant increase in degree of arm movement in group 2 and 3.*
Conclusion: *Our study showed postoperative wound infiltration with ropivacaine provided superior analgesia and preoperative EMLA favourable intraoperative hemodynamics.*
Keywords: *EMLA, Postoperative Wound Infiltration of Ropivacaine.*

Introduction

In 2016, cancer incidence rate in India was 106.6 per 100,000 people while in the state of Kerala it was 135.3 per 100,000 people[1]. The highest number of breast cancer cases in India was detected from the Kerala[1]. Surgical management with or without chemotherapy or radiotherapy is the mainstay of treatment.

Breast cancer surgery is associated with mild to moderate pain, but some procedures including axillary nodes dissection are more painful[2]. In patients undergoing mastectomy with axillary clearance, postoperative pain may prevent mobilisation of the corresponding arm. Studies have shown that intensity of postoperative pain will partly contribute to the development of

chronic pain syndrome[3]. Opioid-based anesthesia is associated with increased nausea and vomiting, respiratory depression, prolonged sedation, urinary retention, ileus, increased postoperative pain (hyperalgesia), tolerance, and chronic pain. The possibility of higher risk of metastasis has also been reported with opioid use[4-9]. In this study we attempt to study the analgesic efficacy preoperative EMLA application and postoperative ropivacaine infiltration and thus reducing the use of opioids.

Effect of preoperative and postoperative application of local anaesthetics in reducing the pain and development of chronic pain syndrome has been studied separately. No such studies are there, within our knowledge, where the combined effect of preoperative and postoperative local anaesthetic effect in mastectomy has been studied. Preoperative local anaesthetic infiltration has disadvantages of invasiveness, risk of seedling the tumour cells whereas application of EMLA cream is devoid of such problems.

Surgical wound infiltration with a local anaesthetic solution is currently performed in many surgical procedures including, abdominal hysterectomy, caesarean section and inguinal hernia repair [10]. Wound infiltration is reported to provide immediate postoperative pain control lasting for several hours[11]. In addition, long term benefits have been suggested such as prevention of chronic pain syndrome after surgery[10]. Ropivacaine, a long-acting amide local anaesthetic, is chemically related to bupivacaine but it has less cardiac and central nervous system toxicity [12]. This drug acts on sodium channels but additionally binds to the internal entrance of the potassium pore and blocks the channel in an open position[13]. Ropivacaine also produces cutaneous vasoconstriction that restricts systemic absorption of the drug and increases its local duration of action[14]. Moreover, ropivacaine possesses anti-inflammatory activity that may further reduce pain when administered locally[15].

The investigators wanted to assess the analgesic effect of combination of preoperative EMLA cream and postoperative wound infiltration with ropivacaine, in terms of intra-operative hemodynamic stability, postoperative pain score, analgesic requirement and degree of arm movement.

Method

This prospective randomised single blind trial is carried out after obtaining Ethical Committee approval in a tertiary care cancer centre from October 2017 to April 2018. American Society of Anaesthesiologists Physical Status 1 and 2, being posted for unilateral modified radical mastectomy aged between 18-60 years are included in our study. Patient receiving opioid or any other analgesic for chronic pain, with history of drug allergy, with acquired or genetic hemostatic abnormality, not able to co-operate with the study, breast lump infiltrating to chest wall or skin are excluded from the study.

A total of 60 patients are randomised into four groups comprising 15 in each using numbers from randomisation table and allocation concealement is made by envelope method. The envelope is opened by the principal investigator.

First group, preoperatively EMLA cream is applied over the incision area one hour before the proposed surgery. The principal investigator apply about 5-10 gm of EMLA cream over the incision marked, as 2 mm thick film and an occlusive dressing is applied over it. In the second group, preoperative EMLA along with postoperative wound infiltration of wound with ropivacaine, 18ml into deeper layers and 2ml along the humoral insertion of pectoralis major. In the third group, at the end of surgery wound is infiltrated with 18 ml 0.5% ropivacaine solution into deeper layers of the wound and 2 ml into the humoral insertion of pectoralis major. In the fourth group no such interventions are made. Solutions are prepared and provided by the anaesthetist in charge of the patient in the operating theatre to the surgeon. All patients are operated by the same surgeon.

Irrespective of the group, all patients are operated under general anaesthesia, using propofol 2.5 mg/kg and fentanyl 1.0 mcg/kg for induction, and sevoflurane 1.0-1.5% and nitrous oxide oxygen mixture for maintenance. Vecuronium 0.8mg/kg is used for orotracheal intubation. Dexamethasone 4 mg is given intravenously after anaesthetic induction for prevention of postoperative nausea and vomiting.

