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A prospective randomized controlled trial to compare the efficacy of wound instillation with 0.25% bupivacaine, 0.2% ropivacaine and normal saline for postoperative analgesia in breast surgery

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ABSTRACT

Background and Aims: Modified Radical Mastectomy (MRM) is the commonly used surgical procedure for operable breast cancer, which involves extensive tissue dissection. We hypothesized that instillation of 0.25% bupivacaine and 0.2% ropivacaine through chest and axillary drains into the wound may provide postoperative analgesia, even better than infiltration along the line of incision.

Materials and Methods: In this prospective randomized controlled study 68 patients aged more than 18 years were divided into four groups. All patients were administered general anesthesia. At the end of the procedure, axillary and chest drains were placed before closure. Group C was the control group with no instillation, group B received 40 ml 0.25% bupivacaine, group R received 40 ml 0.2% ropivacaine and group S received 40 ml normal saline (20ml through each drain) and the drains were clamped for 10 mins. After extubation, pain score was evaluated using Visual Analogue Scale (VAS) at rest, cough and overhead abduction of the arm at 0,1,2,3,4,8,12 and 24 hours. Rescue analgesia was injection tramadol, given if the pain score ≥ 3. Statistical analysis was performed using SPSS version 21.

Results: There was a significant difference in the cumulative analgesic requirement and the number of analgesic demands between the groups ($p<0.001$). The mean duration of analgesia in the ropivacaine, bupivacaine, saline group and the control group were 10.64 hours, 10.07 hours, 7.49 hours and 2.3 hours respectively.

Conclusion: Wound instillation with local anesthetics is a simple and effective means of providing good analgesia without any major side effects.

1. Introduction

Breast cancer is the most common form of cancer in women and is expected to surpass as the leading cause of cancer death among women in a few years.[1,2] Even though early screening techniques and multimodality treatment has reduced the cancer mortality in western countries; it still continues to have a high prevalence in the developing countries. After diagnostic confirmation, vast majority of breast disease patients undergo definitive surgery like modified radical mastectomy (MRM) or lumpectomy with axillary dissection.

These surgical procedures are routinely performed under general anaesthesia followed by inpatient hospitalization but complications like post operative nausea, vomiting and incisional pain tend to increase the hospital stay, as well as cost.[3,4] Nearly 30-40% patients after breast surgery experience significant acute post operative pain, which reflects inadequacy of conventional pain management.[5] Patient controlled intravenous analgesia with opioids remains a common strategy for management of postoperative pain[6] but its efficacy is suboptimal and adverse effects such as nausea, vomiting and sedation are frequent. Hence, there is a need to search for alternative

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analgesic regimens which may reduce the above mentioned unsought side effects.

With wound infiltration, afferent impulses from the site of injury are reduced, which further reduces the hyperalgesia. Therefore, it causes a decrease in post operative analgesic demand and the VAS scores.

The aim of this study was to assess the role of wound instillation with bupivacaine, ropivacaine and normal saline through surgical drains in alleviating early postoperative pain after MRM. According to a study done previously a prolongation in the duration of analgesia has been noted even with use of saline.[7,8] Therefore, we compared saline with bupivacaine and ropivacaine, and no instillation (as control group).

2. Materials and Methods

After approval from our institutional ethical committee 68 female patients of ASA physical status I or II, aged more than 18 years, scheduled for modified radical mastectomy gave written informed consent to participate in this randomized double-blinded study were included.

Exclusion criteria were patient refusal, age < 18 years, ASA grade> 2, patients with notable respiratory, cardiac, renal, hepatic and neurological disorders, allergy to agent used, coagulation disorders, pregnancy, lactating mothers. Patients with a history of chronic analgesic drug usage (for more than a month) were also excluded from the study. Patient's with major blood loss and excessive blood collection into the drains were eliminated following recruitment.

