ORIGINAL ARTICLE

A randomized, placebo-controlled, double-blind study of the analgesic efficacy of extraperitoneal wound instillation of bupivacaine and morphine in abdominal surgeries

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ABSTRACT

Background: The use of opioid for blockage of peripheral receptors has been used previously in many surgical settings but with a variable response. However, the use of morphine for extraperitoneal instillation after abdominal surgery has not been studied. We designed this study to evaluate the analgesic efficacy of extraperitoneal wound instillation of bupivacaine and morphine in abdominal surgeries. We also evaluated whether using this combination could lead to improvement of the respiratory functions.

Methodology: After ethical committee clearance, this prospective, randomized, placebo-controlled, double blind study was carried out in sixty patients of age group 18-65 years, undergoing abdominal surgery and specifically requiring midline incision. In the operating room, a standardized technique of general anesthesia was followed. At the end of the surgery a multiport Romovac® suction catheter (Romsons Group of Companies India) was placed along the length of the wound between the peritoneal layer and muscle layers and led out through a separate stab wound. The patients were then randomized into three groups: Group C (n-20): Wound perfused with normal saline; Group B (n-20): Wound perfused with 0.5% bupivacaine; Group BM (n-20): Wound perfused with 0.5% bupivacaine along plus morphine (0.05 mg/kg). 15 ml of solution was given as slow bolus over 2-3 minutes via the catheter. Rescue analgesia was provided with intravenous tramadol (50 mg) if VAS score $>$ 30 mm. The VAS score at rest and on coughing was noted at 1, 3, 6, 9, 12, 24 hours. Time to demand the first rescue analgesia was recorded. Vital signs, peak expiratory flow rate and inspiratory flow rate were also recorded at 1, 3, 6, 9, 12 and 24 hour after operation.

Results: The demographic profile, type of surgery, duration of surgery were comparable among the three groups ($p > 0.05$). The peak expiratory flow rate was maximum at any point of time in Group BM as compared to Group C and B (p value < 0.05). But inspiratory flow rate with respect to time was almost same in the three groups (p value > 0.05). The VAS scores (on rest and cough) were significantly lower at all time intervals in Group BM as compared to Group B and C (p value (0.001). The first rescue analgesia was demanded at 1.25 ± 0.3 hours in Group C as compared to 3.68 ± 0.71 hours in Group B and 10.7 ± 4.1 hours in Group BM (p value 0.001).

Conclusion: We observed from our study that wound perfusion with 0.5% bupivacaine and morphine combination reduces pain and thus the need of rescue analgesia. The combination was also associated with significant improvement in lung functions postoperatively without any additional side effects.

Key words: Extra peritoneal perfusion; Bupivacaine; Morphine; Postoperative analgesia

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INTRODUCTION

Abdominal surgeries are usually associated with respiratory complications due to inadequate breathing if pain is not adequately controlled. Systemic opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), epidural block and peripheral nerve block are the commonly utilized techniques for postoperative pain relief, but none has been proven to be technique of choice and every technique has at least some known side effects and associated limitations. The presence of peripheral opioid receptors that mediate analgesia by endogenous as well as exogenous opioid agonists has been reported in literature.[1] It is being speculated that blockage of such peripheral receptors should lead to better and long lasting analgesia with avoidance of associated side effects like respiratory depression, nausea, vomiting and pruritis.[1] The use of opioid for blockage of peripheral receptors has been used in previous various surgical settings but with a variable response.[2-7] The use of morphine for installation extraperitoneally after abdominal surgery has not been studied.

The present prospective randomized study was therefore designed to evaluate the analgesic efficacy of extraperitoneal wound instillation of bupivacaine and morphine in abdominal surgeries. We also evaluated whether using this combination of drugs for enhancing the quality of analgesia could lead to improvement of the respiratory functions.

METHODOLOGY

After institutional ethical committee clearance, this prospective, randomized, placebo-controlled, double blind study was carried out at Department of Anesthesiology, SCB Medical College Hospital, Cuttack, Orissa, India. Sixty patients of age group 18-65 years, American Society of Anesthesiologists physical status I and II, undergoing abdominal surgeries requiring vertical midline incision were enrolled in the study. After explaining the study procedure, written informed consent was taken from all of the patients. Patients with a history of clinically significant cardiovascular, pulmonary, hepatic, renal, neurologic, psychiatric, or metabolic disease were excluded from the study. Patients with known allergy to local anesthetics, patients on analgesics and candidates for surgery involving possible wound contamination were also excluded. After thorough preoperative examination, use of visual analogue scale (VAS) was explained to all patients. Premedication with oral diazepam (10 mg) and ranitidine (150 mg) was ordered the night before and one hour prior to surgery.

