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**Original Research Article**

# "EFFECT OF PORT SITEOXYTOCIN INFILTRATION ON POSTOPERATIVE PAIN IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERY UNDER GENERAL ANESTHESIA: A RANDOMIZED CONTROLLED STUDY"

**Dr. DEEPAK VIJAYKUMAR KADLIMATTI[1], *Dr. V PRAVEEN KUMAR[2], Dr. SANTOSH KUMAR[3], Dr. MANJUNATH M H[4], Dr. VINUTHA PATIL C N[5], HARSOOR S S[6]**

**1. ASSITANT PROFESSSOR, DEPARTMENT OF ANAESTHESIOLOGY, DR. B R AMBEDKAR MEDICAL COLLEGE & HOSPITAL, K G HALLI, BANGALORE, KARNATAKA, INDIA.**

**2. ASSITANT PROFESSSOR, DEPARTMENT OF ANAESTHESIOLOGY, MALLA REDDY INSTITUTE OF MEDICAL SCIENCES, SURARAM 'X' ROADS, JEEDIMETLA, QUTHBULLAPUR, HYDERABAD, TELANGANA – 500055.**

**3. ASSOCIATE PROFESSOR, DEPARTMENT OF ANAESTHESIOLOGY, DR. B R AMBEDKAR MEDICAL COLLEGE & HOSPITAL, K G HALLI, BANGALORE, KARNATAKA, INDIA.**

**4. 5.POST GRADUATE, DEPARTMENT OF ANAESTHESIOLOGY, DR. B R AMBEDKAR MEDICAL COLLEGE & HOSPITAL, K G HALLI, BANGALORE, KARNATAKA, INDIA.**

**6. PROFESSOR & HOD, DEPARTMENT OF ANAESTHESIOLOGY, DR. B R AMBEDKAR MEDICAL COLLEGE & HOSPITAL, K G HALLI, BANGALORE, KARNATAKA, INDIA.**

***CORRESPONDING AUTHOR: Dr. V PRAVEEN KUMAR, ASSITANT PROFESSSOR, DEPARTMENT OF ANAESTHESIOLOGY, MALLA REDDY INSTITUTE OF MEDICAL SCIENCES, SURARAM 'X' ROADS, JEEDIMETLA, QUTHBULLAPUR, HYDERABAD, TELANGANA – 500055.**

**Abstract:**

**Background**:Pre-emptive analgesia is an anti-nociceptive intervention given before incision which helps to reduce pain sensitization to transmission of pain signals evoked by tissue damage.Oxytocin has recently been recognized as an important mediator of endogenous analgesia. The present study aimed to assess the effectiveness of preemptive port site subcutaneous oxytocin infiltration in reducing post-operative pain as compared to post-operative infiltration in patients undergoing laparoscopic surgeries.

**Methods:**The study was a randomised controlled study conducted with 64 patients after applying the inclusion and exclusion criteria**.** Patients were randomly allocated into either of the two groups**:** 1**)** study group which received preincisional port site subcutaneous Inj. Oxytocin 4 ug (2.5 IU) diluted to 4 cc with sterile water at each port site incisionand the 2**)** control group

which received post-surgical subcutaneouswith Inj. Oxytocin 4 ug(2.5 IU) diluted to 4 cc with sterile water at each port site incision.Each group comprised of Thirty-two patients**.** Intraoperative hemodynamic parameters, duration of surgery, analgesia characteristics**(**requirement and doses of rescue analgesia**).** Visual analogue scale **(**VAS**)** was used to assess intensity of post-operative pain during recovery and 24 hrs after surgery**.**

**Results:**Both groups were comparable based on demographic and general clinical characteristics**.** Postoperative pain intensity was significantly lower in study group compared to controls at 2 hrs, 4 hrs, 6 hrs and 24 hrs**.** Significant Attenuation of hemodynamic response **(**mean heart rate, sysytolic and diastolic BP**)** was observed in the study group which was not blunted in control group patients**.**

**Conclusion:** Preemptive/preincisional port site subcutaneous infiltration of oxytocin was effective in reducing post-operative pain in adult patients undergoing laparoscopic surgeries under general anesthesia compared to controls. It was also effective in attenuating the cardiovascular response to intra-operative nociceptive stimuli compared to controls.

**Keywords**: Preemptive analgesia, oxytocin, subcutaneous infiltration, post-operative pain intensity, hemodynamic response.