Sample size was calculated at 80% study power and α error 0.05 assuming a 25% decrease in the postoperative analgesic requirements to be relevant. Thus sample size obtained was 17 patients in each group. Patients were randomized by an opaque sealed envelope into Group C (Control) with no drug instillation, Group B (0.25% bupivacaine), Group R (0.2% ropivacaine) and Group S (Saline). The patients were thoroughly explained about the use of visual analogue scale and on demand analgesia for post-operative pain. Patients were advised pre-operative fasting for a period of 8 hours and were premedicated with tab. midazolam 7.5mg on night before the surgery.

On arrival to the operating room, the patients were examined to confirm the findings of pre-anaesthetic checkup and enquired about the fasting status. Standard monitoring was applied for heart rate, non invasive blood pressure, pulse oximetry, ECG. Pre-anaesthetic medication consisting of glycopyrrolate (0.2 mg), ondansetron (4 mg) and fentanyl (2μg/kg) was administered. After pre-oxygenation general anaesthesia was induced by propofol (2-3 mg/kg) and vecuronium bromide (0.1mg/kg) intravenously. Three minutes after vecuronium administration, a Endotracheal tube (size 7-8) was inserted and patient ventilated with 100% oxygen through Bain's circuit. Anaesthesia was maintained with isoflurane (0.8-1.2%) titrated to signs of an adequate depth of anaesthesia. At the end of the surgical procedure two drains, one in the axilla and the second in the chest wall below the skin flap (over the pectoral muscles) were placed by the surgeon before closing the incision (Figure 1).

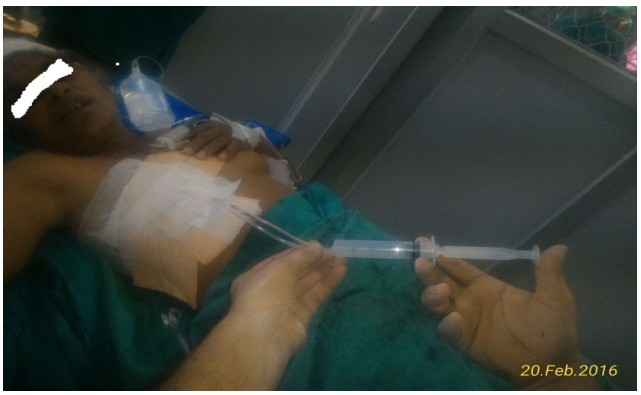

Fig. 1:

Patients were randomly allocated to four groups of 17 each. The study drug was given through each drain as per randomisation after the incision was closed.

Group C (Control group) patients received no instillation

Group B (Bupivacaine group) - 40 ml of 0.25% Bupivacaine

Group R (Ropivacaine group) - 40 ml of 0.2% Ropivacaine

Group S (Saline group) - 40 ml of normal saline

(Instillation was 20 ml through each of the drain in all groups)

After instillation of the study drug the drains were clamped for a period of 10 minutes; after which the test solution was allowed into the negative pressure suction drain. Endotracheal tube was removed upon meeting the criteria for extubation and after reversal of residual neuromuscular blockade with neostigmine 2.5mg and glycopyrrolate (Subsequently, patients were transferred to the ward for further monitoring.

The primary outcome of our study was the accumulative consumption of intravenous tramadol over 24 hours in all groups. Pain score was measured using a 10 points (0-10) Visual Analogue Scale (VAS), where 0 = no pain and 10 = worst pain imaginable. The VAS was recorded on rest (R), cough(C), movement (M-overhead abduction of arm) at 0, 1, 2, 3, 4, 8, 12 and 24 hours postoperatively (0 hours - the time when patient shifted from operation theatre to ward). Time for first rescue analgesic (tramadol 100mg intravenously) was noted, which was given whenever VAS $\geq$ 3 or on patient's own demand. The duration of analgesia was defined from the time of instillation of the study drug to the time when the first dose of rescue analgesic was administered. After that patient received tramadol whenever

VAS > 3 or on demand, the number of demands and the total cumulative analgesic requirement was also noted for 24hrs. Surgical site related untoward effects like wound dehiscence, hematoma, infection, delayed wound healing etc were observed clinically till the patient was discharged. Observer's Assessment of Alertness and Sedation (OAA/S) score[9] was used to assess the level of postoperative alertness and sedation. Patient satisfaction score was recorded 24 hours after the operation as 'very satisfactory', 'satisfactory' or 'unsatisfactory'.