Intraoperatively heart rate variability (HRV) and blood pressure variability (BPV) are assessed. Rise in heart rate(HR) more than ten beats per minute from baseline and rise in systolic blood pressure more than 20 mm of mercury is considered significant. Any significant HRV or BPV is initially managed by titrating the sevoflurane concentration up to 1 MAC (Minimum Albeolar Concentration). If it was not controlled bolus doses of fentanyl 20 microgram are given.

On awakening from anaesthesia, immediately at the end of surgery, patients are transferred to post anaesthesia care unit. Pain score and analgesic requirement are assessed. Time of reporting the first pain is recorded and paracetamol is given thereafter. Static and dynamic pain score are assessed. Pain is managed with injection paracetamol 1gram sixth hourly till oral intake is started. Thereafter oral paracetamol 650 mg is administered sixth hourly for two days. If pain is not controlled by paracetamol 30 microgram of fentanyl is given as rescue analgesic.

Measurements are recorded by the first co-investigator blinded for patient allocation, for pain at rest, pain on movement and degree of maximum abduction of the operated arm. Pain intensity is measured by verbal rating score 0-10. Pain at rest is recorded at 0 hour, 6 hours after the end of surgery, and also before discharge and drain removal. Assessment of pain on movement is performed at 6 hours after the end of surgery, before discharge and drain removal. In our institution, patients are discharged at the first postoperative period and drain removal at third week if there are no complications. The value of

maximum arm abduction angle (MAAA) is noted for each patient. Patient is asked to abduct her arm as much as possible, after making sure that abducted arm is in line with the shoulder and the angle is noted (Fig. 1).

Statistical Analysis

The sample size is calculated based on the decrease in opiod consumption as primary outcome and is calculated as 15 in each group, with 80% power and significance level (alpha) fixed at 5%[16]. The secondary outcomes are the extent of limb movements, decrease in pain score. The categorical variables are summarised by frequency and relative proportion. The continuous variables are summarised using mean and standard deviation. To find the significant difference between the groups, the categorical data (surgery side, adjuvant chemotherapy) is analysed using Chi square test. Comparison of quantitative parameters among groups is carried out using One way ANOVA test (F test) with Scheffe Multiple Comparisons (Post Hoc Test). Kruskal Wallis Test is used to compare the VAS among the group. Value of p less than 0.05 is considered the threshold for statistical significance. Statistical analyses is performed by using the statistical software package SPSS, version 20.0

Results

Background variables like age, weight, body mass index (BMI) were uniformly distributed among the four groups (Table 1). When variables like distribution of comorbidities, site of breast carcinoma and surgery, presence of adjuvant chemotherapy were analysed, they did not show any significant preponderance among the groups (Table 2). Duration of surgery was also uniform among the four groups. HRV and BPV at the time of incision was more in groups 3 and 4 (Table2). Thus intra-operative analgesia requirement was more in those groups at p value of 0.01 level. The significance again confirmed using Scheffe Multiple Comparison, after pairing among the groups.

Table 1 Comparison of background characteristics based on anaesthesia

Characters	Anaesthesia	Mean	SD	N	t	p
Age	EMLA only	52.9	8.9	15	1.19	0.321
	EMLA plus ropivacaine	49.3	9.4	15		
	Ropivacaine only	53.7	6.9	15		
	Control	54.5	7.6	15		
Weight	EMLA only	58.1	11.2	15	1.73	0.172
	EMLA plus ropivacaine	66.7	7.3	15		
	Ropivacaine only	60.7	14.0	15		
	Control	60.1	9.9	15		
BMI	EMLA only	25.2	3.7	15	1.38	0.259
	EMLA plus ropivacaine	27.9	2.7	15		
	Ropivacaine only	26.5	5.3	15		
	Control	25.5	3.7	15		