In the operating room, routine monitors including electrocardiogram, pulse oximeter, non invasive blood pressure were attached and baseline vitals were noted. After securing intravenous access, general anesthesia was induced with fentanyl (2μg/kg), propofol (2.5 mg/kg) and vecuronium bromide (0.1 mg/kg); airway was secured with suitable size endotracheal tube. After the induction of anesthesia, end-tidal CO_2 concentration and temperature were monitored and the urinary bladder catheterized. Anesthesia was maintained with isoflurane in oxygen and nitrous oxide (50:50) (MAC 1) and vecuronium boluses, whenever required. Intraoperative analgesia was provided with boluses of intravenous fentanyl (0.5μg/kg). At the end of the surgery a multipore Romovac® suction catheter (Romsons Group of Companies India) was placed along the length of the wound between the peritoneal layer and muscle layers and led out through a separate stab wound. The tube was then connected to bacterial filter. After closing the wound no topical antiseptic or antibiotic preparation were applied. The patients were then randomized in three groups by a computer generated random number table;

Group C (n-20): Wound perfused with normal saline

Group B (n-20): Wound perfused with 0.5% bupivacaine

Group BM (n-20): Wound perfused with 0.5% bupivacaine along with morphine (0.05 mg/kg).

15 ml of solution according to group allocated was prepared by an independent anesthesiologist not involved in patient observation. The solution was given as a slow bolus over 2-3 minutes via the catheter. After the surgery residual neuromuscular blockade was antagonized by neostigmine and glycopyrrolate. Postoperatively, repeat bolus of 15 ml of the same solution according to the group allocated was repeated after 12 hours of first dose. Rescue analgesia was provided with intravenous tramadol (50 mg bolus) if VAS score $>$ 30 mm. The VAS score on rest and on coughing was noted at 1, 3, 6, 9, 12, 24 hours. Time to demand of first rescue analgesia was recorded. Vital signs, peak expiratory flow rate, inspiratory flow rate were also recorded at the same time intervals after the operation. This was accomplished with a Wright's Spirometer and Mini Wright peak expiratory flow meter and recorded as an average of best of three readings with the patient in semi-recumbent position. Any adverse effect was noted.

Statistical Analysis: The sample size was calculated on the basis of assuming a difference of VAS of 20 mm in the combination group of bupivacaine and morphine as compared to bupivacaine alone. Data are expressed as numbers, percentages, median or mean$\pm$SD. Demographic and anesthetic data, as well as doses of

drugs administered were analyzed and compared by using Student's *t*-test. The number of patients receiving rescue tramadol as well as the incidence of nausea, vomiting, dizziness, drowsiness, and fever, was analyzed by using Fisher's exact test. Patient-generated VAS was analyzed with the Mann-Whitney *U*-test. In all cases, $P < 0.05$ was considered to be statistically significant.

RESULTS

The demographic profile, ASA physical status, type of surgery and duration of surgery were comparable among the three groups ($p > 0.05$) (Table 1).

The peak expiratory flow rate was maximum at any point of time in Group BM as compared to Group C and group B showing the improved lung functions (p value < 0.05) (Table 2). But inspiratory flow rate with respect to time was almost same in the three groups (p value > 0.05) (Table 3).

The VAS scores (on rest and on coughing) were significantly lower at all time intervals (1, 3, 6, 9, 12, 24 hours) in Group BM as compared to Group B and Group C (p value (0.001) (Figure 1, 2). The first rescue analgesia was demanded at 1.25± 0.3 hours in Group C as compared to 3.68± 0.71 hours in Group B and 10.7±4.1 hours in Group BM (p value 0.001).

At 24 h after surgery, the incidence of fever, nausea, and sleepiness was similar between the groups (p value > 0.05). No wound infection, impaired wound healing, drug toxicity was observed in any of the patients in any groups.