Statistical data was analyzed by using MS excel, Epi Info 6 and SPSS version 21. Quantitative data is represented as arithmetic mean ± standard deviation and analyzed by using Student t- test or ANOVA as per need. Qualitative data is represented as number (proportion or %) and analyzed with chi square test. P<0.05 is considered statistically significant.

3. Results

The four groups were comparable with respect to demographic data as well as duration of surgery (Table 1). The mean duration of analgesia was 2.30±1.42, 10.07±2.97, 10.64±2.25 and 7.49±1.84 hours of the groups C, B, R and S respectively. Statistically, there was highly significant difference (<0.001) in the duration of analgesia in between the four groups except B/R (p value 0.53). The groups B and R were comparable with respect to the duration of analgesia.

The mean rescue analgesic dose requirement at 24 hours post-operatively was 282.35±30.30, 141.18±49.22, 135.29±49.26 and 200±70.71 mg in the groups C, B, R and S respectively. Statistically, there was highly significant difference in the total rescue analgesic (tramadol) requirement in between the four groups (<0.01) except B/R (p value 0.73). The groups B and R were comparable with respect to the total rescue analgesic requirement. Total number of doses of rescue analgesic varied significantly in the four groups (p<0.001). All the groups required tramadol for postoperative pain relief; pain was highest in control group as 14 out of 17 patients asked for three doses of tramadol (100 mg given every time), whereas four patients in the saline group and none of the patients in the other two groups had such demands. There were no wound haematomas, infection or delayed wound healing in any of the patients.

Overall, the mean VAS scores of the groups receiving bupivacaine and ropivacaine were significantly lower than the control group as well as saline group, at all times (Fig 2). This signifies that the patients in these two groups experienced better postoperative analgesia. The following are the mean VAS scores of the groups C, S, B and R respectively:

1. 2.17±1.21 > 1.32±0.95 > 0.97±0.77 > 0.85±0.73 (at rest).
2. 2.49±1.35 > 1.71±0.88 > 1.36±0.90 > 1.23±0.76 (on cough).
3. 2.79±1.32 > 2.11±0.88 > 1.63±0.93 > 1.54±0.82 (on movement).

4. Discussion

In this prospective randomised controlled study, the results unveiled that patients who received instillation with 0.25% bupivacaine and 0.2% ropivacaine through surgical drains following the procedure encountered better postoperative analgesia in contrast to patients who received saline and the control group. Cumulative rescue analgesic consumption and number of demands for analgesia in the first 24 hours were significantly lower in the bupivacaine and ropivacaine groups compared to the other two groups (P < 0.001).

Wound infiltration is found to be efficient in various surgical sub disciplines as a part of multimodal pain management. This technique resulted from the consideration that patients whose surgical procedures were performed under regional anaesthesia techniques have lower postoperative analgesic consumption. Infiltration in the pain sensitive planes reduces the transmission of afferent impulses from the site of injury. Blockade of the nociceptive input into central nervous system reduces the development of central hyperexcitability resulting in less pain and analgesic requirements. They also interfere with local inflammatory mechanisms at the site of injury. In a Randomised Controlled Trial of 38 healthy women undergoing caesarean section,[10] subcutaneous wound infusion of bupivacaine 0.5% was compared with normal saline and wound exudate was sampled through a drain at different time intervals for 24 hours. Significant reductions in levels of interleukin 10 and increases of substance P was observed in wounds in the bupivacaine group when compared to the saline group.