**Introduction:**

Laparoscopic surgical procedures have become increasingly populardue tolower rates of complications, minimized incision size and trauma resulting in quicker postoperative recoveryand discharge.[(1)] Incidence of post-operative pain and analgesic requirementis reducedin laparoscopic surgeries compared to open surgery. Port pain, pelvic organ nociception, dia-phragmatic irritation from residual pneumo-peritoneum contributes to the total post-operative pain experience. [(2)]Post-operative pain after laparoscopic surgical techniques is often of short duration but isintense and can affect patient recovery. [(3)]

Postoperative pain is complex, multifactorial and a thoughtful choice from a variety of perioperative analgesic modalities is required to obtain optimal clinical outcomes.[(4)]Multimodal analgesic modalities imply use of drugs and regional blocks with local anesthetics, in addition to general anesthesia and are being increasingly used.[(5,6)]Single wound infiltration with local anesthetic (WI) or continuous local anesthetic infusion through catheters placed into surgical wounds have been re-introduced as componentsof multimodal analgesia for post-operative pain control.[(4,7)]

Pre-emptive analgesia is an anti-nociceptive intervention given before incision or surgery which helps to reduce sensitization of peripheral and central pain pathways to transmission of pain signals evoked by tissue damage. It has potential to be more effective than the same treatment

administered after incision or surgery. [8]First proposed by Wall in 1988, pre-emptive analgesia also has neuroprotective properties. [9]

In preemptive analgesia, local infiltration is done frequently using local anaesthetics and adjuvants but their adverse effectssignificantly limit their use. Thus there is great scope for newer and safer analgesics.The endogenous nonapeptide, oxytocin (OXY) has recently been recognized as an important mediator of endogenous analgesia due to preliminaryevidence linking it to nociception and pain in largely animal and few human studies with encouraging results.[10,11] Central(intrathecal) , peripheral (subcutaneous) and intranasal administration have been evaluated albeit in very few studies . [10-13]

Asthere are very few studies exploring peripheral role of oxytocin in reducing post-operative pain, aim of the present study was to assess the effectiveness of preemptive port site subcutaneous oxytocin infiltration in reducing post-operative pain as compared to post-operativeinfiltration in patients undergoing laparoscopic surgeries.

**Objective:**To assess the effectiveness of preemptive port site subcutaneous oxytocin infiltration in reducing post-operative pain as compared to post-operative infiltration in patients undergoing laparoscopic surgeries.

**Materials and Methods:**

Approval was obtained from institutional ethics committee prior to commencement of the study. The present study was a randomized controlled study conducted over a period of one yearfrom February 2021 to January 2022 in department of Anesthesiology, Dr. B R Ambedkar Medical College& hospital, K G Halli, Bangalore, Karnataka, India.

Eligible study population was patients between 18 to 50years, American Society of Anesthesiologists (ASA) physical class I and II,scheduled to undergo elective laparoscopic surgeries.Patients taking chronic analgesic treatment e.g. non-steroidal anti-inflammatory drugs, opioids and patients with hypersensitivity to study drug were excluded from the study. Patients who underwent intra-operative complications(excessive bleeding (>500cc), conversion to open laparotomy) were also excluded from the study.

Data collection instrument was a structured proforma which included patient's sociodemographic deatils, indication for surgery, anaesthetic details, intra-operative monitoring parmeters, post-operative vitals andVAS score.Taking alpha error of 0.05, standard deviation of 0.2, the minimum calculated sample sizewas 60 patients.

The present study included 64 patients to avoid possible dropouts during study period. Pre-operatively, the patients were explained about the VAS score with end point to be labelled as 0 = no pain and 10 = excruciating worst possible pain.

Premedication: All patients were pre-medicated with IV Inj. Glycopyrrolate (0.005mg/kg), Inj. Ondansetron (0.1 mg/kg IV), Inj. Midazolam (0.02 mg/kg) and Inj Fentanyl(0.002mg/kgIV).

**Anesthetic procedure:**

On receiving patient in operating room, all standard monitors were attached, and baseline heart rate (HR), mean arterial pressure, and oxygen saturation (SpO2) recorded. Patients wererandomly allocated into either of two groups based on computer generated results:

**Group I**(study group) patients received pre-incisional subcutaneous infiltration with Inj. Oxytocin 4 ug (2.5 IU) diluted to 4 cc with sterile water at each port site incision.

**Group II**(control group) patients receivedpost-surgical infiltration with Inj. Oxytocin 4 ug(2.5 IU) diluted to 4 cc with sterile water at each port site incision.