Table2. Comparison of selected variables based on anaesthesia

Selected variables		Test Groups – no., percentage in brackets				χ^2	p
		EMLA only	EMLA plus ropivacaine	Ropivacaine only	Control		
Diagnosis	Right carcinoma breast	9 (60)	7 (46.7)	7 (46.7)	6 (40)	1.27	0.737
	Left carcinoma breast	6 (40)	8 (53.3)	8 (53.3)	9 (60)		
Surgery	Right MRM	9 (60)	7 (46.7)	7 (46.7)	6 (40)	1.27	0.737
	Left MRM	6 (40)	8 (53.3)	8 (53.3)	9 (60)		
Adjuvant chemotherapy	Yes	5 (33.3)	4 (26.7)	10 (66.7)	7 (46.7)	5.7	0.127
	No	10 (66.7)	11 (73.3)	5 (33.3)	8 (53.3)		
HR variability at the time of incision	Less than 10	14 (93.3)	14 (93.3)	2 (13.3)	4 (26.7)	36.28**	0.000
	10 - 20	0 (0)	1 (6.7)	9 (60)	5 (33.3)		
	20 - 30	1 (6.7)	0 (0)	4 (26.7)	6 (40)		
BP variability at the time of incision	Less than 20	14 (93.3)	14 (93.3)	2 (13.3)	4 (26.7)	36.28**	0.000
	20 - 30	0 (0)	1 (6.7)	9 (60)	5 (33.3)		
	30 - 40	1 (6.7)	0 (0)	4 (26.7)	6 (40)		

**Significant at p value 0.01 level

When VAS at rest analysed using Krusal Wallis Test; VAS at rest, at 0 hour, at discharge and drain removal was significantly low with Group 2 and 3, although no significant reduction of VAS score at 6 hours (Fig 2).

Similarly VAS on movement, when analysed, showed significant reduction in VAS score in group 2 and 3 at the time of discharge and drain removal. Reduction in VAS on movement in them was significant at p value 0.01 during drain removal (Fig 3)

The MAAA analysed using ANOVA test showed significant increase in ease of hand movement with group 1 and 3 at 6 hours. When each groups were analysed separately using Scheffe Multiple comparisons, there was significant increase in degree of arm movement in group 2 and 3 when compared with the group 4 at p value 0.05 level. But they didn't show any significant increase when compared with group 1 (Table 3). When each group analysed using ANOVA test fail to establish any significant increase in arm movement at the time of discharge and drain removal. But when analysed separately using Scheffe Multiple Comparisons, groups 2 and 3 showed significant improvement at p value 0.01 level, when compared with the control group (Table 4, 5).

Table 3 Comparison of time of MAAA at 6 Hrs based on anaesthesia

Anaesthesia	Mean	SD	N	F	p	Scheffe Multiple Comparisons		
						Pair	F`	p
EMLA only	99.7	35.8	15	6.3**	0.001	1 &2	2.23	0.094
EMLA plus ropivacaine	134.3	34.5	15			1 & 3	2.41	0.077
Ropivacaine only	135.7	42.1	15			1 & 4	0.2	0.897
Control	89.3	33.6	15			2 & 3	0	1.000
						2 & 4	3.76*	0.016
						3 & 4	3.99*	0.012

**Significant at p value 0.01 level, *Significant at p value 0.05 level

Table 4. Comparison of MAAA at Discharge based on anaesthesi

Anaesthesia	Mean	SD	N	F	p	Scheffe Comparisons		Multiple
						Pair	F`	p
EMLA only (Group 2)	134.7	43.7	15			1 &2	1.42	0.248
EMLA plus ropivacaine (Group1)	161.7	33.5	15	6.91	< 0.01	1 & 3	1.06	0.375
Ropivacaine only (Group3)	158.0	30.3	15			1 & 4	1.28	0.290
Control (Group 4)	109.0	34.7	15			2 & 3	0.03	0.994
						2 & 4	5.39**	0.003
						3 & 4	4.66**	0.006

**Significant at p value 0.01 level

Table 5 Comparison of MAAA at Drain removal based on anaesthesia

Anaesthesia	Mean	SD	N	F	p	Scheffe Multiple Comparisons		
						Pair	F`	p
EMLA only (Group 2)	161.0	29.5	15			1 &2	1.17	0.331
EMLA plus ropivacaine (Group 1)	177.3	10.3	15	8.48	< 0.01	1& 3	0.74	0.534
Ropivacaine only (Group 3)	174.0	23.2	15			1 & 4	2.38	0.079
Control (Group 4)	137.7	27.8	15			2 & 3	0.05	0.986
						2 & 4	6.87**	0.001
						3 & 4	5.77**	0.002

**Significant at p value 0.01 level

Time to the initial dose of paracetamol is significantly increased with and group 2 and 3. Rescue fentanyl dose requirement is significantly lower in groups 2 and 3 (Table 6).