There are various benefits with the use of this technique: the hazards associated with parenteral administration of analgesics, with central neuraxial block and nerve blocks are escaped. As a part of multimodal technique, there can be a reduction in the intake of opioids. It is technically easier, cost-effective and also requires no follow ups like catheter removal. Non-analgesic beneficial effects of wound instillation include their bacteriostatic and bactericidal actions[11] along with apoptosis of the breast tumour cells.[12]

Newer drugs with lower potential for systemic toxicity and longer duration of action like ropivacaine provide additional depth to local infiltration techniques. The duration of analgesia of group receiving ropivacaine was slightly more than that of bupivacaine, though it was not significant. This could be attributed to the fact that ropivacaine has been found to have dose-dependent vasoconstrictive activity[13] which increases its duration of action, especially after local infiltration. Other agents that can be efficiently used with local anaestheics

Table 1: Patient characteristics & observations

Variables and Parameters	Group C (n=17)	Group B (n=17)	Group R (n=17)	Group S (n=17)	P value
Age (years)	53.82±11.54	50.88±10.62	45.88±12.13	50.06±11.84	0.25
Weight (kg)	60.47±5.81	61.82±8.03	60.06±6.28	60.12±5.42	0.62
Pre-op fentanyl (μg)	120.59±11.44	122.94±15.63	119.41±13.45	120.00±10.00	0.86
Duration of surgery (mins)	88.82±12.69	86.18±11.82	87.94±12.13	87.35±11.87	0.93
Duration of analgesia (hours)	2.30±1.42	10.07±2.97	10.64±2.25	7.49±1.84	<0.001
Rescue analgesic requirements in 24 hours (in mg)	282.35±39.30	141.18±49.22	135.29±49.26	200 ±70.71	<0.001
Number of demands in 24 hours	2.82±0.39	1.41±0.49	1.35±0.49	2.00±0.71	<0.001

Data are given as mean±SD, Test applied : ANOVA, n : number of patients

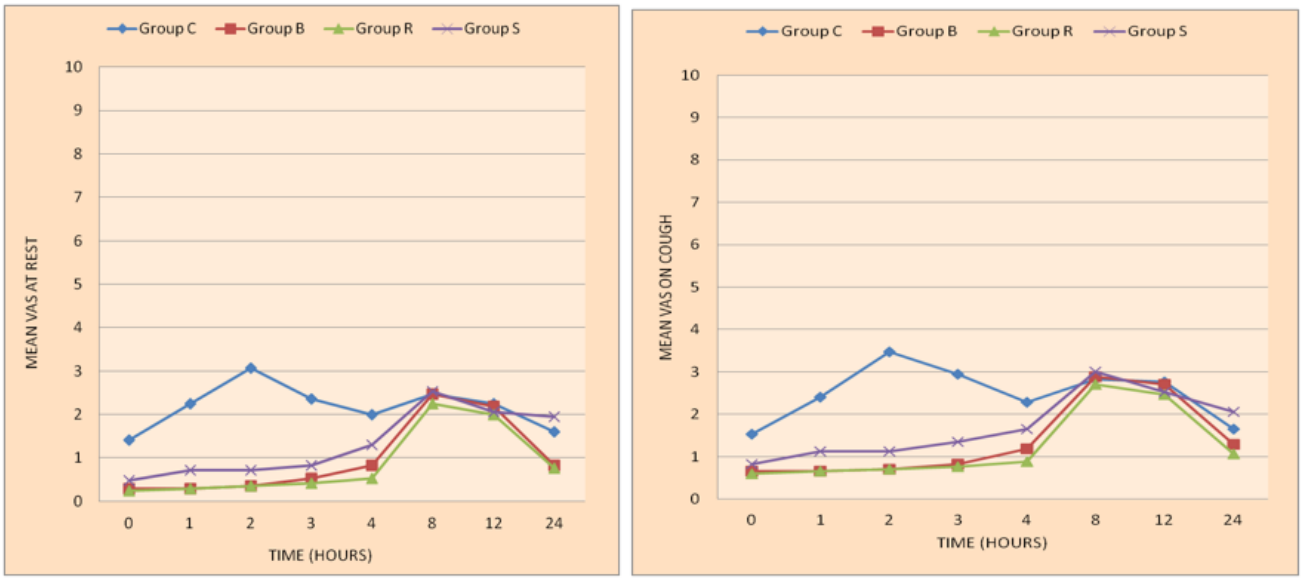

Fig. 2: Comparison of VAS on rest, cough and movement measured postoperatively, at varied time intervals in between the group

are epinephrine, ketorolac and NSAIDS,[14,15] tramadol, dexmedetomidine[16] etc.