Each group comprised of 32 patients. The standard anesthetic technique was used in patients of both groups and muscle relaxation achieved by Inj. Atracurium (0.5 mg/kg). Maintenance of anesthesia wasa achieved with Air in $O_2$ and Isoflurane. Muscle relaxation was maintained with Inj. Atracurium (0.5 mg/kg) as and when required. Tidal volume of 6–10 ml/kg body weight and end-tidal carbon dioxide maintained between 35 and 45 mmHg. During surgery, intra-abdominal pressure was maintained at 12–15 mmHg and airway pressure below 30 mmHg. Heart rate, systolic BP, diastolic BP, mean arterial pressure, oxygen saturation were monitored at baseline, and every 5 min till the end of surgery.

Neuromuscular blockade was reversed by Inj. Neostigmine (0.05 mg/kg) and Inj. Glycopyrrolate (0.01 mg/kg) and trachea extubated when adequate recovery was observed. The total duration of surgery and anesthesia wasrecorded. All patients were kept in the post anesthesia care unit for 2 hrs and vitals were recorded. Heart Rate, blood pressure, oxygen saturation ($SpO_2$), and VAS were observed and recorded at 1, 2, 4, 6and 24 hrs. In case of inadequate analgesia (VAS score >3), patients of both groups received IV Inj.Paracetamol(15mg/kg) as rescue analgesia. Postoperatively, the following parameters were observed: quality and duration of analgesia, hemodynamic parameters and time to the first dose of rescue analgesia, sedation and any postoperative complication or side effects.Duration of analgesia was defined as the time interval between the adminstration of oxytocin to the adminstration of first dose of rescue analgesic.

**Statistical Analysis:**

Statistical analysis was performed using SPSS. Numerical data were expressed as mean, standard deviation, and categorical data as percentages. Oneway repeated measures analysis of variance (oneway ANOVA) was used to compare the changes in cardiovascular parameters.The independent t test was used for comparison of total duration of analgesia and surgery in the two groups. As total duration of Control group analgesia, total doses of rescue analgesia and VAS scores were not normally distributed non-parametric test (Mann Whitney U test) was used for the

comparison between study group and control group groups. Statistical significance was considered at p-value< 0.05.

**OBSERVATIONS & RESULTS:**

**Table 1**: **General and Clinical Variables in the Study and Control Group**

| Characteristic | Study Group | Control Group | P-Value |
|---|---|---|---|
| Age (years) | 38.5 ± 16.3 | 35.4 ± 12.2 | 0.061 |
| Gender (Males/ Females)(%) | 56/42 | 44/58 | 0.343 |
| ASA – PS<br>1<br>2 | <br>14 (50)<br>14 (52) | <br>14 (50)<br>13 (48) | 0.891 |
| Mean Heart rate (BPM) | 93.5 ± 17.9 | 91.9 ± 18.3 | 0.743 |
| Mean Systolic blood pressure (mmHg) | 124.5 ± 14.9 | 126.0 ± 11.6 | 0.687 |
| Mean Diastolic blood pressure (mmHg) | 72.4 ± 11.4 | 79.4 ± 10.6 | 0.023* |
| Mean arterial pressure (mmHg) | 89.9 ± 10.9 | 95.3 ± 10.5 | 0.067 |
| Mean $SPO_2$(%) | 98.3 ± 0.9 | 98.6 ± 0.9 | 0.228 |
| Total Duration Of Anaesthesia (Min) | 82.9 ± 34.1 | 80.0 ± 38.3 | 0.695 |
| Total Duration Of Surgery (Min) | 74.1 ± 33.9 | 70.0 ± 38.3 | 0.681 |
| Total Duration Of Post-Op Analgesia (Hours) | 10 (8, 11) | 7 (6, 8) | < 0.001** |
| Total Doses Of Rescue Analgesia | 2 (2, 3) | 3 (3, 3) | < 0.001** |
| Mean VAS Score<br>@ 15min<br>@30 Min<br>@ 45 Min<br>@ 60 Min<br>@ 2 Hr | <br>1 (1,1)<br>1 (1,1)<br>1 (1,1)<br>1 (1,2)<br>2 (1,2) | <br>1 (1,1)<br>1 (1,1)<br>1 (1,1)<br>2 (1,2)<br>2 (2,2) | <br>1.000<br>1.000<br>0.718<br>0.056<br>0.002* |

| | | | |
|---|---|---|---|
| @ 4 Hr | 2 (2,2) | 3(3,3) | 0.006* |
| @ 6 Hr | 2 (2,3) | 3 (3,3) | 0.001** |
| @24 Hr | 2(2,3) | 3(3,3) | 0.001** |

Demographic and clinical variables of patients in the study and control group were not found to be statistically significantly different. ($p>0.05$)

**Duration of Surgery and Analgesiaparameters:**

Total duration of analgesia and total duration surgery in study and control group patients were not significantly different. Total duration of post-operative analgesia was significantly lower in control group ($p < 0.001$).