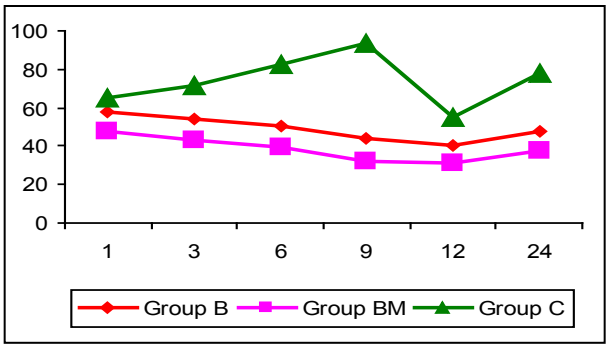

Figure 1: VAS at rest

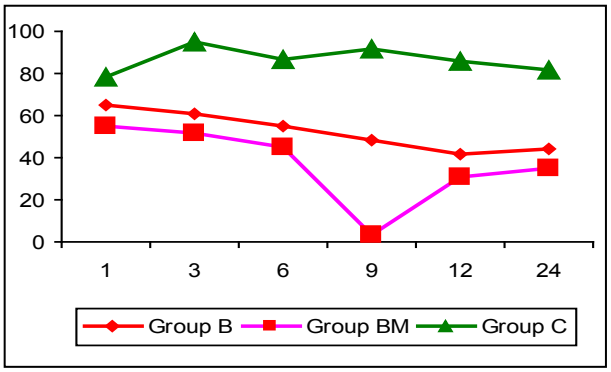

Figure 2: VAS on coughing

DISCUSSION

We observed from our study that wound perfusion with 0.5% bupivacaine and morphine combination reduces pain and thus the need of rescue analgesia.

Table 1: Demographic profile in the three groups

Parameters	Group C (n-20)	Group B (n-20)	Group BM (n-20)	P value
Age, (Mean ± SD) (Years)	52.5±12.7	56.5±11.3	55.0±13.0	0.61
Sex (M:F) (n)	6:14	7:13	6:14	0.91
Weight (Kg)	51.3±12.5	50.4±10.5	51±12.2	0.59

Table 2: PEFR (L/min) in the three groups

Group	Pre-op	Post-op (hrs) (% of the pre-op reading)					
		1	3	6	9	12	24
C	320	37.2	39.3	45.8	49.2	53	51
B	300	40.8	51.2	52.3	54.7	58	56
BM	330	40.2	54	55.8	59.3	59	58

Table 3: Inspiratory flow rate (ml/min) in the three groups

Group	Pre-op	Post-op (hrs) (% of the pre-op reading)					
		1	3	6	9	12	24
C	1200	50	50	54	58	63	61
B	1200	52	52	58	59	62	61
BM	1200	54	54	58	60	64	62

The combination was also significantly associated with improved lung functions post operatively without any additional side effects.

Now-a-days patients' do demand for adequate intraoperative as well as postoperative pain relief. This requirement has forced anesthesiologists to extend the adequate pain free period well beyond the surgery itself, by adopting a combination of methods but also researchers paying more attention towards this field.

Even today opioids remain the preferred analgesics for post-operative pain management and morphine is still the gold standard even though it carries several side effects through its centrally mediated action. It has been reported that the opioids (e.g. morphine) have several peripheral actions in addition to their central action at brain and spinal cord.[8,9] These peripheral opioid actions on corresponding receptors are without significant central side effects; so we planned this study to evaluate the effect of morphine on peripheral receptors and thus its impact on analgesia and the lung functions. Local tissue infiltration of local anesthetics with or without opioids is a reliable and time-honored postoperative pain relief technique. Extraperitoneal instillation of local anesthetics is also a useful, simple and safe technique for postoperative pain relief.

There are several clinical studies published regarding the analgesic properties of peripheral use of opioids and numerous mechanisms have been established for this action through peripheral receptors. Because of changes in the calcium current in the neurons due to presence of opioids, there is a decrease in neurotransmitter release as well as the calcium dependent release of excitatory inflammatory compounds like substance P, thereby enhancing the anti-inflammatory and analgesic properties.