Fayman M et al.[17] conducted a comparative analysis of bupivacaine and ropivacaine for infiltration analgesia for bilateral breast surgery and concluded that the duration of analgesia of both the groups was similar and somewhere between 6 and 10 hours postoperatively. Similarly, Rakesh Babu et al.[18] also noted that both bupivacaine 0.25% and ropivacaine 0.20% were equally effective for intraperitoneal instillation at the end of laparoscopic cholecystectomy for post operative pain relief which lasted upto 12 hours. The above two studies inferred that the analgesic efficacy of both the drugs is comparable; but as with this technique large volumes of local anesthetic drug is used, it is therefore advisable to use a drug with lower toxicity and greater safety profile.

Nirmala Jonnavithula et al.[19] found the mean duration of analgesia in the bupivacaine group (B) was 14.6 h, 10.3 hours in the saline group (S) and 4.3 hours in the control group (C). There was a significant difference between Group C and Group B ($P < 0.0001$). The analgesia with saline was variable and there was no difference in the duration of analgesia, when compared to Group C ($P = 0.059$) or Group B ($P = 0.266$). The total rescue analgesic requirement and number of rescue analgesic demands were higher in Group C in comparision to Group B and Group S but there was no significant difference between Group B and S. The probable explanation for the analgesic action of saline was attributed to the mechanical pressure exerted on the nerve to stimulate the fast conducting type A fibres which causes pain inhibition. This is the same principle on which acupuncture and TENS work.[7,19] There was nerve capsule distension rather than blockade

of autonomic nerves. As nerve capsule distension is not the only factor and analgesia was also required, therefore, the efficacy of saline was less than local anesthetics. This theory was also confirmed by M Amirian and colleagues[20] who found that normal saline is as effective as lidocaine 1% in low pain in curettage; but when pain intensity increased lidocaine becomes much more effective. Another probable mechanism of the action of saline could be that it washes away or dilutes the pain producing substances, and the inflammatory mediators thereby decreasing the postoperative pain.

There were two studies done previously which were contrary to our study. These two studies have also provided reasons for failure. The first was done by Fredman et al.[21] in 2001 and the second by Talbot et al.[22] in 2004. Both of them found that repeated wound instillation of bupivacaine solution did not decrease postoperative pain or opioid requirements. Here the authors opined that the lack of uniform distribution or rather spread of the drug was unpredictable, and also the dose of the local anaesthetic was insufficient. This could be because of malpositioned drain, blockade of some holes of the drain or unequal distribution of the local anaesthetic due to gravity, and concluded that further refinement in the technique was needed. To overcome this problem, in our study we have instilled the drug through both - the chest wall and axillary drains. This resulted in more uniform distribution of the drug improving the efficacy of the technique.

5. Conclusion

Wound instillation with local anaesthetics is a non invasive, simple, effective, inexpensive means of providing adequate analgesia for patients following the MRM procedure without any major side effects. Local anaesthetics are generally well tolerated, provided they are used correctly and in the correct doses. We used bupivacaine 0.25% and ropivacaine 0.20% and found that both are equally effective for wound instillation at the end of Modified Radical Mastectomy for post operative pain relief upto 10 hours. Duration of analgesia was also found to be higher in the group receiving saline compared to the control group. The VAS scores of groups B, R and S were noted to be lower than the control group. This was explained by pressure exerted over the nerve endings by saline, blocking the conduction of nerve impulses. There is also dilution of the pain producing substances and inflammatory mediators producing pain. There was a decrease in the total 24 hour analgesic requirements and the number of demands by the patient for analgesic drug in the groups B, R and S. Ropivacaine 0.20% is an equally effective alternative for bupivacaine 0.25% with the added advantage of cardiovascular safety. This technique of wound instillation for providing postoperative analgesia should be included in the armamentarium of multimodal analgesia.

6. Source of Funding

None.

7. Conflict of Interest

None.

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