**Rescue Analgesia:**

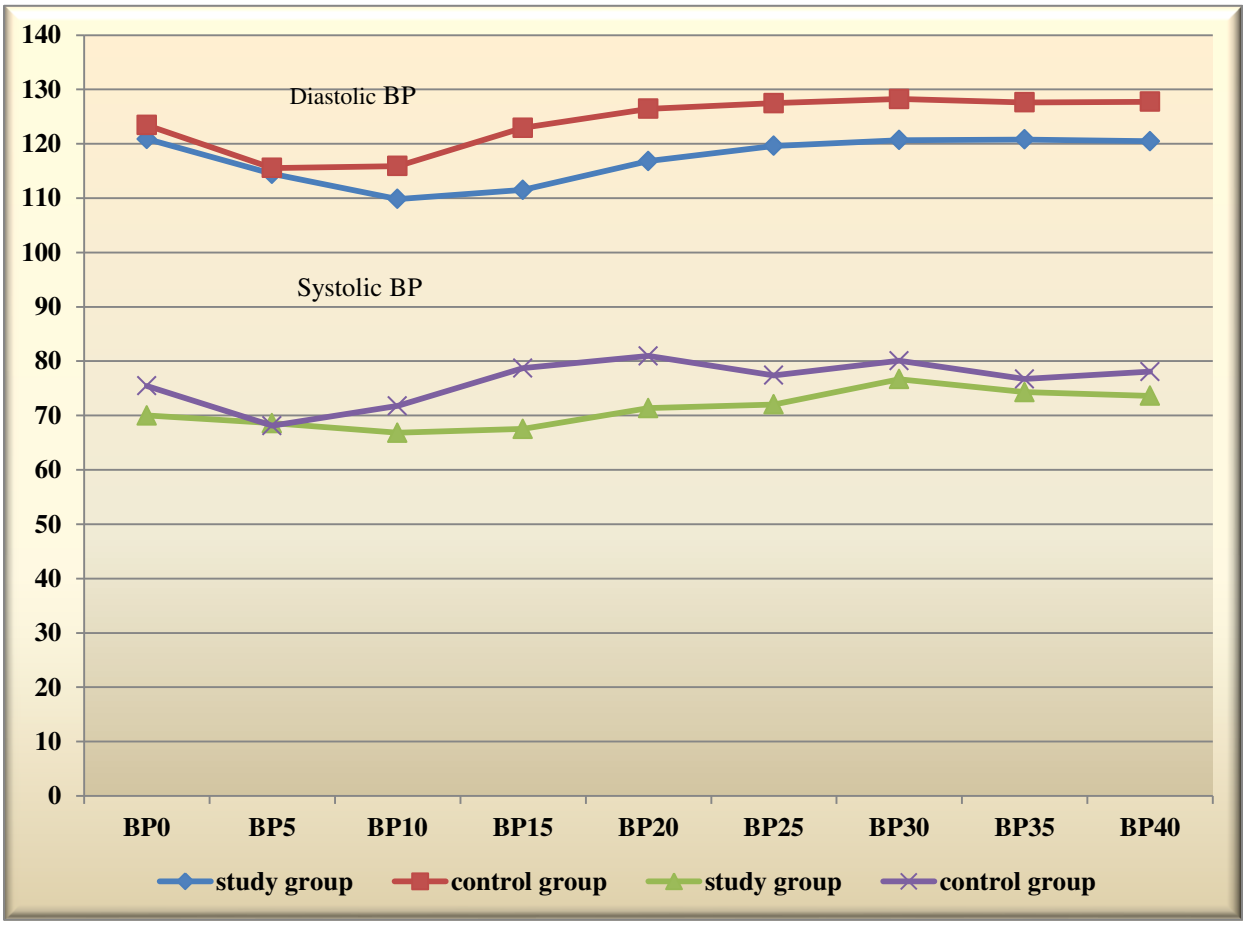
Requirement of rescue analgesia was assessed at 2 hrs, 4 hrs, 6 hrs, 12 hrs and 24 hrs. Requirement of rescue analgesia at 4 hrs and 12 hrs was significantly higher in control group patients ($p = 0.040$, ($p = 0.002$ respectively) and total doses of rescue analgesia were also significantly higher in control group ($p < 0.001$).