Table 6 Comparison of rescue fentanyl dose based on anaesthesia

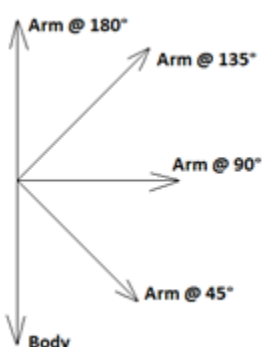| Rescue fentanyl dose	Test Groups – no., percentage in brackets				χ^2	p
	EMLA only	EMLA plus ropivacaine	Ropivacaine only	Control		
No	9 (60)	14 (93.3)	15 (100)	11 (73.3)	10.13	0.017
Yes	6 (40)	1 (6.7)	0 (0)	4 (26.7)		

Fig. 1 Angle of arm abduction
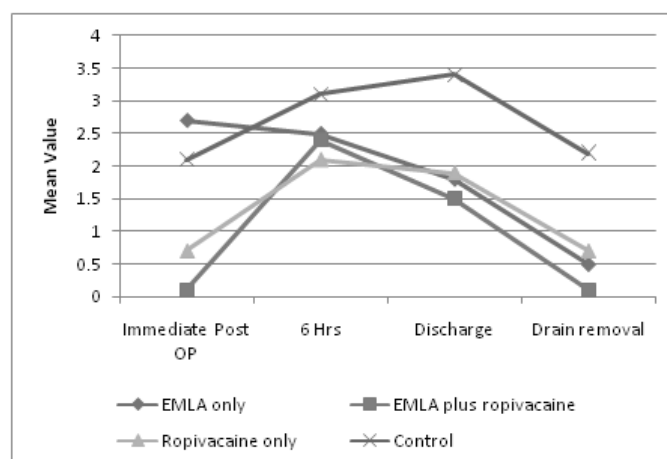

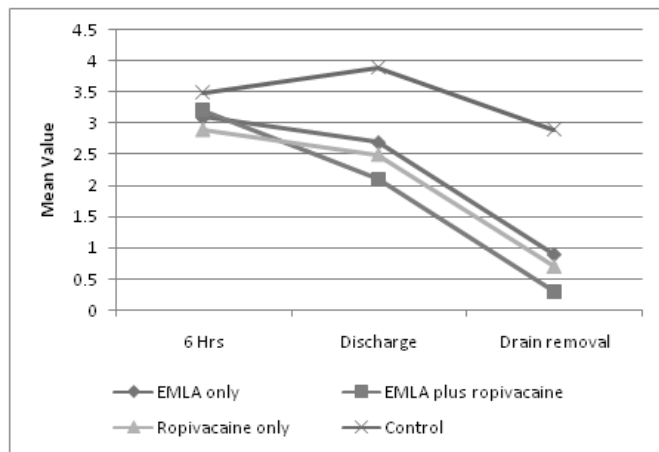**Fig 2**. Comparison of VAS at rest at different interval of time

Fig 3. Comparison of VAS at movement at different interval of time

Discussion

Our study documents significant benefit to postoperative analgesia and postoperative arm movement (ie., MAAA) at the time of discharge and drain removal in patients who had postoperative wound infiltration with ropivacaine (Group 2 and 3). This is in contrast to previous studies. Meta analysis of randomised controlled trials in effect of wound infiltration with ropivacaine or bupivacaine revealed decrease in immediate postoperative pain but no reduction in postoperative pain at 12 hours and 24 hours[17]. Also, another study reported, failed to show any benefit in post-operative arm movement although it had some benefits in postoperative analgesia[18]. This may be because our site of infiltration also included the deltoid insertion site of pectoralis major.

In our study, patients who had preoperative EMLA application showed stable intra-operative hemodynamics which is in accordance with previous studies[19] Stable intraoperative hemodynamics is beneficial to better surgical clearance of the tumor. In a study reported, EMLA was applied preoperatively and postoperatively for four days found that pain was less till fourth day and again less in third month and arm movements were better[20]. But our study fails to prove any absolute benefit in arm movement with application of EMLA, although there was significant improvement in arm movement in groups 2 and 3 when compared with control group using Scheffe Multiple Comparisons (Table 3, 4, 5). This can be attributed to the difference in method of application and absence of postoperative use.

Since postoperative wound infiltration with ropivacaine has significant effect on pain reduction, time of initial dose of paracetamol is significantly increased with group 2 and 3 which means duration of more with them, so also the rescue fentanyl is requirement is less with them.

Conclusion

Our study showed postoperative ropivacaine infiltration over the wound and deltoid insertion of pectoralis major provided superior analgesia and better postoperative arm movement as evidenced by first demand of analgesic and reduced consumption of rescue analgesic. Preoperative application of EMLA cream along the incision site proved no benefit other than stable intraoperative hemodynamics with reduced intra-operative opiod consumption and better intra-operative hemodynamics.

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