Inflammation enhances the anti-nociceptive effects of opioids in the following ways; first, presence of inflammation disrupts the perineurium (normally an impermeable membrane) facilitating the entry of mediators e.g. corticotrophin releasing hormones, interleukin 1B and other related cytokines.[8] These in turn stimulate the release of opioid peptides from immune cells leading to activation of opioid receptors. Secondly, inflammations not only activate the previously inactive opioid receptors but also enhance the receptor up-regulation (increase in their number in peripheral nerve terminals) leading to potentiation of analgesic properties of opioids.[9] By the concomitant infiltration of local anesthetics the anti-nociceptive actions of peripheral opioids increase further, by increasing perineural permeability. The analgesic effect of extraperitoneal infiltration of morphine and bupivacaine in the nociceptive pathways in the nerve axon works in the same way as explained above. Adverse effect related to toxicity, local infection, impaired would healing[2] were not encountered in our study. However, because of the short duration of action associated with local anesthetic drugs, the need for repeated drug administration constitutes a major limitation for their widespread use. So we planned to insert the catheter for repeat administration of the drugs to provide analgesia.

Various opioids including pethidine, morphine and fentanyl have been used earlier at the peripheral tissues to study its effects with variable results.[11-13] When morphine was evaluated for analgesia, it was injected at the abdominal incision after hysterectomy, no improved pain relief was observed.[7] The probable reason mentioned by authors included the response of this technique on visceral pain was not optimal. Also local release of histamine by morphine could activate nociceptors and release of substance P and bradykinin. In our study, addition of morphine may have led to beneficial effect and thus an improved analgesia, similar results were noted by a study carried out by Tanu et al,[3] where the addition of opioids to bupivacaine improved analgesic efficacy. However, in an another study when morphine was added to local anesthetics for sub mucosal infiltration in dental surgery, improved postoperative analgesia lasting for up to 24 hours was noted.[5] Also, the use of combination of lignocaine and fentanyl has been found to be effective in improving analgesia after wound infiltration in patient undergoing cholecystectomy.[1] It has also been observed that bupivacaine wound instillation decreases opioid requirements after total abdominal hysterectomy and bilateral salpingo-oophorectomy.[14,15]

The improved analgesia in our study by the use of morphine and bupivacaine combination includes two components of somatic pain and visceral pain. Somatic pain is attenuated by the combined effect of opioid and local anaesthetics. Local anesthetics modulate peripheral pain transduction by inhibiting the transmission of noxious impulses from the site of injury[15] the visceral pain was controlled by the combined effect of local anesthetics and opioid. Probably, the systemic absorption of local anesthetic drugs may induce a systemic analgesic effect which has been earlier observed that when administered systemically to the decerebrated animals, local anesthetics decrease dorsal horn neuronal excitability.[4-7,9] Also, repeated local anesthetic wound instillation decreases injury-induced C-fiber activity with consequent attenuation of peripheral and central sensitization.[16] Many studies failed to show any beneficial effects of extraperitoneal infiltration of bupivacaine alone, but almost all of these studies were carried on in laparoscopic hernia repair patients.[17-19] This is in contrast to our study in which some benefit of bupivacaine was seen as the first rescue analgesia was demanded much

earlier in Group C as compared to in Group B (1.25± 0.3 vs. 3.68± 0.71 hours). The time to first rescue was significantly delayed in the combination group as compared to the control as well as the bupivacaine group.

At times pain in between usual narcotic supplementation and spasm of abdominal musculature leads to impairment of lung function. To some extent peritoneal irritation leads to spasm and decrease excursion of the diaphragm also contribute to decreased lung function. To counteract such episodes, local perfusion with anesthetic agents appears to be a better option. Also, with the wound perfusion the possibility of motor blockade is better avoided as seen with extradural blockade.

The peak expiratory flow rate was improved in patients receiving the combination of morphine and bupivacaine. Though the inspiratory flow rate was not changed in the three groups but it did not showed a fall because of the use of local anesthetics agent. It has been reported earlier that patients receiving wound infiltration with the fentanyl and lignocaine after cholecystectomy have better pulmonary functions.[1]

In our study wound perfusion with local anesthetics have not affected anyway the process of healing of wound and no complications related to our technique were observed.

Our study sample was quite small and perhaps studies with a larger sample size would be more suitable to confirm or reject our results.

CONCLUSION

To conclude, extraperitoneal instillation of 15 ml of solution of morphine (0.05 mg/kg) and 0.5% bupivacaine after abdominal surgeries requiring midline abdominal incision leads to a better pain relief and prolonged duration of analgesia without any additional side effects. The lung functions are also better preserved after infiltration with this combination.

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