**Post-Operative Pain:**

Visual analogue scale **(**VAS) scores were assessed at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 2 hrs, 4 hrs and 6 hrs. Initially (on arrival in PACU) both groups were comparable regarding post-operative analgesia. At 2 hrs,4 hrs, 6 hrsand 24 hrs,VAS scores were significantly higher in control group patients. ($p=0.002$, $p = 0.001$ at 2 and4,6,24 hr respectively). VAS scores at other observed time points were not significantly different between groups. Comparison of the general and clinical variables in the study and control group is presented in table 1.

**Cardiovascular Parameters:**

**Fig 1: Intra-operative mean Systolic and Diastolic Blood Pressure of Study and Control Groups**




The meanheart rate, systolic and diastolic blood pressure was significantly lower in subcutaneous oxytocin Infiltration preemptively group compared to post-operative oxytocin Infiltration group ($p<0.001$). This indicates significantblunting of nociceptive response to surgical incisionsand trocar insertions. Mean systolic and diastolic blood pressure at different assessment points are depicted in figure1.

**Respiratory Parameters:**

There were no significant differences between the groups in mean oxygen saturation assessed by pulse oximetry ($SPO_2$) and end-tidal CO2 during the procedure.

**Adverse Effects:**

None of the patients in the study or control groups manifested local or systemic adverse effects.

**Discussion:**

There has been a considerable shift toward regional anesthesia techniquesfor post-operative pain management for procedures under general anesthesia since the past few years. These techniques include pre and /post-operative wound infiltration (WI) as single/continuous infiltration (CWI) of local anesthetic agentswith or without adjuvants and have been shown to result insignificant anti-hyperalgesic effects.[14-16]

Oxytocin is one such potentialagent. Predominantly produced in the supraoptic and paraventricular nuclei (SON & PVN respectively) of the hypothalamus and performs peripheral and central actions. Oxytocinergic neurons of the PVN have axonal projections to the spinal cord which form synaptic connections with neurons in the dorsal horn. Oxytocin not only performs key functions in parturition and lactation but is also deeply implicated in social and psychological functions including maternal attachment, anxiety, depressive mood, memory, appetite, sexual function and stress regulation. [11,17]It has direct and indirect effects on painmodulating nociceptive transmission, pain perceptionand reduces pain sensitivity also when administered exogenously.[11]

In the present study, preemptive (preincisional) port site subcutaneous infiltration of oxytocin was significantly more effective in reducing post-operative pain as compared to post-surgical infiltration of oxytocin in controls. Comparable effectiveness of subcutaneous oxytocin over lidocaine has been reported by a recent study by Zayas-González H et al. [13] No other study apart from the aforementioned two has evaluated analgesic effect of subcutaneous oxytocin infiltration. Findings of the present study and study by Zayas-González H et al. [13] corroborate with findings of recent basic science studies [18]where activation of peripheral oxytocin receptors found in skin nerve terminals were able to produce long-lasting inhibition of nociception.

In the present study the cardiovascular response to nociceptive stimuli during surgery was bluntedin the study group compared to the control group. This diminution of cardiovascular response has been recently linked to effective post-operative pain control.[13] A study by Uchida et al [19] suggested that heart rate variability may be predictive of the appearance of postoperative pain. However results have been shown to vary with type of anesthetic agents and additional clinical evidence is clearly needed to further assess the relationship between opioids, inhalation anaesthesia, duration of exposure to halogenated agents and autonomic nervous system response.[11,20]

Effective methods to significantly decrease post-operative are a combination of pre-emptive analgesia and multimodal pain management. Multimodal analgesic techniques reduce the dosage of any single drug and thus reduce risk of significant adverse effects associated with its administration.They use agents like dexmedetomidine, lidocaine, with/without non opioid adjuvants (NSAIDS, beta blockers, ketamine, gabapentine etc) [14] and oxytocin could be an effective inclusion in the group.

**Strengths of the study:**

Findings of the present study add to the very limited evidence on the effectiveness of preemptive subcutaneous infiltration of oxytocin in reducing postoperative pain in patients undergoing laparoscopic surgeries.

**Limitation of the study:**

The present study was a single center study with relatively smaller sample size. Multi-centric randomized controlled trials with multiple arms and larger sample sizes are essential to explore further the role of preemptive subcutaneous oxytocin infiltration in reducing post-operative pain and improving clinical outcomes.

**Conclusions:**

Preemptive/preincisional port site subcutaneous infiltration of oxytocin was effective in reducing post-operative pain in adult patients undergoing laparoscopic surgeries under general anesthesia compared to controls. It was also effective in attenuating the cardiovascular response to intra-operative nociceptive stimuli in study group compared to controls

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